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The Graeme Robertson Memorial Lecture, 1982

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Multiple Sclerosis: Fifty Years On

*J. M. Sutherland**

To have been invited to deliver the Graeme Robertson Memorial Lecture for the current year is a significant honour and I thank you for this and particularly for the opportunity of paying a tribute to an outstanding neurologist and a great Australian.

When in 1956, I was appointed Senior Lecturer in Medicine to the University of Queensland, to my shame I knew little of Australia and less of Brisbane, but I did know of E. Graeme Robertson. Indeed, his writings on pneumoencephalography, a subject on which he was a world authority, were compulsory reading for all aspiring neurologists and neurosurgeons.

Subsequently, I came to know and to appreciate fully this highly competent, quiet, almost retiring man from meeting him at AAN meetings and by learning of him from my friend and colleague the late Dr K.G. Jamieson who had been one of the many to benefit from his teaching and example at the Royal Melbourne Hospital. As the years passed, knowing developed into an affection for a colleague who despite the many calls on his time was never too busy to give of his knowledge and experience.

I felt I could best honour Graeme Robertson by discussing some of the developments in our knowledge of multiple sclerosis, particularly those aspects I have been interested in, against the background of his professional lifetime. I chose multiple sclerosis as my topic because it was a subject of mutual interest and because the first paper I gave to this Association in 1960, with Graeme Robertson as Chairman, was on 'The Clinical Features of Multiple Sclerosis'.

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Edward Graeme Robertson was born in 1903 and, after attending Scots College, graduated with honours from Melbourne University in 1927. He attained his doctorate in 1930.

At this time multiple sclerosis was 100 years old, having been recognised as a pathological entity by Carswell and Cruveilhier in the 1830s. Later, through the French school of Charcot, Vulpian and Marie the disease became widely recognised (McAlpine, 1955; Bailey, 1959). In Britain, the clinical aspects of multiple sclerosis had been well reviewed by Bramwell (1904; 1905) while Dawson (1916) had placed the histology of the disease on a sound footing. In the year that Graeme obtained his MD, the current status of multiple sclerosis had been critically reviewed by Brain (1930).

In 1930 Dr Robertson went to London, obtained Membership of the Royal College of Physicians and joined the National Hospital for Nervous Diseases, Queen Square. Since the opening of the National Hospital in 1860 and the establishment of the London Infirmary for Epilepsy and Paralysis (later Maida Vale Hospital for Nervous Diseases), British neurology had flourished under such men as Hughlings Jackson, Gowers, Ferrier and Horsley. When 'on the house' at Queen Square the 27-year-old Dr Robertson had joined a hospital at the peak of its prestige and influence. There, and in London generally, he was to be variously influenced by men of the calibre of Adie, Brain, Brinton, Collier, Critchley, Denny-Brown, Holmes, McAlpine, Purves-Stewart, Riddoch, Symonds, Walshe, Wilson, Williams and others of similar professional stature. This period of his life was to have a lasting effect on Graeme Robertson and, in consequence, on Australian neurology.

It is of interest to note, in summary, what was known of multiple sclerosis when Graeme practised in London. For this we are indebted to the late Lord Brain (Brain, 1930). The estimated prevalence of the disease in England and Wales was 16/100,000 and in the United States of America 5/100,000. The incidence was above average in Slavs, Scots, Germans, English and Irish and highest in the Scandinavians and French. A familial incidence was considered rare and an inherited predisposition unlikely to play any part in the aetiology of the disease. Males were affected more than females in a ratio of 3 : 2 and in 68% of cases the onset was between 20 and 40 years of age. The case for a spirochaetal aetiology was considered unproven while a viral aetiology, with particular reference to *Spherula insularis*, remained in doubt.

The symptoms and objective signs of the disease were fully discussed by Brain and with only a few additions would not be out of place in any neurological textbook today. With regard to CSF findings, the cell count was stated to be normal in about half the cases; the total protein to range round the upper limit of normal, and the Nonne-Apelt and Pandy tests for globulin occasionally to yield a positive response; the colloidal gold test furnishing a paretic curve in about half the cases; the Wassermann reaction being negative.

Turning to treatment, mention was made, *inter alia*, of pyrexial treatment with typhoid vaccine, neo-arsphenamine, vaccine employing *Spherula insularis*, serum from non-progressive cases of the disease and diathermy to the spinal cord. However, Brain concluded that, 'the multiplication of remedies is eloquent

of their inefficacy' and, 'the cure of disseminated sclerosis awaits an increase in our knowledge of the causal organism, of the nature of immunity, and of the factors upon which depend the remarkable variations in the course of the disease'. This comment would not be out of place in 1982.

On leaving the National Hospital, Dr Robertson was appointed to the consultant staff of St Bartholomew's and the Post Graduate Medical School, Hammersmith. In 1934 he returned to Melbourne where he carried on the great traditions of Queen Square. He was a gifted teacher, an outstanding clinical neurologist in the classic mould and, in addition to writing numerous scientific papers, he became a world authority on pneumoencephalography. His first monograph on this subject was published in 1941, the last in 1975.

Major Investigations: 1930-1977

During the years 1930-1960, work on multiple sclerosis was carried out particularly on three fronts: the possibly infective nature of the disease, its geographical distribution, and the role of altered immune processes in its pathogenesis.

The Infective Nature of Multiple Sclerosis

Working with Dr D.K. Adams, at the Western Infirmary, Glasgow, it appeared that not only was multiple sclerosis more common in certain areas than others but that the disease might have a district incidence also, and that exposure to animals, particularly sheep, was a frequent occupational factor. Three diseases of sheep were considered: louping ill, scrapie and swayback.

Louping ill. A virus disease transmitted by the tick, *Ixodes ricinus*, louping ill can affect humans producing a meningo-encephalitis with recovery. It was considered unlikely that the virus was implicated in multiple sclerosis.

Scrapie. Scrapie is also a virus disorder of sheep producing an encephalomyelitis. The virus of scrapie may remain latent for prolonged periods and there is a marked geographical and breed incidence. The latter has been shown to be genetically determined by Parry (1979). With the cooperation of Dr D.R. Wilson of the Animal Diseases Research Association, Moredun Institute, Edinburgh, we were able to show that mid-zone precipitation of the gold sol in Lange's colloidal gold test occurred in the cisternal fluid of 4 out of 7 scrapie sheep while in 13 control sheep no precipitation of the gold sol occurred. To avoid any bias in reading the results, the cisternal CSF was obtained by Dr Wilson at the Moredun Institute, Edinburgh, and sent 'blind' to the Western Infirmary, Glasgow, where the colloidal gold tests were carried out (Sutherland, 1950).

Subsequently, Dr Wilson and I in November, 1948, inoculated six 7-month-old lambs with blood and CSF from 3 cases of multiple sclerosis (Sutherland and Wilson, 1951). During the follow-up period of 17 months one animal died ac-

cidentally from suffocation. Although there had been no clinical evidence of disease of the nervous system in this lamb, histology revealed a meningo-encephalitis of subacute type for which no cause was found. There was no demyelination and the appearances were not those of scrapie. The significance of this finding remains uncertain but in view of more recent work on 'associated agents' it is possible that the multiple sclerosis material was responsible for this inflammatory condition in the nervous system. Unfortunately the surviving sheep were not autopsied.

Swayback. Swayback is a demyelinating disease of lambs and, although copper deficiency appears to play a part, it is unlikely that a simple copper deficiency in pastures is responsible. A defect in copper metabolism is probably more likely. In 1947, Campbell and his coworkers reported the occurrence of multiple sclerosis in 4 veterinary research officers who had worked on swayback. Three of the patients developed symptoms of multiple sclerosis within months of one another and within a few years of exposure to the pathological material. All 4 patients are now deceased; the first and the fourth had necropsies performed, the findings being those of multiple sclerosis (Campbell, 1963: Millard and Mitchinson, 1967). A possible association between swayback in sheep and multiple sclerosis in humans remains uncertain; the subject has been reviewed by Symonds (1975).

Recent findings

In more recent years evidence has been adduced to support the view that an altered measles virus may play a role in the aetiology of multiple sclerosis. Prineas (1972) has found paramyxovirus particles (the group of viruses to which the measles virus belongs) in the brain of a multiple sclerosis subject in relation to perivenous demyelinating lesions. Pathak and Webb (1976) reported a similar finding and considered the inclusions were likely to be related to measles rather than to other paramyxoviruses. Prasad et al. (1977) found that a virus, antigenically that of measles, could be readily recovered from the jejunum of multiple sclerosis patients. It is relevant to these findings that Poskanzer, Schapira and Miller (1963) drew attention to the similarities in epidemiological pattern of multiple sclerosis and paralytic poliomyelitis. A similar correlation obtained in Australasia (Eadie et al., 1965) and it may be that the disease results from a widespread subclinical viral infection acquired in childhood, clinical manifestations of the disease, however, occurring many years later and only in certain individuals.

In both scrapie and multiple sclerosis at least two viruses appear to be present (Adams, 1976). Thus, in scrapie, in addition to the scrapie virus, there is a scrapie associated agent (SAA) which can be serially transmitted in mice but which does not produce scrapie. It is therefore possible that the multiple sclerosis associated agent (MSAA), described by Carp et al. (1972), by Koldovsky et al. (1975), and by Henle et al. (1975) is similar to SAA. The relationship of these viruses to each other and to the respective disease processes remains unclear.

Table I. Prevalence rates 100,000 for multiple sclerosis in Northern Scotland[1]

	Population	Prevalence
Mean prevalence	231,116	67
Mainland Counties	146,076	62
Outer Hebrides: Skye	44,439	38
Orkney and Shetland	40,601	118

1 Sutherland (1956)

However, Fraser (1977) concluded that 'multiple sclerosis could well be a slow virus disease, or more likely, a virus-induced immune disease'.

Geographical Aspects of Multiple Sclerosis

In the first half of the present century, assessments of the prevalence of multiple sclerosis were based largely on mortality statistics, hospital admissions and on the opinion of astute observers. The only accurate method of assessing prevalence, however, is to determine the number of patients within an area, at a certain time, and to relate this figure to the population at risk at that time. Among the earliest workers to apply this technique were Allison and Millar (1954), who obtained a prevalence rate of 79/100,000 for all age groups over 20 years of age in Northern Ireland.

Previously impressed with the possibility that the prevalence of multiple sclerosis varied from area to area, I continued to pursue this line of enquiry on my being appointed to the Inverness region in 1950. The Northern Counties of Scotland were surveyed and, although administered medically from Aberdeen, the Orkney and Shetland Islands were included in the survey partly because in those days they were relatively closed communities and partly because geographically and ethnically they provided a contrast to the mainland counties and to the Outer Hebrides. The determined prevalence day was 31st May, 1954, and the prevalence rates obtained in this survey are summarised in table I (Sutherland, 1956).

Shetland, lying between latitudes 60-61°N and with a population of 19,343, was found to have the highest prevalence rate – 129/100,000 – followed by Orkney, latitude 59°N, population 21,258, with a prevalence rate of 108/100,000, and Caithness, latitude 58°N, population 22,705, with a prevalence rate of 88/100,000. The Isle of Lewis, latitude 58°N, population 23,732, in the Outer Hebrides had the lowest prevalence rate – 21/100,000. The very high prevalence (subsequently found to be the highest in the world) in the Shetlands and Orkney Islands was confirmed by Allison (1963) from Belfast, and by Fog and Hyllested (1966) from Denmark.

The populations of Shetland and Orkney and to a lesser extent Caithness are essentially of Nordic extraction in contrast to the predominantly Celtic qualities of the Hebridean. It seemed possible that some disadvantageous genetic factor which predisposed them to multiple sclerosis might exist in those of Nordic

stock. No environmental factor of aetiological significance was uncovered with two possible exceptions. Water supplies in Shetland and Orkney, outside the two capital towns, showed heavy contamination, being largely derived from surface wells. Secondly, a later statistical analysis of trace elements in the water supplies indicated a relatively high proportion of molybdenum (Layton and Sutherland, 1975). It was considered possible that a high molybdenum/copper ratio creates a trace element imbalance which favours the development of multiple sclerosis. This would account for the anomaly between the high prevalence of the disease in Shetland-Orkney and the low prevalence in the Faroe Islands (see below). These two island groups are similar in many ways but have a different solid geology.

The importance of ascertaining the high prevalence of multiple sclerosis in the small communities on Shetland and Orkney, however, lay in the hope that in these islands the cause of the disease might be found. Poskanzer and his colleagues took up this challenge. The prevalence of multiple sclerosis was reviewed on two further occasions, in 1970 and 1974, and an exhaustive series of epidemiological, virological and genetic studies have been carried out (Poskanzer et al., 1976; Roberts et al., 1979 a,b; Poskanzer et al., 1980 a-e; Taylor et al., 1980). A dramatic increase in the prevalence of multiple sclerosis was found in the 4 surveys which have been conducted over a 20-year period. Thus, the prevalence of multiple sclerosis in Orkney rose from 111/100,000 in 1954 (the figure adjusted for estimated population at the time) to 309/100,000 in 1974. The prevalence rate for Shetland showed a much lesser increase from 134/100,000 in 1954 to 184/100,000 in 1974. Since the incidence of the disease was shown to have remained similar in 5-year periods since 1941 (Poskanzer et al., 1976) the increased prevalence appears to be due to longer duration of the disease, and an increased awareness of the disorder perhaps related to repeated intensive studies.

The Poskanzer studies support the view that both an infective and a genetic factor are operative in multiple sclerosis although neither factor could be clearly defined. It is of interest that there is a tendency for multiple sclerosis patients in Shetland to have consumed 'potted head' (pig's brain) (Poskanzer et al., 1980, b). This is reminiscent of kuru (Mathews, 1968) and of Morley's report of a possible association between multiple sclerosis and eating lamb's brain (Morley, 1971).

Lying between latitudes 61° 30 and 62° 30 some 312km (approximately 195 miles) north-west of the Shetlands, are the Faroe Islands. Kurtzke and Hyllested (1979) reported that only 2 cases of multiple sclerosis were known to have occurred in the Faroes before World War II. Between 1940 and 1945 these islands were occupied by British, mainly Scottish, troops and between 1943 and 1960, 23 cases of multiple sclerosis occurred in native Faroese. Subsequent to 1970 only one further case occurred. According to Kurtzke (1977) the sudden onset and the equally sudden disappearance suggests that multiple sclerosis is a transmissible disease.

The world prevalence of multiple sclerosis is now known not to be uniform and in both hemispheres the prevalence of the disease increases with increasing latitude and with the possible exception of extreme latitudes (Kurland, 1970;

Table II. Prevalence/100,000 of multiple sclerosis in Australia

Area	Latitude	Prevalence
North Queensland[1]	17°-21°	7
Darling Downs[1]	27°-28°	12
Newcastle[2]	32°	20
Perth[2]	32°	20
Hobart[2]	43°	32

1 Sutherland et al. (1966)
2 McCall et al. (1968)

Acheson, 1972, 1977; Alter, 1977; Kurtzke, 1977). The hemispheres can be subdivided into high risk zones with a prevalence in excess of 40/100,000; intermediate risk zones with a prevalence between 20 and 39/100,000; and low risk zones with a prevalence of 0-19/100,000. Surveys in Australia suggest that from 17° to 28°S is a low risk zone and from 32° to 43°S an intermediate risk zone (table II). The pattern of increasing prevalence with increasing latitude is typical of multiple sclerosis and although future studies will almost certainly furnish higher prevalence rates, it is probable that the prevalence gradient will remain.

It would appear that genetic or ethnic factors may be capable of altering this latitude effect. Thus, the South Island of New Zealand is a high risk zone yet Japan, resembling New Zealand in relative latitude, climate, soil and general geological characters is a low risk zone (Layton and Sutherland, 1975). Similarly, the incidence of the disease is low in Beijing, China, and the surrounding area (Feng, 1980).

The evidence obtained from epidemiological studies supports the concept of some environmental factor or factors being the cause of multiple sclerosis while genetic-ethnic factors may modify the prevalence or expression of the clinical disease.

Altered Immune Reactions

Although suggestions of an abnormal allergic reaction in multiple sclerosis have been made for over 50 years, Honor Smith and her colleagues (1957, 1961), employing purified protein derivative of tuberculin intrathecally, were among the first to demonstrate an abnormal immunological reaction in multiple sclerosis patients.

Holmes et al. (1967) reported the occurrence of multiple sclerosis in one twin and of systemic lupus erythematosus in her identical twin sister, while the coexistence of multiple sclerosis and recognised autoimmune disorders has been discussed by Baker and his colleagues (1972). Similarly, Knight (1977) has emphasised that similarities exist between multiple sclerosis and autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus.

The CSF of patients with multiple sclerosis has furnished further evidence of disturbed immune system function. Fischer-Williams (1971) has shown that

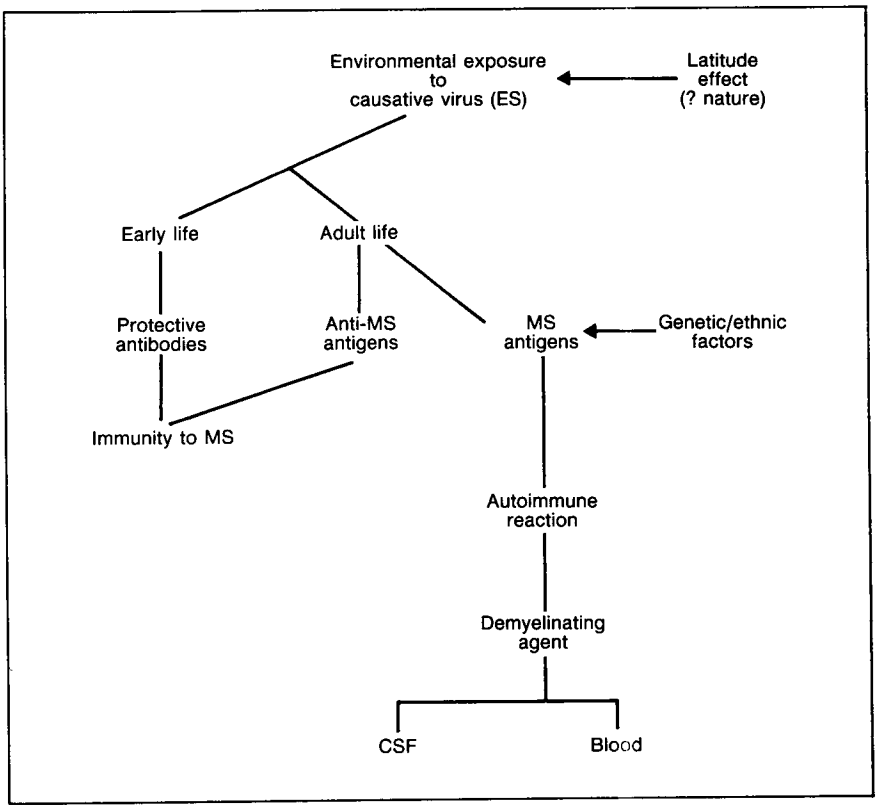

Fig. 1. Aetiology and pathogenesis of multiple sclerosis – an hypothesis.

the gamma globulin fraction of CSF was above 14% of total protein in 94% of multiple sclerosis patients compared with 7.7% of controls while in 75% of multiple sclerosis patients the IgG content was above 14%.

The recognition of histocompatibility-linked determinants related to the HLA (human lymphocyte-antigen) system (HLA-A3 and HLA-B7 and the related antigens DW2 and DR2) in a significant portion of patients may explain the genetic factor and has strengthened the concept of altered immune function in the pathogenesis of the disease (Fielder et al., 1981). A multiple sclerosis susceptibility gene, possibly linked to the DW2 gene and which may alter the host response to viral infection of the central nervous system, was described previously by Comings (1979).

It would seem possible that the causative agent or agents of multiple sclerosis may be widespread in nature and whether or not a pathological process develops is determined by the HLA make-up of the individual. Thus, the disease may remain completely subclinical; in one-third of cases the disease may be arrested or remain in prolonged remission (McAlpine, 1961); there may be a

genetically determined inability to mount an adequate immunological response so that the classical disease develops (Wisniewski, 1977). This concept of multiple sclerosis is summarised in figures 1 and 2.

Two aspects of practical importance emerge from this concept. In evaluating treatment it should be recalled that in about one-third of patients there will be a spontaneous remission for an indefinite period of time, certainly over 10 years. Secondly, in the majority of cases there is a tendency for remissions and any treatment which may enhance this tendency will be of value, provided it is safe to employ and provided it is employed before irreversible changes occur in the central nervous system.

These, then, are my views on some developments in the understanding of multiple sclerosis which have occurred over the past 50 years. A cynic might observe that we know little more about the disease and we are as little able to influence its course now as we were in 1930. However, with a multidisciplinary approach to the problem taking place both in this country and overseas, multiple

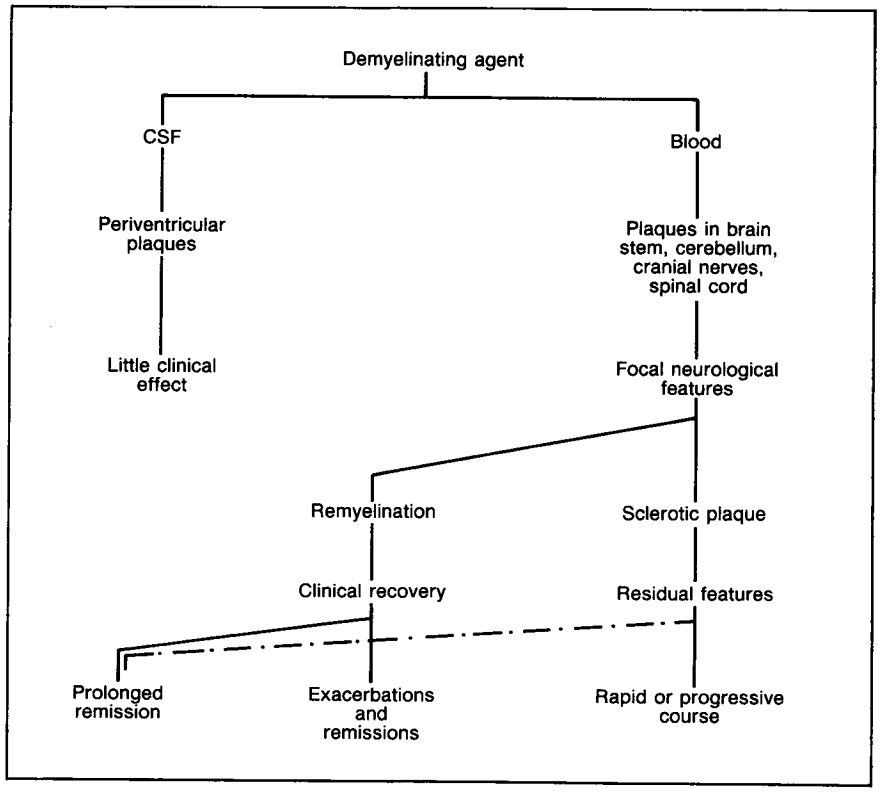

Fig. 2. Pathogenesis of multiple sclerosis – an hypothesis.

sclerosis, the sphinx of the nervous system, may yield its secrets in the foreseeable future.

During the years under review Dr Graeme Robertson not only carried out original work and conducted a busy private and hospital practice but in 1950, in association with Leonard Cox, Kenneth Noad, Eric Susman, Gerald Moss, Sydney Sunderland, John Game and John Billings, he assisted in founding our Association. He was the second President of the AAN and it was under Graeme's aegis that the first volume of The Proceedings of the Australian Association of Neurologists appeared in 1963. Dr Graeme Robertson indeed bequeathed to us and to Australia a neurological heritage for which we will always be grateful.

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References

Acheson, E.D.: The epidemiology of multiple sclerosis: in McAlpine, Lumsden and Acheson, Multiple Sclerosis: A Reappraisal, pp.3-42 (Churchill Livingstone, Edinburgh 1972).

Acheson, E.D.: Epidemiology of multiple sclerosis. British Medical Bulletin 33: 9-14 (1977).

Adams, D.H.: Relation between Carp (multiple sclerosis associated) agent and multiple sclerosis. Lancet 2: 444-446 (1976).

Allison, R.S. and Millar, J.H.D.: Prevalence and family incidence of disseminated sclerosis. Ulster Medical Journal 23 (Suppl. 2): 9-22 (1954).

Allison, R.S.: Some neurological aspects of medical geography. Proceedings of The Royal Society of Medicine 56: 71-76 (1963).

Alter, M.: Clues to the cause based upon the epidemiology of multiple sclerosis: in Field (Ed) Multiple Sclerosis: a Clinical Conspectus, pp.35-82 (M.T.P. Press, England 1977).

Bailey, P.: Multiple sclerosis: in Guillaim J.M. Charcot 1825-1893: His Life and Work, pp.111-113 (Pitman Medical Publishing Company, London 1959).

Baker, H.W.G.; Balla, J.I.; Burger, H.G.; Ebling, P. and Mackay, I.R.: Multiple sclerosis and autoimmune diseases. Australian and New Zealand Journal of Medicine 3: 256-260 (1972).

Brain, W.R.: Critical Review: Disseminated sclerosis. Quarterly Journal of Medicine 23: 343-391 (1930).

Bramwell, B.: Disseminated sclerosis with special reference to the frequency and aetiology of the disease; in Bramwell Clinical Studies Vol. 2, pp.193-210 (R. and R. Clark Ltd., Edinburgh 1904).

Bramwell, B.: in Disseminated sclerosis with special reference to mode of onset and symptomatology of the disease; in Bramwell Clinical Studies Vol. 3, pp.1-28 (R. and R. Clark Ltd., Edinburgh 1905).

Campbell, A.M.G.; Daniel, P.; Porter, R.J.; Russell, W.R.; Smith, H.V. and Innes, J.R.M.: Disease of the nervous system occurring among research workers on swayback in lambs. Brain 70: 50-58 (1947).

Campbell, A.M.G.: Veterinary workers and disseminated sclerosis. Journal of Neurology, Neurosurgery and Psychiatry 26: 514-515 (1963).

Carp, R.I.; Licursi, P.C.; Merz, P.A. and Merz, G.S.: Decreased percentage of polymorphonuclear leucocyte in mouse peripheral blood after inoculation with materials from multiple sclerosis patients. Journal of Experimental Medicine 136: 618-629 (1972).

Comings, D.E.: Pc 1 Duarte: a common polymorphism of a human brain protein, and its relationship to depressive disease and multiple sclerosis. Nature 277: 28-32 (1979).
Dawson, J.W.: The histology of disseminated sclerosis. Edinburgh Medical Journal 17: 311-344, 377-410 (1916).
Eadie, M.J.; Sutherland, J.M. and Tyrer, J.H.: Multiple sclerosis and poliomyelitis in Australia. British Medical Journal 1: 1471-1473 (1965).
Feng, Y.K.: Clinico-electroencephalographic studies of multiple sclerosis; in Tyrer and Eadie (Eds) Clinical and Experimental Neurology 17: 47-57 (Adis Press 1980).
Fielder, A.H.L.; Batchelor, J.R.; Vakarelis, B.N.; Compston, D.A.S. and McDonald, W.I.: Optic neuritis and multiple sclerosis: Do factor B alleles influence progression of the disease? Lancet 2: 1246-1248 (1981).
Fischer-Williams, M. and Roberts, R.C.: Cerebrospinal fluid proteins and serum immunoglobulins. Occurrence in multiple sclerosis and other neurological diseases: Comparative measurement of Y globulin and the IgG class. Archives of Neurology 25: 526-534 (1971).
Fog, M. and Hyllested, K.: Prevalence of multiple sclerosis in the Faroes, the Orkneys and Shetland. Acta Neurologica Scandinavica 42 (Suppl. 19): 9-11 (1966).
Fraser, K.B.: Multiple sclerosis: A virus disease? British Medical Bulletin 33: 34-39 (1977).
Henle, G.; Koldkovsky, V.; Koldovsky, P.; Henle, W.; Ackermann, R. and Haase, G.: Multiple sclerosis-associated agent: neutralisation of the agent by human sera. Infection and Immunity 12: 1367-1374 (1975).
Holmes, F.F.; Stubbs, D.W. and Larsen, W.E.: Systemic lupus erythematosus and multiple sclerosis in identical twins. Archives of Internal Medicine 119: 302-304 (1967).
Knight, S.C.: Cellular immunity in multiple sclerosis. British Medical Bulletin 33: 45-49 (1977).
Koldovsky, U.; Koldovsky, P.; Henle, G.; Henle, W.; Ackermann, R. and Haase, G.: Multiple sclerosis-associated agent: transmission to animals and some properties of the agent. Infection and Immunity 12: 1355-1366 (1975).
Kurland, L.T.: The epidemiological characteristics of multiple sclerosis; in Vinken and Bruyn (Eds) Multiple Sclerosis and Other Demyelinating Diseases pp.63-84 (North Holland, Amsterdam (1970).
Kurtzke, J.F.: Multiple sclerosis from an epidemiological viewpoint; in Field (Ed) Multiple Sclerosis. A Critical Conspectus, pp.83-142 (M.T.P. Press, England 1977).
Kurtzke, J.F. and Hyllested, K.: Multiple sclerosis in the Faroe Islands. 1. Clinical and epidemiological features. Annals of Neurology 5: 6-21 (1979).
Layton, W. and Sutherland, J.M.: Geochemistry and multiple sclerosis: A hypothesis. Medical Journal of Australia 1: 73-77 (1975).
McAlpine, D.: Historical note in McAlpine, Compston and Lumsden. Multiple Sclerosis, pp.1-6 (E. and S. Livingstone, Edinburgh and London 1955).
McAlpine, D.: The benign form of multiple sclerosis. A study based on the 241 cases seen within 3 years of onset and followed up until the 10th year or more of the disease. Brain 84: 186-203 (1961).
McCall, M.G.; Brereton, T. Le G.; Dawson, A.; Millingen, K.; Sutherland, J.M. and Acheson, E.D.: Frequency of multiple sclerosis in three Australian cities – Perth, Newcastle and Hobart. Journal of Neurology, Neurosurgery and Psychiatry 31: 1-9 (1968).
Mathews, J.D.: A transmission model for kuru. Proceedings of the Australian Association of Neurologists 5: 325-329 (1968).
Millard, P.R. and Mitchinson, M.J.: Swayback and multiple sclerosis. Lancet 2: 1147 (1967).
Morley, J.B.: Consumption of sheep's brain by patients with disseminated sclerosis. Lancet 1: 1065 (1971).
Parry, H.B.: Elimination of natural scrapie in sheep by sire genotype selection. Nature 277: 127-129 (1979).
Pathak, S. and Webb, H.E.: Paramyxovirus-like inclusions in brain of patient with severe multiple sclerosis. Lancet 2: 311 (1976).
Poskanzer, D.C.; Schapira, K. and Miller, H.: Multiple sclerosis and poliomyelitis. Lancet 2: 917-921 (1963).
Poskanzer, D.C.; Walker, A.M.; Yonkondy, J. and Sheridan, J.L.: Studies in the epidemiology of multiple sclerosis in the Orkney and Shetland Islands. Neurology 26: 14-17 (1976).

Poskanzer, D.C.; Prenney, L.B.; Sheridan, J.L. and Yonkondy, J.: Multiple sclerosis in the Orkney and Shetland Islands. 1. Epidemiology Clinical factors and methodology. Journal of Epidemiology and Community Health 34: 229-239 (1980a).

Poskanzer, D.C.; Sheridan, J.F.; Prenney, L.B. and Walker, A.M.: Multiple sclerosis in the Orkney and Shetland Islands. II. The search for an endogenous aetiology. Journal of Epidemiology and Community Health 34: 240-252 (1980b).

Poskanzer, D.C.; Terasaki, P.I.; Prenney, L.B.; Sheridan, J.L. and Park, M.S.: Multiple sclerosis in the Orkney and Shetland Islands. III. Histocompatibility determinants. Journal of Epidemiology and Community Health 34: 253-257 (1980c).

Poskanzer, D.C.; Sever, J.L.; Sheridan, J.L. and Prenney, L.B.: Multiple sclerosis in the Orkney and Shetland Islands. IV. Viral antibody titres and viral infections. Journal of Epidemiology and Community Health 34: 258-264 (1980d).

Poskanzer, D.C.; Sever, J.L.; Terasaki, P.I.; Prenney, L.B.; Sheridan, J.L. and Park, M.S.: Multiple sclerosis in the Orkney and Shetland Islands. V. The effect on viral titres of histocompatibility determinants. Journal of Epidemiology and Community Health 34: 265-270 (1980e).

Poskanzer, D.C.; Walker, A.M.; Prenney, L.B. and Sheridan, J.L.: The etiology of multiple sclerosis: temporal-spatial clustering indicating two environmental exposures before onset. Neurology 31: 708-713 (1981).

Prasad, I.; Pertschuk, L.P.; Broome, J.D.; Gupta, J. and Cook, A.W.: Recovery of paramyxovirus from the jejunum of patients with multiple sclerosis. Lancet 1: 1117-1119 (1977).

Prineas, J.: Paramyxovirus-like particles associated with acute demyelination in chronic relapsing multiple sclerosis. Science 178: 760-763 (1972).

Roberts, D.F.; Roberts, M.J. and Poskanzer, D.C.: Genetic analysis of multiple sclerosis in Orkney. Journal of Epidemiology and Community Health 33: 229-233 (1979a).

Roberts, D.F.; Papiha, S.S. and Poskanzer, D.C.: Polymorphism and multiple sclerosis in Orkney. Journal of Epidemiology and Community Health 33: 236-242 (1979b).

Smith, H.V.; Espir, M.L.E.; Whitty, C.W.M. and Russell, W.R.: Abnormal immunological reactions in disseminated sclerosis. A preliminary report. Journal of Neurology, Neurosurgery and Psychiatry 20: 1-10 (1957).

Smith, H.V.; Hughes, I.E. and Hunter, G.: Intrathecal tuberculin in disseminated sclerosis: the immunological aspects. Journal of Neurology, Neurosurgery and Psychiatry 24: 101-117 (1961).

Sutherland, J.M.: A clinical and experimental investigation into various aspects of disseminated sclerosis. MD Thesis, University of Glasgow pp.25-26 (1950).

Sutherland, J.M. and Wilson, D.R.: Disseminated sclerosis in man and experimentation with sheep. Glasgow Medical Journal 32: 302-310 (1951).

Sutherland, J.M.: Observations on the prevalence of multiple sclerosis in northern Scotland. Brain 79: 635-654 (1956).

Sutherland, J.M.; Tyrer, J.H.; Eadie, M.J.; Casey, J.H. and Kurland, L.T.: The prevalence of multiple sclerosis in Queensland, Australia. A field survey. Acta Neurologica Scandinavica 42 (Suppl. 19): 57-67 (1966).

Symonds, C.P.: Multiple sclerosis and the swayback story. Lancet 1: 155-156 (1975).

Taylor, R.; Illsley, R. and Poskanzer, D.C.: Multiple sclerosis in the Orkney and Shetland Islands. VI. The effects of migration and social structure. Journal of Epidemiology and Community Health 34: 271-276 (1980).

Wisniewski, H.M.: Immunopathology of demyelination in autoimmune diseases and virus infections. British Medical Bulletin 33: 54-59 (1977).

Measles Encephalitis

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Despite the development of an effective vaccine, measles virus infections still account for 1.5 million childhood deaths annually worldwide. The majority of these deaths results from pneumonia and diarrhoeal disease in which secbacterial and other viral infections play an important role. These complications have been attributed to the immunosuppressive effect of measles virus infections as documented by depressed responses of patients' lymphocytes to mitogens for as long as 4 weeks after clinical measles. The second major complication and the major cause of long term morbidity following measles is measles encephalitis. The encephalitis has an acute onset, usually days after the rash, and the pathology of a perivenular inflammatory demyelination resembles experimental allergic encephalomyelitis (Johnson, 1982). Both the acute delayed onset and the pathological changes suggest that this may be an autoimmune disease. Thus we are faced with a paradox in which the serious complications of measles, on the one hand, appear to be due to immunosuppression and, on the other, to allergy.

Virological and Immunological Studies

A collaborative study of measles virus infections was carried out in Lima. Lima has sufficient population increases to support annual epidemics and, despite the latitude of only 13°S, abrupt seasonal changes cause epidemics between January and March. In addition, unlike serious measles epidemics in many developing countries, all ages are involved since the population increases not only as a result of the high birth rate but also because of migration from isolated mountain areas to the city. Therefore, measles is seen in many patients over the age of 2, in whom encephalitis is more frequent.

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Subjects

During 1980 and 1981 106 patients with measles were studied, as well as 45 patients with other infectious or neurological diseases. Of the 106 with measles, 15 patients, ranging from 12 months to 13 years of age, had encephalitis. The median age of the encephalitis patients was 4 years, fully 2 years older than that of the subgroup with pneumonia. Encephalitis usually began abruptly, as the rash was fading, with a sudden increase in temperature and decrease in the level of consciousness. In 13 patients encephalitis occurred within the first week after the rash, but in 1 patient it developed before the rash and in 1 patient it occurred 3 weeks after. Of the patients with encephalitis 9 had seizures, 5 had hemiparesis, 5 had signs of paraparesis, 4 had cerebellar ataxia (although this was the primary symptom in only 1 patient), and 1 patient had severe choreoathetosis. Four patients became comatose and 2 had prolonged periods of coma, 1 with decerebrate and 1 with decorticate posturing.

Sequelae

All survived but the majority had sequelae. Of 6 patients examined 1 to 2 years after their disease, only one was normal. Others had deficits that ranged from minor asymptomatic neurological signs or behavioral abnormalities with normal neurological examination, to very severe sequelae, e.g. 1 patient with severe mental retardation without focal neurological signs, and 1 patient who had had decerebrate posturing and who was left with severe persistent cerebellar ataxia and choreoathetosis despite total recovery of mental faculties.

CSF Findings

CSF was examined in 14 of the 15 patients. In 8 specimens the protein content exceeded 45 mg/dl, ranging as high as 230 mg/dl. A lymphocytic pleocytosis was found in 10 of 14 patients, with over 300 cells/mm^3 in 2 patients. As reported in other studies some CSF samples had a normal protein content with pleocytosis (Ojala, 1947). Eleven CSF specimens from 8 patients were tested by immunoassay for myelin basic protein (Cohen et al., 1976). Eight of 11 were positive in 5 of 8 patients. In 3 patients with sequential CSF examinations, levels of myelin basic protein were higher earlier in disease. Nine CSF specimens tested for immune complexes showed only 1 with a mildly positive reaction.

Lymphocyte Response

Lymphocyte cultures were established using standard methods followed by stimulation with phytohaemagglutinin and pokeweed mitogens as well as measles virus and myelin basic protein antigens (Hirsh et al., 1981). Measurement of tritiated thymidine-uptake by cells was used to measure responsiveness. Profound depression of responsiveness to both phytohaemagglutinin and pokeweed mitogens was confirmed. In addition the degree of suppression was not different

in those with complicated measles (pneumonia and encephalitis) from those with uncomplicated measles. The response to antigens, however, was surprising. Patients with uncomplicated measles and measles encephalitis showed brisk lymphoproliferative responses to measles virus antigens, suggesting a possible abnormality in immune regulation rather than universal immunosuppression. Responses to myelin basic protein were seen in 6 of 13 patients with encephalitis, in 3 of 24 with pneumonia, and in 3 of 13 with uncomplicated measles. Similar responses were also seen in a patient with myeloradiculitis following rabies virus vaccine, and patients with postvaricella and postrubella encephalomyelitis. Lymphocytes responded in 3 of 14 children with other neurological diseases and not at all in 4 normal children. Responses to myelin basic protein simulate lymphocyte responses in experimental allergic encephalomyelitis. By contrast, in multiple sclerosis lymphocytes the responses to myelin basic protein usually are not found.

Virus Isolation and Antibody Activity

With several notable exceptions, in most studies it has not been possible to recover measles virus from the central nervous system (ter Meulen et al., 1972; Purdham and Batty, 1974). Our preliminary studies using immunoperoxidase staining of one fatal case of encephalomyelitis failed to show measles virus antigen in the brain. Using an enzyme-linked immunosorbent assay, measles virus antibody was compared in serum and CSF pairs from 13 serum and CSF samples obtained from patients with measles encephalitis. After diluting the serum and CSF to contain 1μg of gammaglobulin/ml, comparisons of optical densities showed no evidence of increased antimeasles antibody in CSF in any of the patients with measles encephalitis.

The usual failure to isolate virus, the lack of evidence of antigen in the nervous system and, most important, the lack of evidence of antigenic stimulation within the central nervous system all argue against the direct invasion of the nervous system by measles virus during measles encephalitis.

Summary

In measles encephalitis we:
1. Confirmed the decrease in mitogen responses and have shown that it does not correlate with complications.
2. Demonstrated that the 'immunosuppression' is not universal but may be an abnormality of immune regulation as shown by the response to measles virus and myelin basic protein and by an abnormality of suppressor cell activity in patients with measles.
3. Have evidence that there is early demyelination, and a response to myelin basic protein in a large proportion of the patients, and a lack of evidence of direct virus invasion of the brain.

These findings lead to our present hypothesis that measles virus infection,

probably of lymphoid cells, leads to a breakdown of immune regulation. This lack of regulation may lead to dissemination and allow secondary infection. It may also lead to a break in tolerance leading to autoimmune demyelination, a regulation which as Patterson (1979) has said 'may effectively restrain our ever present capacity to react immunologically against our own nervous tissue'.

Acknowledgement

I wish to express my gratitude to the Australian Association of Neurologists and Roche-ICI for giving me the opportunity to participate in this meeting.

References

Cohen, S.R.; Herndon, R.M. and McKhann, G.M.: Radioimmunoassay of myelin basic protein in spinal fluid. New England Journal of Medicine 295: 1455-1457 (1976).

Hirsch, R.L.; Mokhtarian, F.; Griffin, D.E.; Brooks, B.R.; Hess, J. and Johnson, R.T.: Measles virus vaccination of measles seropositive individuals suppresses lymphocyte proliferation and chemotactic factor production. Clinical Immunology and Immunopathology 21: 341-350 (1981).

Johnson, R.T.: Viral Infections of the Nervous System. (Raven Press, New York 1982).

ter Meulen, V.; Muller, D.; Kackell, Y.; Katz, M. and Meyermann, R.: Isolation of infectious measles virus in measles encephalitis. The Lancet, 2: 1172-1175 (1972).

Ojala, A.: On changes in the cerebrospinal fluid during measles. Annales Medicinae Internae Fenniae, 36: 321-331 (1947).

Paterson, P.Y.: Neuroimmunologic diseases of animals and humans. Reviews of Infectious Disease 1: 468-482 (1979).

Purdham, D.R. and Batty, P.F.: A case of acute measles meningoencephalitis with virus isolation. Journal of Clinical Pathology 27: 994-996 (1974).

Experimental Demyelinating Optic Neuropathy: A Model for Combined Morphological and Electrophysiological Studies

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There have been few detailed combined histological and electrophysiological studies of experimental optic nerve disease (Clifford-Jones, et al., 1980; Loewenstein and Lessell, 1980) and none in which selective demyelination has been studied. While the morphological changes in a number of different optic nerve lesions have been reported, ranging from cyanide (Lessell and Kuwabara, 1974) and ethambutol intoxication (Lessell, 1976) to optic nerve section and the effects of retinal photocoagulation (Anderson, 1973), only with the cryosurgical optic nerve lesion (Loewenstein and Lessell, 1980) and the intraorbital compressive optic neuropathy (Clifford-Jones et al., 1980) has electrophysiological monitoring been attempted. Primary demyelination of the cat optic nerve (Cook, 1978) and the diphtheria toxin lesion of the cat chiasm (Eames et al., 1977) have been studied in some detail histologically, but electrophysiological studies were not performed although the recovery of spatial vision, tested behaviourally, was reported by Jacobson et al. (1979) in the cat diphtheria toxin model.

In contrast, there have been a number of sophisticated studies of the morphological and electrophysiological changes following the microinjection of lysophosphatidyl choline (LPC), diphtheria toxin and immune sera into peripheral nerves (Hall, 1967; Morgan-Hughes, 1968; Saida et al., 1980) and dorsal columns (McDonald and Sears, 1970; Smith and Hall, 1980). Interestingly, partial or complete reversal of the abnormalities of conduction was observed in the LPC and myelin antisera-induced lesions consequent upon remyelination. The discrepancy between these findings in the experimental models and the persistence of impaired conduction in the human visual pathway, as shown by visual evoked

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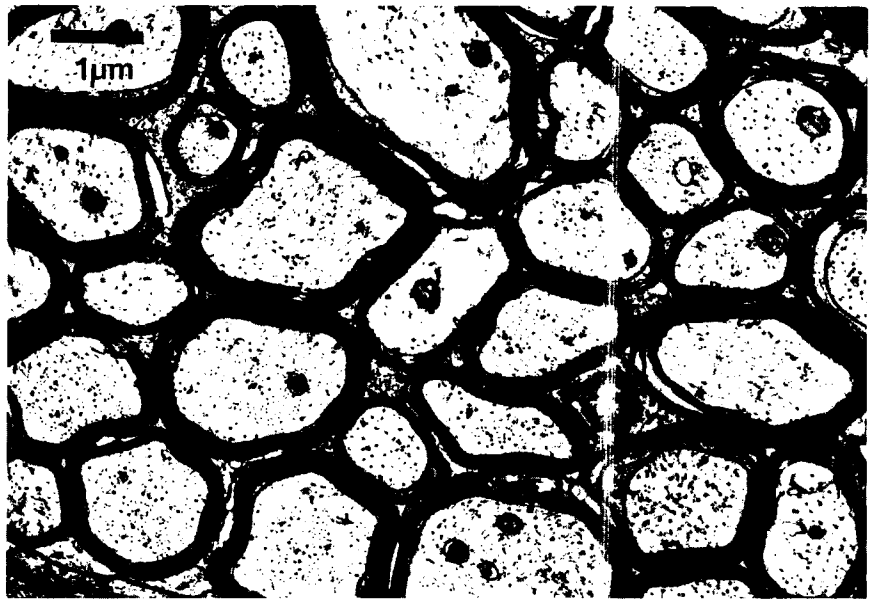


Fig. 1. High power electronmicrograph of normal rat optic nerve.

potential (VEP) recordings, in patients who have recovered from demyelinative optic neuropathy, is a fundamental and unresolved question. Similarly, it remains to be determined why VEP latencies return to normal in only a minority of patients with isolated optic neuritis or with multiple sclerosis and visual pathway involvement. In an attempt to throw light upon these questions, and to investigate the pathophysiological processes occurring in demyelinative optic neuropathy, we have developed an experimental model in the rat.

Methods

Male albino Wistar rats were used exclusively to minimise any possible effect of the oestrous cycle on the VEP (Dyer et al., 1978) and entered the study at about 12 weeks of age (330 to 350g) when maturational changes in the optic nerve fibre diameter spectrum are complete (fig. 1; Matheson, 1970).

Visual Evoked Potentials

Monocular flash VEPs were recorded from implanted cranial epidural electrodes using a modification of the technique described by Adams and Forrester (1968) and Creel et al. (1970). Recordings were made 20 minutes after light sedation with intraperitoneal droperidol. One hundred and twenty eight flashes

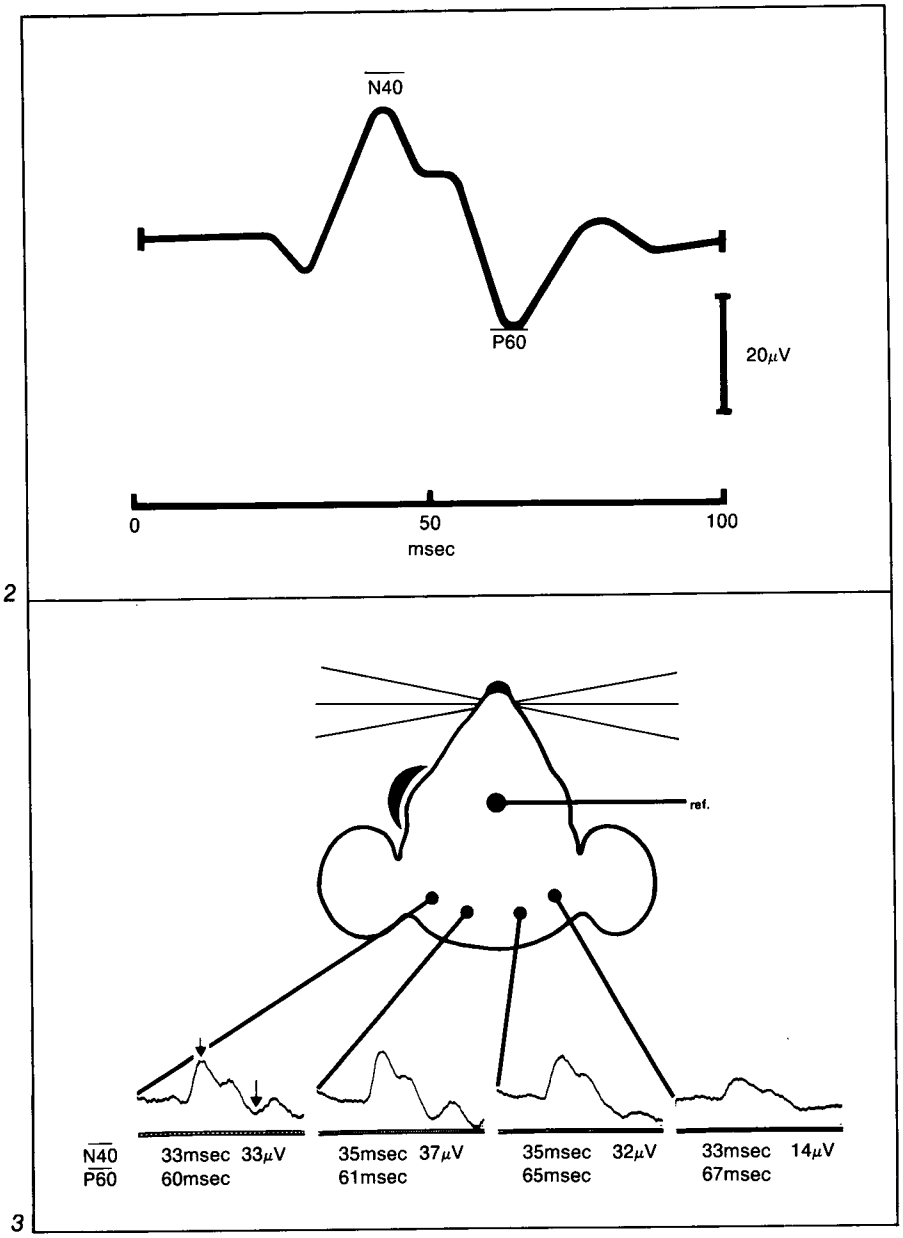


Fig. 2. Schematic drawing of a typical rat transient luminance VEP recorded to monocular flash stimulation showing the N40 and P60 components. Positive is downgoing.

Fig. 3. Topography of the rat flash VEP after right monocular stimulation showing the contralateral (left sided) distribution.

Table I. Means and standard deviations of the $\overline{N40}$ and $\overline{P60}$ component latencies from each eye of 15 male Wistar rats and the interocular latency difference (ILD) for each component.

	$\overline{N40}$	$\overline{P60}$
Right eye	36.4 ± 4.0	58.2 ± 5.2
Left eye	35.7 ± 3.7	58.2 ± 5.1
ILD	0.4 ± 2.1	0.7 ± 2.0
ILD Upper limit ($\bar{x}$ + 2.5 SD[1])	5.7	5.6

1 SD = Standard deviation.

were delivered to the interior of a recording chamber lined with reflective material using a Beckman flash unit. An average of 100 msec of poststimulus EEG was obtained after differential amplification with a band pass of 1.6Hz to 1.6 kHz. A typical VEP is shown schematically in figure 2. Because the rodent visual pathway is largely crossed, and because the amount of crossing is greater in albinos (fig. 3) VEPs were recorded from the hemisphere contralateral to the stimulated eye.

During each testing session 2 consecutive recordings were made for each eye to check reproducibility, and this procedure was then repeated at least twice for each eye. Interocular comparisons could then be made and mean interocular latency differences (ILD) were calculated for each animal. Two prelesion recordings were made approximately 1 week apart thus providing an index of the inter-recording ILD (IRILD) for each component of the VEP. VEPs were then recorded serially after the production of the optic nerve lesion until the termination of the experiment.

Optic Nerve Lesions

Under halothane and nitrous oxide anaesthesia the intraorbital portion of the right optic nerve was exposed and 5 to 10μl of 0.1% LPC, Gal-C antiserum, control non-immune serum or normal saline was introduced by slow pressure micro-injection.

Morphological Studies

Animals were sacrificed at varying intervals up to 4 weeks postlesion. Under thiopentone sodium anaesthesia intracardiac perfusion with glutaraldehyde and paraformaldehyde was carried out and the eyes, optic nerves and chiasm were postfixed in sodium tetroxide and embedded in araldite. One-micron sections for light microscopy were stained with toluidine blue and thin sections for electron microscopy were stained with lead citrate and examined with a Philips 300 electron microscope.

Table II. Means and standard deviations (in msec) for $\overline{N40}$ and $\overline{P60}$ component interrecording (IR) interocular latency differences from 7 Wistar rats. The mean IR interval was 8.7 days (range 3-17 days).

	$\overline{N40}$	$\overline{P60}$
Mean	1.5	1.3
SD[1]	1.0	1.0
Range	0.4-3.5	0-2.5
Upper limit	4.0	3.8

1 SD = Standard deviation.

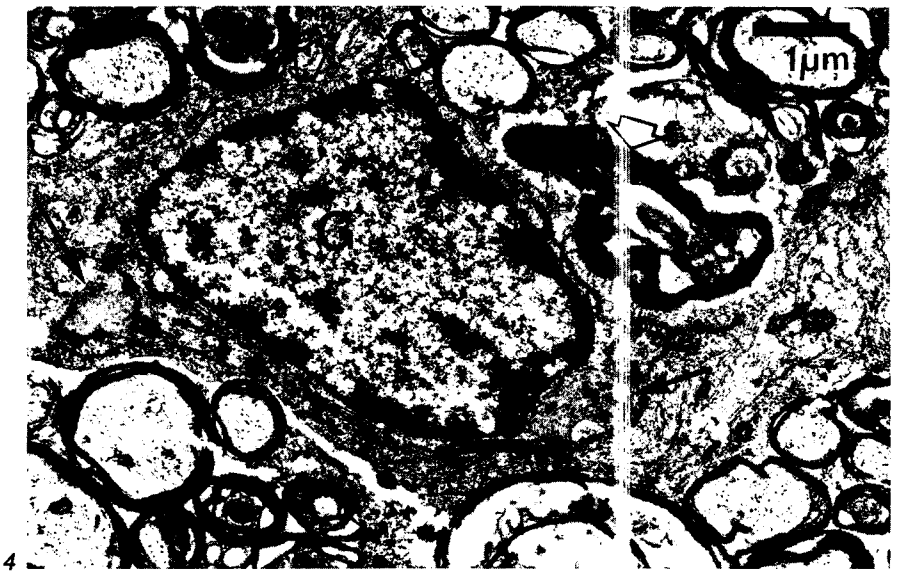
Results

VEPs – Normative Studies

Because of the known variability in the waveform and in the latency of the flash VEP, the main response parameter used for analysis was the ILD for the $\overline{N40}$ and $\overline{P60}$ components. Table I shows the means and standard deviations for the latencies of the $\overline{N40}$ and $\overline{P60}$ components in 15 male Wistar rats and the ILD for these components. The calculated upper limits of normal (mean + 2.5 standard deviations) for the ILD were 5.6 msec for $\overline{N40}$ and 5.7 msec for $\overline{P60}$. The 2 prelesion recordings made from 7 of the 15 animals studied provided an index of the IRILD for each component; the upper limits for the IRILD over a mean interval of 8.7 days (range 3 to 17 days) were 4.0 msec for $\overline{N40}$ and 3.8 msec for $\overline{P60}$ (table II).

Optic Nerve Lesions

The injection of normal saline or non-immune sera led to scattered isolated nerve fibre degeneration in the optic nerve. With LPC an extensive lesion was produced in which axonal swelling and degeneration were most prominent but with some areas of primary demyelination. Evidence of remyelination was seen at later stages but this was less complete than in lesions induced by Gal-C antisera. Figure 4 illustrates the effect of 10μl of 0.1% LPC injected 15 days earlier. With Gal-C antiserum a lesion of variable severity and extent developed but usually involving 30 to 35% of the cross-sectional area of the nerve. The areas of demyelination were mainly confined to the immediate injection site, and generally to the peripheral portions of the optic nerve. Evidence of myelin breakdown with sparing of axons, and phagocytic activity was found at 5 days, and at this time fibres lacking a myelin sheath as well as thinly myelinated fibres were seen. In some nerves these changes were scattered through the lesion. Sections taken between 14 and 24 days showed more striking changes (fig. 5) comprising well demarcated areas of demyelination involving fibres of all diameters. Only a few randomly distributed swollen fibres undergoing axonal degeneration were evident. Astrocytic proliferation was seen maximally during this period. At 3 weeks evidence of remyelination by oligodendroglia was found (fig. 5).



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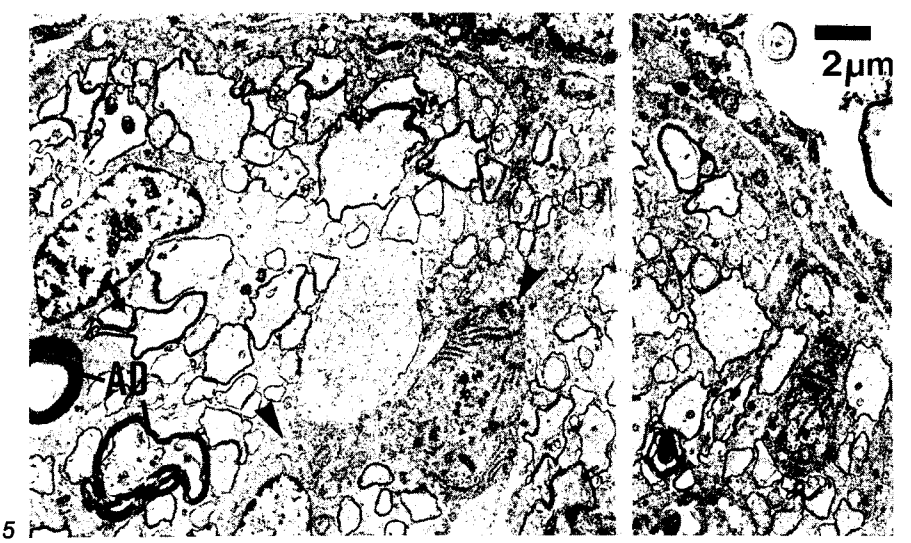

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Fig. 4. Electronmicrograph of rat optic nerve 15 days after the micro-injection of 10μl of 0.1% lysophosphatidyl choline. A number of fibres undergoing axonal degeneration and myelin breakdown are seen (open arrows). Myelin breakdown products (solid arrows) are present in a glial cell (G).

Fig. 5. Low power electronmicrograph of rat optic nerve 20 days after the micro-injection of galactocerebroside antiserum. The majority of fibres have very thin myelin sheaths while some are completely demyelinated. Occasional fibres undergoing axonal degeneration (AD) and reactive oligodendroglial cells (arrowheads) are also seen.

Correlative Studies

Figure 5 shows the demyelinated region of rat optic nerve 20 days after injection of Gal-C antiserum. In this lesion approximately 30% of the transverse area of the optic nerve was demyelinated and evidence of remyelination was also found. Figure 6 shows a prelesion and 3 postlesion VEP recordings obtained from this animal, and figure 7 summarises the ILD for the $\overline{N40}$ and $\overline{P60}$ components in relation to the ILD limits (central shaded area) during the study period. The prelesion waveforms and ILDs were normal. At R_1, 2 hours post-injection of 6μl of Gal-C antiserum into the right optic nerve, the right eye $\overline{N40}$ component was attenuated, though of normal latency (see fig. 6). Seven days later at R_2 the right eye VEP had changed considerably so that ILDs could not be calculated. Instead of the usual biphasic potential a single positivity with a peak latency of 48 msec was recorded and the overall amplitude remained attenuated. The left eye VEPs did not alter appreciably. After a further 6 days the basic waveform of the right eye response had returned but the $\overline{N40}$ latency was prolonged (fig. 7) and the positivity at 48 msec persisted between the $\overline{N40}$ and $\overline{P60}$ components.

Discussion

The present study has described a sensitive technique for producing a predominantly demyelinative lesion and for monitoring optic nerve function in the rat. The electrophysiological and morphological changes in Gal-C antiserum-induced demyelination of the rat sciatic nerve have been well documented (Saida et al., 1980). Using Gal-C antiserum we have reproduced the peripheral nerve lesion and the consequent reversible conduction block and have shown demyelination of central nerve fibres.

The optic nerve lesion induced by Gal-C antiserum bears a close resemblance to that reported by Williams et al. (1980) following the injection of canine central nervous system myelin antisera into the posterior columns of guinea pigs. Although the study by these workers was terminated 10 days postlesion, they observed the commencement of remyelination at 7 to 10 days. With Gal-C antiserum, optic nerve remyelination begins at about the same time and by 24 days appears to be more complete than that which follows the injection of LPC. Thus Gal-C antiserum is myelinotoxic for central as well as peripheral nerve fibres and appears not to be fibre-diameter selective. How these experimental demyelinative lesions of both central and peripheral nerves, produced by the direct exposure to Gal-C antiserum, relate to their human counterparts is uncertain. Nevertheless, the efficacy of plasmapheresis in improving the rate of recovery in some patients with inflammatory demyelinating polyneuropathy and rabbits with experimental allergic neuritis (Antony et al., 1981), the demyelination of the sciatic nerves of experimental animals when patient sera is injected subperineurally (Saida et al., 1982) and the finding of antineural antibodies in such sera (Dalakas and Engel, 1980) provides evidence for humoral mechanisms in these

diseases. As such, Gal-C antiserum-mediated demyelination is likely to be a more accurate model with which to study demyelinative lesions than LPC or diphtheria toxin.

Conduction in the rat visual pathway has been studied intensively since the 1960s. Techniques have included direct stimulation and recording (Kimura, 1962;

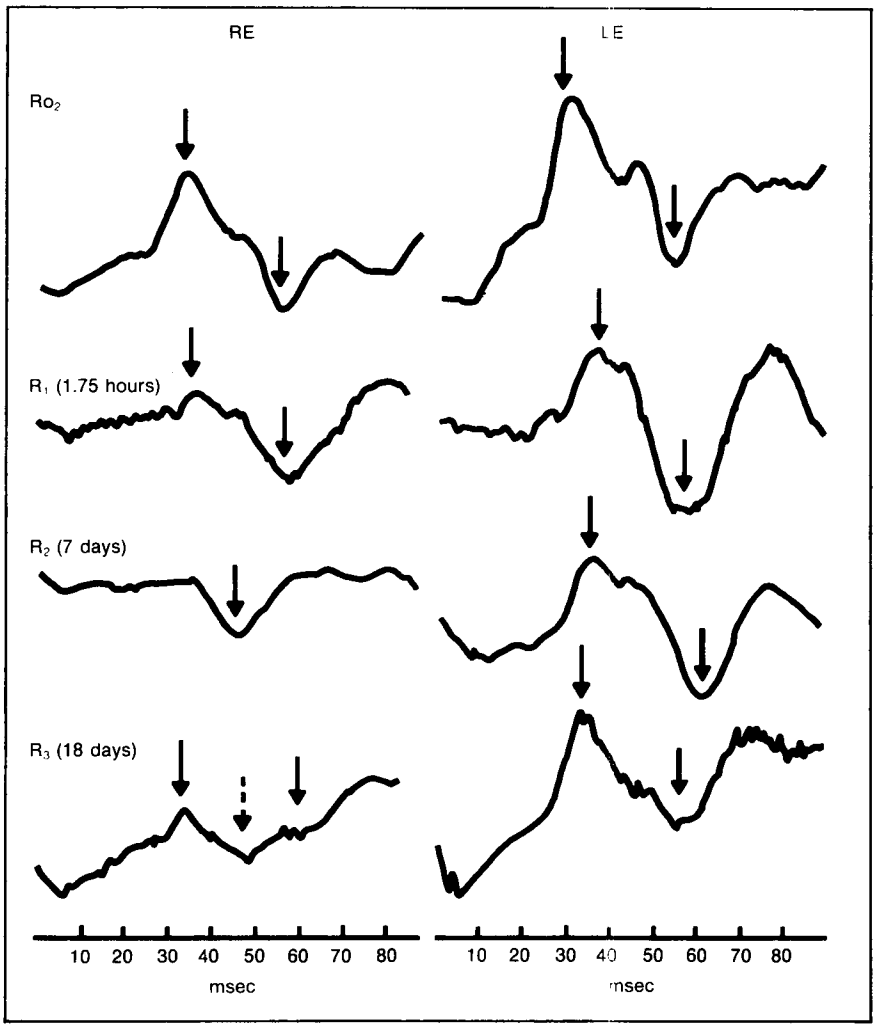

Fig. 6. Serial monocular VEP recordings from animal No. 13 (fig. 5). Ro_2 is the second prelesion recording and R_1 to R_3 are the 3 postlesion records. $\overline{N40}$ and $\overline{P60}$ components are marked with arrows as in figure 1. Note the change in the waveform of the response from the right eye at R_2 and the return of the prelesion waveform for this eye at R_3. Waveform and latencies from the left eye are essentially unaltered.

Sefton and Swinburn, 1964; Sefton and Burke, 1965; Arikuni and Iwama, 1967; Noda and Iwama, 1967; Sumitomo et al., 1969) and the more functional recording of cortical VEPs (Ginés et al., 1963; Adams and Forrester, 1968; Creel et al., 1970; Dyer et al., 1978). From the studies of Sefton and coworkers (Sefton and Swinburn, 1964; Sefton and Burke, 1965; Burke and Sefton, 1966, a.b.c.; Sefton, 1968; 1969; Sumitomo et al., 1969), at least 3 different classes of fibres have been identified based on the conduction velocities and latencies to various stations in the visual pathway. These studies have shown mean conduction velocities of approximately 5, 11 and 19 $msec^{-1}$. Kimura (1962), recording from epidural and intracortical electrodes, determined the first cortical response to be a positive deflection at 22 to 25 msec. The earliest component of the VEP recorded from epidural electrodes overlying the contralateral visual cortex in the present study was a positive deflection with a latency of approximately 20 to 30 msec. However, because these early components were variable, the later more stable $\overline{N40}$ and $\overline{P60}$ components were analysed to facilitate serial studies. VEP latencies and waveforms of the present study are comparable with the published data (Adams and Forrester, 1968; Creel et al., 1970) although the $\overline{N40}$ and $\overline{P60}$ component ILDs should provide a more sensitive index for the detection of

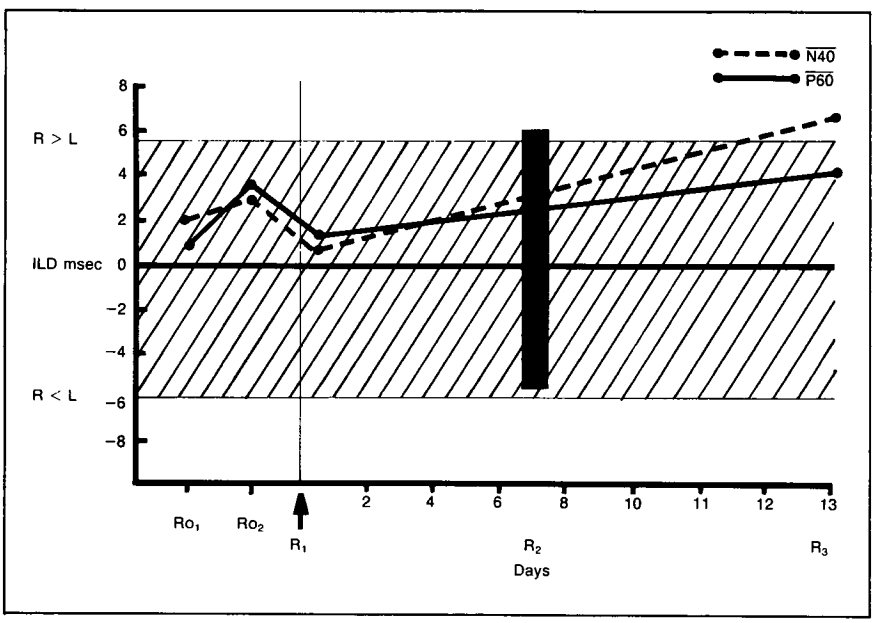

Fig. 7. Summary of the ILD changes for the $\overline{N40}$ and $\overline{P60}$ components for both pre and postlesion recordings of animal No. 13. The central lined region of the graph defines the ILD limits, the vertical bar at day 7 indicates that the waveform changes at R_2 (fig. 6) precluded the determination of the ILD and the arrow indicates the time of the optic nerve lesion. Note the progressive rise in the latencies for both the $\overline{N40}$ and $\overline{P60}$ components from the right eye.

disturbed conduction and the IRILD assists in quantifying the serial latency variations.

From our experience to date with this VEP technique, the results are encouraging. Saline injected into the optic nerve showed only a few fibres undergoing axonal degeneration 30 days after the injection and the $\overline{N40}$ and $\overline{P60}$ ILDs have remained within the normal range. The VEP changes accompanying at the Gal-C antiserum lesion (fig. 6) were more notable. Approximately one-third of the cross-sectional area of the optic nerve was demyelinated (fig. 5), and the VEPs showed a marked change in waveform (see R_2, fig. 6) and a latency increase (fig. 7) – features reminiscent of those seen in human demyelinating optic neuropathy (Halliday, 1981; Carroll et al., 1982).

Studies of the relationship between the extent of the demyelinative lesion and its repair and the VEP waveform and latency changes are continuing. For the present the model promises to distinguish specific from nonspecific optic nerve lesions and to permit a critical analysis of serial observations. Finally, the predominantly demyelinating optic neuropathy produced by Gal-C antiserum provides a further, possibly more accurate, model of human demyelinating optic neuropathy.

Summary

A model is described for the morphological and electrophysiological study of demyelinative optic neuropathy in the rat. Cortical visual evoked potentials (VEPs) to flash stimuli were recorded before and after the intraneural microinjection of lysophosphatidyl choline (LPC) and galacto-cerebroside (Gal-C) antiserum. Progress was monitored by calculating the interocular latency differences (ILD) for the $\overline{N40}$ and $\overline{P60}$ components of the rat VEP, thus allowing a longitudinal evaluation of optic nerve function. Histological examination of the visual pathway using light and electron microscopy was performed at intervals through the course of the study. LPC produced a less selective lesion than did Gal-C antiserum. In lesions induced by the latter there was relatively little accompanying anoxal degeneration and subsequent remyelination was prominent. Control serum did not result in demyelination. This model should permit accurate electrophysiological and morphological correlations to be made during the developing and the reparative phases of demyelinative optic neuropathy and the assessment of potential therapeutic manoeuvres.

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References

Adams, A.D. and Forrester, J.M.: The projection of the rats' visual field on cerebral cortex. Quarterly Journal of Experimental Physiology 53: 327-336 (1968).

Anderson, D.R.: Ascending and descending optic atrophy produced experimentally in squirrel monkeys. American Journal of Ophthalmology 76: 693-711 (1973).

Antony, J.H.; Pollard, J.D. and McLeod, J.G.: Plasmapheresis of rabbits with experimental allergic neuritis. Clinical and Experimental Neurology 18: 198-199 (1981).

Arikuni, T. and Iwama, K.: Functional changes in optic tract fibres and lateral geniculate neurons following chronic ablation of visual cortex in rats. Medical Journal of Osaka University 17: 223-236 (1967).

Burke, W. and Sefton, A.: Discharge patterns of principal cells and interneurons in lateral geniculate nucleus of rat. Journal of Physiology (London) 187: 201-212 (1966a).

Burke, W. and Sefton, A.: Recovery of responsiveness of cells of lateral geniculate nucleus of rat. Journal of Physiology (London) 187: 213-229 (1966b).

Burke, W. and Sefton, A.: Inhibitory Mechanism in lateral geniculate nucleus of rat. Journal of Physiology (London) 187: 213-246 (1966c).

Carroll, W.M.; Halliday, A.M. and Kriss, A.: Improvements in the accuracy of pattern visual evoked potentials in the diagnosis of visual pathway disease. Neuro-ophthalmology 2: 237-253 (1982).

Clifford-Jones, R.E.; Landon, D.N. and McDonald, W.I.: Remyelination during optic nerve compression. Journal of the Neurological Sciences 46: 239-243 (1980).

Cook, R.D.: Primary demyelination in cat optic nerves associated with surgically induced axonal degeneration. Neurological Pathology and Applied Neurobiology 4: 357-368 (1978).

Creel, D.J.; Dustman, R.E. and Beck, E.C.: Differences in visually evoked responses in albino versus hooded rats. Experimental Neurology 29: 298-309 (1970).

Dalakas, M.C. and Engel, W.K.: Immunoglobulin and complement deposits in nerves of patients with chronic relapsing polyneuropathy. Archives of Neurology 37: 637-640 (1980).

Dyer, R.S.; Eccles, C.U. and Annau, Z.: Sex and strain differences in the visual evoked potentials of albino and hooded rats. Journal of Pharmacology, Biochemistry and Behaviour 9: 301-306 (1978).

Eames, R.A.; Jacobson, S.G. and McDonald, W.I.: Pathological changes in the optic chiasm of the cat following local injection of diphtheria toxin. Journal of the Neurological Sciences 32: 381-393 (1977).

Ginés, A.; Bove, I.C.; Macadar, O.; Roig, J.A. and Garćia-Austt, E.: Influence of curarization and anaesthetics upon the visual evoked response in the rat. Journal Acta Neurologica Latinoamerica 9: 204-212 (1963).

Hall, J.I.: Studies on demyelinated peripheral nerves in guinea pigs with experimental allergic encephalomyelitis – a histological and electrophysiological study, Part 2 (Electrophysiological observations). Brain 90: 313-332 (1967).

Halliday, A.M.: New applications of visual evoked potentials in man. 10th ICECN, Kyoto, Japan. Journal of EEG and EMG (Suppl. – didactic lectures): 117-124 (1981).

Jacobson, S.G.; Eames, R.A. and McDonald, W.I.: Optic nerve fibre lesions in adult cats; pattern of recovery of spatial vision. Experimental Brain Research 36: 491-508 (1979).

Kimura, D.: Multiple response of visual cortex of the rat to photic stimulation. Electroencephalography and Clinical Neurophysiology 14: 115-122 (1962).

Lessell, S.: Histopathology of experimental ethambutol intoxication. Investigative Ophthalmology 15: 765-769 (1976).

Lessell, S. and Kuwabara, T.: Fine structure of experimental cyanide optic neuropathy. Investigative Ophthalmology 13: 748-756 (1974).

Loewenstein, J.I. and Lessell, S.: Experiental cryosurgical lesion of the optic nerve. Albrecht Von Graefes Archiv für Klinische und experimentelle Ophthalmologie 215: 97-103 (1980).

McDonald, W.I. and Sears, T.A.: The effects of experimental demyelination on conduction in the central nervous system. Brain 93: 583-598 (1970).

Matheson, D.F.: Some quantitative aspects of myelination in the optic nerve in rat. Brain Research 24: 257-269 (1970).

Morgan-Hughes, J.A.: Experimental diphtheritic neuropathy – a pathological and electrophysiological study. Journal of Neurological Sciences 7: 157-175 (1968).
Noda, J. and Iwama, K.: Unitary analysis of the retino-geniculate response time in rats. Vision Research 7: 205-213 (1967).
Saida, K.; Sumner, A.J.; Saida, T.; Brown, M.J. and Silberberg, D.H.: Antiserum-mediated demyelination; relationship between remyelination and functional recovery. Annals of Neurology 8: 12-24 (1980).
Saida, T.; Saida, K.; Lisak, R.P.; Brown, M.J.; Silberberg, D.H. and Asbury, A.K.: *In vivo* demyelinating activity of sera from patients with Guillain-Barré syndrome. Annals of Neurology 11: 69-75 (1982).
Sefton, A.J.: The innervation of the lateral geniculate nucleus and anterior colliculus in the rat. Vision Research 8: 867-881 (1968).
Sefton, A.J.: The electrical activity of the anterior colliculus in the rat. Vision Research 9: 207-222 (1969).
Sefton, A.J. and Burke, W.: Reverberatory inhibitory circuit in the lateral geniculate nucleus of the rat. Nature 205: 1325-1326 (1965).
Sefton, A.J. and Swinburn, M.: Electrical activity of the lateral geniculate nucleus and optic tract of the rat. Vision Research 4: 315-328 (1964).
Smith, K.J. and Hall, S.M.: Nerve conduction during perpheral demyelination and remyelination. Journal of Neurological Sciences 48: 201-219 (1980).
Sumitomo, I.; Ide, K.; Iwama, K. and Arikuni, T.: Conduction velocity of optic nerve fibres innervating lateral geniculate body and superior colliculus in the rat. Experimental Neurology 25: 378-392 (1969).
Williams, R.M.; Krakowa, S. and Koestner, A.: *In vivo* demyelination by antimyelin antibodies. Acta Neuropathologica (Berlin) 50: 1-8 (1980).

Immunological Studies in Myotonic Dystrophy*

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Myotonic dystrophy is a dominantly inherited disorder in which there is involvement of the skeletal muscles, heart, eye, testes, central and peripheral nervous systems, and the smooth muscle of the gastrointestinal and genitourinary tracts (Walton and Gardner-Medwin, 1974; Harper, 1979). The recent finding of abnormalities of erythrocyte membranes (Roses and Appel, 1973; Butterfield et al., 1974; Plishker et al., 1978), of monocyte (Festoff and Moore, 1979; Tevaarwerk et al., 1979) and skeletal muscle (Moxley, 1977) insulin receptors, of smooth muscle adrenergic receptors (Mechler and Mastaglia, 1981), and of neutrophil function (Seay et al., 1978, 1979), has emphasised the multisystemic nature of the disorder and has led to the concept that an intrinsic defect of cell membranes may underlie the various manifestations of the disease (Rowland, 1976).

A number of abnormalities of immune function have been recognised in myotonic dystrophy but their significance is uncertain. Reduced serum immunoglobulin levels have been well documented (Wochner et al., 1966; Bundey et al., 1970; Grove et al., 1973; Roberts and Bradley, 1977) and evidence of increased immunoglobulin catabolism has been found (Wochner et al., 1966). Humoral antibody responses to antigenic stimulation have been found to be depressed (Grove et al., 1973) suggesting defective B lymphocyte function. Delayed hypersensitivity reactions (Kuroiwa et al., 1980) and T cell responsiveness to mitogen stimulation (Grove et al., 1973) have also been found to be impaired.

We have studied B lymphocyte function in a group of 22 patients with myotonic dystrophy by measuring serum immunoglobulin fractions and by studying

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the phenomenon of lymphocyte capping with antihuman IgG. In addition, we have looked for evidence of defective immunoregulation by assessing the incidence of autoantibodies and of autoimmune disease in this group of patients.

Materials and Methods

Subjects

Twenty-two patients with myotonic dystrophy from 18 families in the Newcastle region were studied. In each case, the diagnosis of the disease was based upon typical clinical and electromyographic findings and a positive family history. Their ages ranged from 2 to 62 years (mean 32.3 years), and the mean duration of symptoms was 10.8 years. Two cases of congenital myotonic dystrophy aged 2 and 3 years were included.

None of the 22 patients had an undue predisposition to infections and, with the exception of 1 female with a history of hypothyroidism, none was known to have an autoimmune disease or to suffer from cancer. None of the patients was taking drugs at the time of the study.

Methods

Serum Immunoglobulins

IgG, IgA and IgM concentrations were measured quantitatively in 11 patients by radial immunodiffusion using H-chain specific antisera in commercial agar gel plates (Mancini et al., 1965). Results were expressed as g/L, and were compared with those in a group of 25 healthy age and sex matched controls.

Autoantibodies

In 15 patients thyroid, gastric parietal cell, reticulin, mitochondrial, smooth muscle and skeletal muscle antibodies, antinuclear factor (ANF) and rheumatoid factor were looked for in the serum (Walker et al., 1982). Native (double-stranded) DNA binding was measured by radio-immunoassay (Holian et al., 1975). Acetylcholine receptor (AChR) antibody titres were measured by using the α-bungarotoxin (α-BGT) precipitation technique (Lindstrom et al., 1976). Results were expressed as nanomoles α-BGT precipitated per litre of serum, and were considered normal if less than 3.0 nm/L.

Peripheral blood B and T cells

In 22 patients B cell numbers were counted after labelling with fluorescein-conjugated rabbit antihuman immunoglobulin (Warner, 1974) and T cell numbers by the sheep red cell rosette technique (Jondal et al., 1972). Results were expressed as percentages of the total peripheral blood lymphocyte count and were compared with those in 25 age and sex matched controls.

Table I. Serum immunoglobulins, B and T-cell proportions and lymphocyte capping results in control subjects and myotonic dystrophy patients. Mean values and standard deviations (SD) are given and significant differences between the two groups are indicated. Numbers of subjects in parentheses.

	Controls	Myotonic dystrophy
Immunoglobulins		
IgG	8.8 g/L (SD 1.5) (25)	3.7 g/L (SD 1.3)* (11)
IgM	1.2 g/L (SD 0.4) (25)	1.3 g/L (SD 1.4) (11)
IgA	1.9 g/L (SD 0.9) (25)	1.1 g/L (SD 0.7)† (11)
B-cells (%)	27.4% (SD 6.7) (25)	25.0% (SD 5.1) (22)
T-cells (%)	45.6% (SD 7.9) (25)	45.4% (SD 8.8) (22)
Lymphocyte capping		
Fully capped (%)	47.5% (SD 14.8) (13)	23.1% (SD 6.7)‡ (14)
'Intermediate' stages (%)§	51.6% (SD 14.0) (13)	74.3% (SD 4.9)‡ (14)

* = $p < 0.0001$; † = $p < 0.02$; ‡ = $p < 0.001$ (Student's t test); § = 'Patchy' or 'clustered' pattern of labelling.

B-lymphocyte capping

A previously described method using antihuman immunoglobulin to cross-link surface immunoglobulin determinants was used (Pickard et al., 1978). Ten millilitres of heparinised venous blood was collected and lymphocytes were separated by gradient centrifugation. The lymphocytes were then counted and a standard number mixed with fluorescein isothiocyanate (FITC) - labelled polyvalent antihuman immunoglobulin. The cells were then incubated at 37°C for one hour, centrifuged, and counted under fluorescent illumination. A minimum of 100 fluorescent cells were classified according to their staining patterns as being either 'uniform' (that is no tendency to capping at all), 'clustered' or 'patchy' (both being intermediate stages in the capping process), or 'fully capped' (Pickard et al., 1978). Capping was studied in 14 myotonic dystrophy cases and 13 age and sex matched controls. Cell counts were done blind on coded blood samples by an experienced technician.

Results

Immunoglobulins

Serum IgG levels were significantly reduced in the myotonic dystrophy patients when compared with controls as were serum IgA levels (table I, fig. 1).

Serum IgM levels showed a wider scatter (fig. 1) and mean levels were not significantly different in patients and controls.

Autoantibodies

With the exception of a single patient who had a low titre of ANF, none of the remaining 14 patients had autoantibodies or a significant titre of rheumatoid factor, and DNA binding was normal in all patients tested. The AChR antibody titre was <3 nm/L in all cases tested.

B and T cell numbers

There was no significant difference in B and T cell proportions in the patients and controls (table I).

Lymphocyte capping

The proportion of fully capped lymphocytes after 1 hour's incubation was significantly smaller in the myotonic dystrophy patients as a group than in the control subjects, while the proportion of labelled cells in the intermediate stages of capping (i.e. showing a 'patchy' or 'clustered' pattern of labelling as described

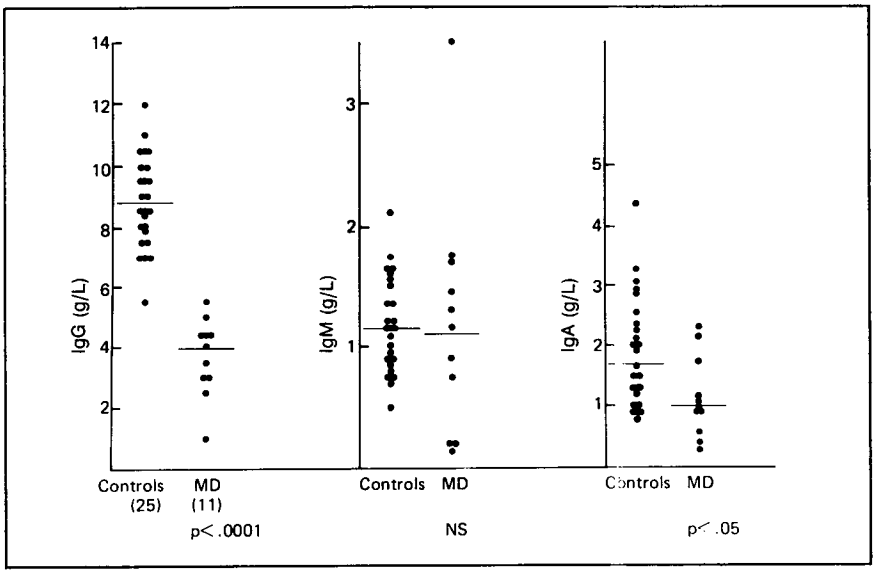

Fig. 1. Serum IgG, IgM and IgA levels in control subjects and patients with myotonic dystrophy. Each point represents a single subject and the horizontal bars indicate median values. P values were calculated using the Mann-Witney non-parametric test.

by Pickard et al., 1978) was significantly higher in the myotonic dystrophy patients (table I, fig. 2). No qualitative differences in the capping sequence were noted in the myotonic dystrophy and control groups.

Discussion

Lymphocyte capping results from the redistribution of integral membrane proteins after cross-linking with polyvalent ligands such as fluorescein-labelled immunoglobulins (Pickard et al., 1978). The mechanism of lateral movement of membrane proteins and cap formation is not well understood, but the rate at which this process occurs is thought to be a measure of membrane fluidity and of intrinsic membrane properties. Lymphocyte capping has been reported to be abnormal in the Duchenne (Verrill et al., 1977; Pickard et al., 1978; Ho et al., 1980), Becker (Goldsmith et al., 1980), limb girdle, fascioscapulohumeral and congenital forms of muscular dystrophy (Pickard et al., 1978).

The present finding of reduced numbers of fully capped cells with increased numbers of cells showing intermediate stages of capping suggests that the time course of the capping process is prolonged in myotonic dystrophy. These findings

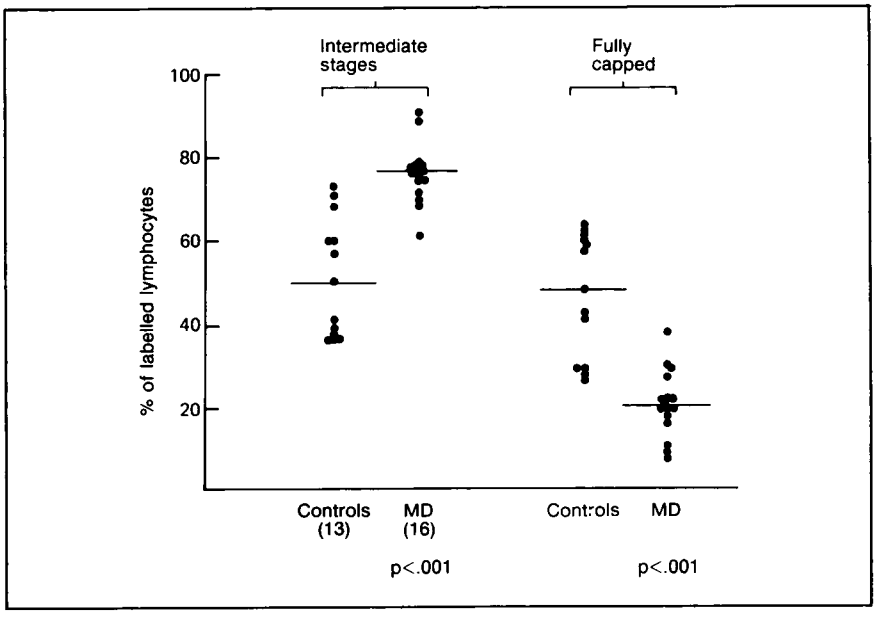

Fig. 2. Percentages of labelled lymphocytes showing different stages of capping after 1 hour incubation in control subjects and patients with myotonic dystrophy. Each point represents a single subject and the horizontal bars indicate median values. P values were calculated using the Mann-Witney non-parametric test.

are in contrast to those of Pickard et al. (1978) who found normal capping in 6 cases of myotonic dystrophy. The reasons for this discrepancy are uncertain but could be related to methodological differences, for example the source of antisera and incubation times which were different in the 2 studies. Our findings raise the possibility that there is an abnormality of the lymphocyte membrane or of some membrane-linked process in myotonic dystrophy.

Reduced serum IgG levels have been reported previously in some studies (Wochner et al., 1966; Bundey et al., 1970; Roberts and Bradley, 1977) but not in others (Oppenheimer and Milhorat, 1961; Grove et al., 1973). In one study serum IgM levels were also reduced (Bundey et al., 1970). We have confirmed the reduction in serum IgG levels and have also found a significantly reduced IgA level in the present group of patients. In an early study, it was shown that the half life of human I^{131}-labelled γ-globulin after intravenous injection was reduced in cases of myotonic dystrophy suggesting an increased metabolism of these proteins (Zinneman and Rotstein, 1956). In a subsequent study, Wochner et al. (1966) concluded that there was a selective hypercatabolism of IgG but not of other immunoglobulin classes. These workers also found that the rates of synthesis of IgG were normal and that IgG from patients with myotonic dystrophy did not show accelerated catabolism when injected into normal subjects. No further light has since been shed on the significance of the reduced immunoglobulin levels in myotonic dystrophy.

In spite of the relatively small number of subjects studied, our findings have shown no evidence of undue predisposition to infection in patients with myotonic dystrophy and no apparent increase in the incidence of autoimmune disease or malignancy. In addition, no evidence of autoantibody formation against muscle or other autoantigens has been found to suggest a disturbance of immune tolerance and immunoregulation.

Summary

Abnormalities of cellular and humoral immunity have been recognised in myotonic dystrophy but their significance is uncertain. To throw further light on this, a group of 22 patients with myotonic dystrophy was investigated, looking specifically for evidence of abnormalities of B lymphocyte function and of disturbed immunoregulation. The previously reported reduction in serum IgG levels was confirmed and, in addition, serum IgA levels were significantly reduced. Autoantibodies to muscle and non-muscle antigens were not found and there was no increase in autoimmune disease or malignancy, suggesting that immunoregulatory mechanisms are not disturbed. The proportions of T and B cells were not significantly different in patients and controls. B-lymphocyte capping with FITC- antihuman IgG was quantitatively altered. the percentage of capped cells after incubation being reduced and the time-course of the capping process being apparently prolonged in the myotonic dystrophy subjects.

While there are a number of possible explanations for these findings, they may reflect an intrinsic abnormality of the lymphocyte membrane. This could

be part of a more generalised membrane defect which has been suggested to underlie the myotonia and certain other manifestations of this multisystemic disorder.

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References

Bundey, S.; Carter, C.O. and Soothill, J.F.: Early recognition of heterozygotes for the gene for dystrophia myotonica. Journal of Neurology, Neurosurgery and Psychiatry 33: 279-293 (1970).

Butterfield, D.A.; Roses, A.D. and Cooper, M.L.: A comparative electron spin resonance study of the erythrocyte membrane in myotonic muscular dystrophy. Biochemistry 13: 5078-5082 (1974).

Festoff, B.W. and Moore, W.V.: Evaluation of the insulin receptor in myotonic dystrophy. Annals of Neurology 6: 60-65 (1979).

Goldsmith, B.M.; Gruemer, H.-D.; Hawley, R.J.; Pickard, N.A.; Verrill, H.L.; Nance, W.E.; Miller, G. and Crawford, R.G.: The contribution of assays for lymphocyte capping and creatine kinase to detection of the Becker-type dystrophy trait. Clinical Chemistry 26: 754-759 (1980).

Grove, D.I.; O'Callaghan, S.J.; Burston, T.O. and Forbes, I.J.: Immunological function in dystrophia myotonica. British Medical Journal 3: 81-83 (1973).

Harper, P.S.: In Myotonic Dystrophy (Saunders, Philadelphia 1979).

Ho, A.D.; Stojakowitz, S.; Reitter, B.; Fiehn, W.; Zipperle, G. and Hunstein, W.: Capping of lymphocytes in patients and carriers of Duchenne muscular dystrophy. Klinische Wochenschrift 58: 377-381 (1980).

Holian, J.; Griffiths, I.D.; Glass, D.N.; Maini, R.N. and Scott, J.T.: Human anti-DNA antibody: reference standards for diagnosis and management of systemic lupus erythematosus. Annals of Rheumatic Diseases 34: 438-443 (1975).

Jondal, H.; Holm, S. and Wigzwill, H.: Surface markers on human T and B lymphocytes: 1. A large population of lymphocytes forming non-immune rosettes with sheep red blood cells. Journal of Experimental Medicine 136: 207-215 (1972).

Kuriowa, Y.; Sugita, H.; Toyokura, Y.; Mizochuchi, M.; Matsuo, H. and Nonaka, Y.: Immunologic derangement in myotonic dystrophy. Abnormal contact sensitization to Dinitrochlorobenzene. Journal of the Neurological Sciences 47: 231-239 (1980).

Lindstrom, J.M.; Seybold, M.E.; Lennon, V.A.; Whittingham, S. and Duane, D.D.: Antibody to acetylcholine receptor in myasthenia gravis: Prevalence, clinical correlates and diagnostic value. Neurology (Minneapolis) 26: 1054-1059 (1976).

Mancini, G.; Carbonara, A.O. and Heremans, J.R.: Immunochemical quantitations of antigens by single radial immunodiffusion. International Journal of Immunochemistry 2: 235-254 (1965).

Mechler, F. and Mastaglia, F.L.: Vascular adrenergic receptor responses in skeletal muscle in myotonic dystrophy. Annals of Neurology 9: 157-162 (1981).

Moxley, R.T. III: Metabolic studies in muscular dystrophy. A role for insulin. Advances in Neurology 17: 161-173 (1977).

Oppenheimer, H.A. and Milhorat, A.T.: Serum proteins, lipoproteins and glycoproteins in muscular dystrophy and related diseases. Annals of the New York Academy of Science (New York) 94: 208-219 (1961).

Pickard, N.A.; Gruemer, H.-D.; Verrill, H.L.; Isaacs, E.R.; Robinow, M.; Nance, W.E.; Myers, E.C. and Goldsmith, B.: Systemic membrane defect in the proximal muscular dystrophies. New England Journal of Medicine 299: 841-846 (1978).

Plishker, G.A.; Gitelman, H.J. and Appel, S.H.: Myotonic dystrophy: Altered calcium transport in erythrocytes. Science 200: 323-325 (1978).

Roberts, D.F. and Bradley, W.G.: Immunoglobulin levels in dystrophia myotonica. Journal of Medical Genetics (London) 14: 16-19 (1977).

Roses, A.D., and Appel, S.H.: Protein kinase activity in erythrocyte ghosts of patients with myotonic muscular dystrophy. Proceedings of the National Academy of Science (Washington) 70: 1855-1859 (1973).

Rowland, L.P.: Pathogenesis of muscular dystrophies. Archives of Neurology (Chicago) 33: 315-321 (1976).

Seay, A.R.; Ziter, F.A. and Hill, H.R.: Defective neutrophil function in myotonic dystrophy. Journal of the Neurological Sciences 35: 25-30 (1978).

Seay, A.R.; Ziter, F.A. and Hill, H.R.: Abnormal leukocyte electrophoretic mobility in myotonic dystrophy. Journal of the Neurological Sciences 44: 13-18 (1979).

Tevaarwerk, G.J.M.; Strickland, K.P.; Lin, C.H. and Hudson, A.J.: Studies on insulin resistance and insulin receptor binding in myotonia dystrophica. Journal of Clinical Endocrinology and Metabolism 49: 216-222 (1979).

Verrill, H.L.; Pickard, N.A. and Gruemer, H-D.: Diminished cap formation in lymphocytes from patients and carriers of Duchenne muscular dystrophy. Clinical Chemistry 23: 2341-2343 (1977).

Walker, G.L.; Mastaglia, F.L. and Roberts, D.F.: A search for genetic influence in idiopathic inflammatory myopathy. Acta Neurologica Scandinavica 66: 432-443 (1982).

Walton, J.N. and Gardner-Medwin, D.: Progressive muscular dystrophy and the myotonic disorders; in Walton (Ed) Disorders of Voluntary Muscle, pp.561-613 (Churchill Livingstone, London 1974).

Warner, N.L.: Membrane immunoglobulins and antigen receptors on B and T lymphocytes. Advances in Immunology 19: 167-216 (1974).

Wochner, R.D.; Drews, G.; Strober, W. and Waldmann, T.A.: Accelerated breakdown of immunoglobulin G (IgG) in myotonic dystrophy: A hereditary error of immunoglobulin catabolism. Journal of Clinical Investigation (New Haven) 45: 321-329 (1966).

Zinneman, H.H. and Rotstein, J.: A study of gamma globulins in dystrophia myotonica. Journal of Laboratory and Clinical Medicine (St Louis) 47: 907-916 (1956).

Substance P in the Trigeminal System at Postmortem: Evidence for a Role in Pain Pathways in Man

*R.D. Helme and J.L. Fletcher**

Substance P is an undecapeptide distributed widely in both central and peripheral nervous systems. It has a role in primary afferent neurotransmission, specifically in nociceptive pathways (Nicoll et al., 1980; Henry, 1980). Substance P is also a potent vasodilator when injected systemically in man (Eklund et al., 1977). The trigeminal nerve probably mediates pain in most headache syndromes. The aetiology and mechanism of pain transmission is poorly understood, however. Vascular reactivity is also involved in some pain syndromes, but the pathophysiology of this association is not clear. Thus it is of particular interest to study the distribution of substance P in the trigeminal primary afferent pathway.

In experimental animals, immunohistochemical methods have been used to demonstrate substance P nerve fibres in mucocutaneous areas supplied by the mandibular and maxillary divisions, but not the ophthalmic division of the trigeminal nerve (Cuello et al, 1978; Paximos et al., 1980). Studies of substance P in the trigeminal nuclei have also been limited (Cuello and Kanazawa, 1978; Cuello et al., 1978; Ljungdahl et al., 1978). No studies have examined substance P in the human trigeminal system.

In the present study indirect immunofluorescence histochemistry was used on cryostat sections of formalin-fixed human postmortem tissue to examine the distribution of substance P in brainstem nuclei, trigeminal ganglion and scalp.

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Methods

Human tissue was obtained at autopsy. The interval between death and postmortem was less than 24 hours. The intracavernous portion of the internal carotid artery was dissected out with the trigeminal nerve and ganglion and cut free before fixing. Two-centimetre sections of the middle cerebral and basilar arteries were dissected free from the brain and brainstem respectively. The temporalis muscle was dissected free of its attachment to the skull. Two-centimetre square full thickness samples of muscle, including the superficial fascia overlying the muscle, were sampled. Skin from the scalp incision line was removed in the midline and anterior and superior to the ear. Samples consisted of skin, superficial fascia, and epicranial aponeurosis or occipitofrontalis muscle, the latter depending on the area taken. Approximately 2cm square samples of dura were taken from the region surrounding the middle meningeal artery and adjacent to the superior petrosal or inferior saggital sinuses. As the leptomeninges were difficult to separate from the unfixed brain, this section of cerebral and cerebellar hemispheres was fixed for 2 days. The leptomeninges were then dissected free and either spread on glass slides and air dried at 4°C for immunofluorescence without further treatment, or spread on cardboard squares and processed as for other tissues.

Tissue Processing

Tissue was fixed in 4% phosphate buffered formaldehyde at 4°C for 2 to 4 days. It was then transferred to 15% sucrose for 1 to 3 days before freezing in a chloroform/dry ice mixture (Helme and Stow, 1980). For long term storage tissues were kept at −85°C. The indirect immunofluorescence technique was used on 10μ cryostat sections. Modifications included use of 1% Triton X-100 in antibody and conjugate solutions, incubation of primary antibody for 24 hours to 3 days at 4°C, and of conjugate for 30 minutes at 37°C. Tissues were kept under coverslips in sealed containers for all incubations. Control sections were treated with conjugate alone, pooled normal serum, substance P antiserum neutralised with 0.15 mmol synthetic substance P, or stained with toluidine blue. The substance P antiserum has been previously characterised by radio-immunoassay (Helme and White, 1981). There is possible cross-reactivity with other substance P-like peptides, as in any immunohistochemical study. Hence substance P-containing nerve fibres referred to in this study may contain related peptides.

Results

Nerve fibres were seen in several sites in the peripheral distribution of the trigeminal nerve.

Nerve trunks

Small nerve bundles, some up to 1 or 2mm in diameter, were seen frequently in the skin, occasionally in muscle, and rarely in the dura and the adventitia of the basilar artery. Rarely, a nerve bundle was seen cut in longitudinal section when long parallel lines of interdigitating fibres were seen for the length of the nerve section.

Vessels

Substance P fibres were seen in the walls of arteries in skin, muscle, dura and the basilar and middle cerebral artery. No fibres were seen in the wall of

the internal carotid artery. In one series of consecutive scalp sections an artery was cut obliquely. Four to six fibres were seen in the media at x16 magnification, while the number visible increased to 6 to 12 at x40 magnification. They followed a tortuous course and frequently branched. Fibres were seen both lying parallel to the endothelial border and ramifying towards it (fig. 1). In the dura containing longitudinal sections of the middle meningeal artery 50 to 60μ fluorescent nerve fibre segments were seen in the media of the artery. These were predominantly longitudinally oriented. In the temporalis and occipitofrontalis muscles, substance P immunofluorescent fibres were seen lying circumferentially in the adventitia and penetrating radially into the media of cross-sectioned arteries. Usually only 1 or 2 fibres were seen per section. In the large cerebral arteries, fibres were more difficult to demonstrate, only short 10 to 15μ fibre segments being seen, and these were not present in all sections. Fibres were seen in the adventitia and peripheral media, most frequently lying circumferentially. In the skin and muscle, short fine fibres were occasionally seen in the adventitia of, or connective tissue close to, veins, although these were not present in every section.

Skin (fig. 2)

The results were the same in scalp sections taken from different areas. Fluorescent fibres were located in 4 sites, viz. in vascular walls, neurovascular bundles, and in subepidermal and perifollicular locations. The intensity of fluorescence varied between tissue samples. Fluorescent fibres were present in the walls and adjacent to larger arterioles, but frequently absent from the smallest vessels. Venules only occasionally contained a single circumferential adventitial fibre. Single fibres were seen beneath the epidermis. These followed a tortuous course, frequently winding in and out of the plane of section, and branching. Under low

Fig. 1. Oblique section of an artery in the dermis. L = lumen. E = endothelium. M = media. N = nerve fibres. Calibration 100μ.

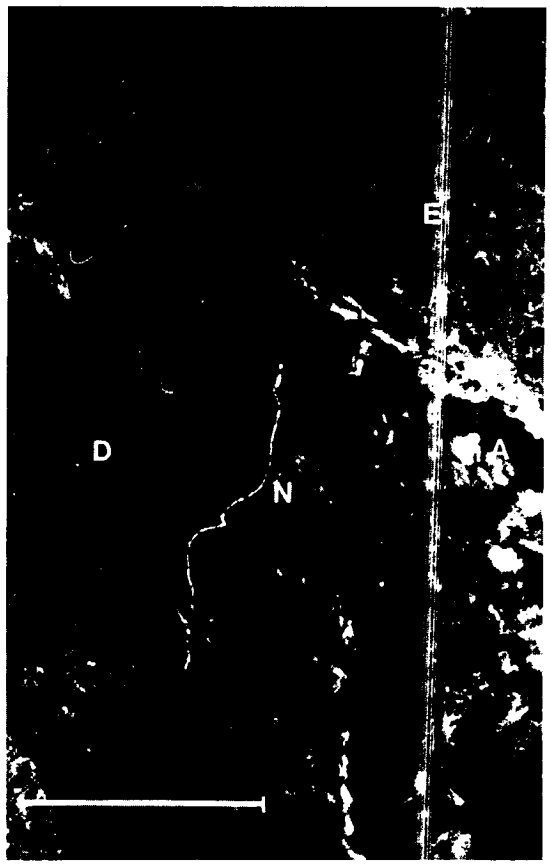

Fig. 2. Skin section showing the tortuous and frequently branching course of fluorescent fibres. E = epidermis. D = dermis. N = nerve fibres. Calibration 100μ.

magnification, discontinuous fibre segments could, in some cases, be followed for several hundred microns. Frequently fibres projected up into dermal papillae where they appeared as short irregular branching segments. Rarely, fibres appeared to enter the epidermis. Fluorescent fibres were present in every section.

Muscle

The pooled normal serum control showed nonspecific granular fluorescence arranged in the epimysial connective tissue. Where muscle fibre bundles were cut in oblique or longitudinal section these granules were often longitudinally

arrayed, thus making differentiation of specific fibres difficult. The only specific substance P immunofluorescent fibres seen in the occipitofrontalis and temporalis muscle sections were in association with nerve bundles and arteries.

Meninges

No specific substance P fluorescence was seen in any leptomeningeal preparations. The only sections of dura to contain substance P immunofluorescent fibres were those adjacent to the middle meningeal artery or dural sinuses. Fibre segments, 40 to 50μ long, were seen scattered along the walls of the sinuses. Fibres within nerve bundles and the wall of the middle meningeal artery were described previously. Occasional 80 to 100μ fibres were seen free in the dura. The fibres lay in straight or slightly wavy lines, usually extending away from an artery or sinus but rarely could be seen several millimetres away from any other structures.

. *Trigeminal Ganglion*

The trigeminal ganglion contained numerous cell bodies with specific substance P fluorescence (fig. 3). The granules were distributed throughout the cytoplasm, but were absent from the central nuclear area. In some cases the granular fluorescence extended into processes emerging from the cell body. The

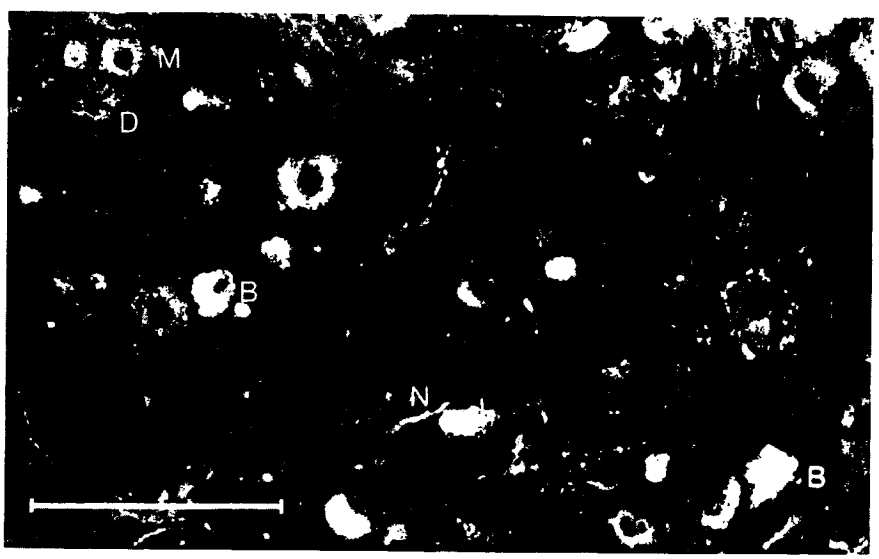

Fig. 3. Trigeminal ganglion section showing distribution of neuronal cell bodies with specific substance P fluorescence. B = 'bright' neurone. M = 'medium' neurone. D = 'dull' neurone. Calibration 100μ.

substance P-containing neuronal cell bodies varied in the intensity of fluorescence and were not distributed homogeneously throughout the ganglion. In some cases, isolated cell bodies were seen. It was more common, however, for most of the brightly fluorescent neurones to be aggregated in one area.

To obtain an estimate of the number of substance P-containing neurones as compared to the total number of neurones in the ganglion, a cell count was performed on 7 sections through the ganglion. 'Medium' intensity neurones comprised one-third and the 'dull' intensity neurones two-thirds of the fluorescent cell bodies, with only scattered 'bright' cell bodies. Substance P-containing cell bodies comprised 14 to 18% of the total ganglionic neurones in the sections studied.

Brainstem

In human brainstem, substance P fluorescence was predominantly granular and fainter than that found in the rat. The distribution of substance P-containing nerve fibres, however, paralleled that of the rat. Dense fluorescence was observed in the peripheral layers of nucleus caudalis and the 2 areas of caudal nucleus interpolaris, with only fainter fluorescence more rostrally. Dorsoventral differences were more prominent in the human than rat nucleus caudalis. A dense area was not seen in human nucleus oralis, which may have been due to incomplete sampling.

Discussion

Human Sample Limitations

A major problem of research into anatomical localisation of substance P in humans is that tissue sampling is an invasive procedure. Access to tissue is easier in studies of postmortem material. The major disadvantage of postmortem tissue sampling, however, is the degeneration in quality of tissue resulting from postmortem autolysis and potential degradation or change in the nature of the substance P during the interval between death and fixation. For this reason, the maximal intervals between death and tissue sampling was limited to 24 hours for the present study. Postmortem tissue samples are also potentially involved in a pathological process. Ultimately, it will be of interest to study substance P in pathological states, but first a 'normal' standard of comparison must be established. Older people have more intracellular lipofuscin and may also undergo degenerative nervous system changes (Hayflick, 1976) so samples were preferentially taken from younger people. Indeed, in this study, the younger brainstems had noticeably less lipofuscin autofluorescence.

Substance P in Pain Pathways

The trigeminal primary afferent pathway is the major pathway for head pain. Many studies have presented evidence which suggests substance P is present in

primary afferent pain pathways in animals, and that its presence is functionally significant. The present study has demonstrated the presence of substance P in the 3 major components of this pathway in humans: in the periphery, in the ganglion cell bodies and in the trigeminal brainstem nuclei. Moreover, its distribution in the periphery and brainstem nuclei is consistent with what is currently known about pathways for head pain. In the periphery, substance P was found in association with pain sensitive structures and absent from pain insensitive structures. The skin of the scalp is pain sensitive, and substance P was found in subepidermal fibres, sometimes appearing to end in a ramification of fibres within a dermal papillae, which is consistent with the distribution reported for pain fibres (Wolff, 1963).

Blood vessels are also sensitive to painful stimuli (Ray and Wolff, 1940) with arteries being much more sensitive than veins. Correspondingly, an extensive plexus of substance P fibres was found within the walls of arteries, with veins showing very few substance P fibres. Leptomeninges are reportedly insensitive to pain (Wolff, 1963) and we are not able to demonstrate substance P in the leptomeninges, although this may reflect a methodological problem rather than a lack of substance P. It is not possible with immunofluorescence to state conclusively that substance P is absent from an area studied. This is illustrated by cases such as the arteries in skin where a change in methodology enabled visualisation of previously unseen fibres.

In the dura, substance P fibres were seen only in areas where pain sensitivity and small diameter fibres have been reported (Wolff, 1963; McNaughton, 1938). This was within 1cm of the walls of the venous sinuses and the meningeal artery. Substance P-containing fibres were seen within these structures, lying adjacent to them and, only rarely, apparently free within the dura. In conclusion, we consider the distribution of substance P in the human trigeminal system sufficiently parallel to clinical studies of pain sensitive structures, to suggest that substance P is involved in nociceptive pathways in man.

Summary

It is suspected that substance P has a role in primary afferent neurotransmission specifically concerned with nociception. This hypothesis has been developed from studies using experimental animals. In the present study indirect immunofluorescence has been used to examine the distribution of substance P-containing neurones in the human trigeminal system. The 5 specimens examined were obtained at autopsy. The antibody has been characterised by radio-immunoassay. In addition, neutralisation tests were performed.

Approximately 15% of the neuronal perikarya observed in the trigeminal ganglia contained substance P-like material. The central nerve terminal distribution of these neurones was observed in the peripheral layers of nucleus caudalis and the caudal regions of the nucleus interpolaris. Peripheral distribution of fibres, presumably axon terminals, was observed in the dermis of the scalp subjacent to the epidermis. Rarely, fibres penetrated the lower layers of the epi-

dermis. Nerve fibres were seen in the media and adventitia at the origin of the major cerebral vessels, the middle meningeal, muscular and scalp arteries. Nerve fibres were not observed elsewhere in muscle, in the leptomeninges or dura mater, except in and immediately adjacent to the venous sinuses. The distribution of substance P-containing neurones correlates closely with clinical studies which document the blood vessels and skin as the major pain sensitive structures of the scalp and cranium. This is evidence in man that substance P is involved in nociceptive pathways.

References

Cuello A.C. and Kanazawa, I.: The distribution of substance P immunoreactive fibres in the rat cerebral nervous system. Journal of Comparative Neurology 178: 129-156 (1978).

Cuello, A.C.; Del Fiacco, M. and Paxinos, G.: The central and peripheral ends of the substance P-containing sensory neurones of the rat trigeminal system. Brain Research 152: 499-509 (1978).

Eklund, B.; Jogestrand T. and Pernow, B.: Effects of substance P on resistance and capacitance vessels in the human forearm; in Von Euler and Pernow (Eds) Substance P, pp.275-285 (Raven Press, New York 1977).

Hayflick, L.: The cell biology of human aging. New England Journal of Medicine 295: 1302-1308 (1976).

Helme, R.D. and Stow, J.L.: Immunological studies of brain-specific antigens. Clinical and Experimental Neurology 17: 211-222 (1980).

Helme, R.D. and White, D.M.: Substance P in the central nervous system. Clinical and Experimental Neurology 18: 156-160 (1981).

Henry, J.L.: Substance P and pain: an updating. Trends in Neuroscience, pp.95-98 (April 1980).

Ljungdahl, A.; Hokfelt, T. and Nilsson, G.: Distribution of substance P-like immunoreactivity in the central nervous system of the rat. I: Cell bodies and nerve terminals. Neuroscience 3: 861-943 (1978).

McNaughton, F.L.: The innervation of the intracranial blood vessels and dural sinuses. Association for Research in Nervous Disease Proceedings 18: 178 (1938).

Nicoll, R.A.; Schenker, C. and Leeman, S.E.: Substance P as a transmitter candidate. Annual Review of Neuroscience 3: 227-268 (1980).

Paximos, G.; O'Brien, M.; Cuello, A.C. and Del Fiacco, M.P.: Substance P in primary afferents and pain; in Peck and Wallace (Eds) Problems in Pain, pp.64-72 (Pergamon Press, Sydney 1980).

Ray, B.S. and Wolff, M.C.: Experimental studies on headache pain – sensitive structures of the head and their significance in headache. Archives of Surgery 41: 813-856 (1940).

Wolff, M.C.: Headache and other pain (2nd ed) (Oxford University Press, New York 1962).

Comparison of Diagnostic Tests in Myasthenia Gravis

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In order to evaluate the acetylcholine receptor (AchR) - antibody test in myasthenia gravis we undertook a survey of the clinical findings and results of edrophonium chloride and electrophysiological (EMG) tests in patients whose serum had been referred for AchR-antibody testing.

AchR-antibody is reported to detect 50% of patients with ocular (Osserman Group I) and 80 to 90% of patients with generalised myasthenia (Osserman Groups II to IV) according to Lindstrom et al., 1976 and Lefvert et al., 1978. We have chosen this simplified clinical classification as AchR and EMG test results vary little in Osserman Groups II to IV and are usually not reported separately.

In EMG studies carried out by Horowitz et al. (1975) on a consecutive group of patients, decremental responses to repetitive stimulation were found in 54% of patients with ocular myasthenia gravis and in 70% of subjects with generalised myasthenia gravis. In a selected series of patients with undoubted clinical myasthenia gravis both ocular and generalised, Ozemir and Young (1976) reported 95% positive results when more than one muscle was tested. Nearly all cases of the disease are positive when single fibre EMG is used (Stalberg, 1980). Figures for single fibre EMG reported by Sanders (1981) were 85% positive for a single muscle and 95% for multiple muscle studies in a group of 129 clinically diagnosed myasthenia gravis patients, compared with 62% for repetitive stimulation studies.

The results reported in the literature cited above are generally from single laboratories using a defined technique and are probably not representative of these tests as used in general clinical neurological practice. We have, therefore, undertaken this survey, which includes clinical results from a number of neurologists and 9 EMG units, to evaluate these tests as used in practice.

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Table I. Diagnostic yield of the 3 tests in ocular and generalised myasthenia gravis expressed as the ratio of positive test results to the number of patients tested

	AchR-antibodies	Edrophonium	EMG
Ocular MG	10/21	17/18	3/10
	48%	94%	30%
Generalised MG	53/55	25/28	18/29
	96%	89%	62%

Table II. Diagnostic tests given in ocular myasthenia gravis[1]

	Edrophonium only	AchR-antibodies only	EMG only	Mixed[1]	Total
No of patients tested	10	4	1	7	22
Percentage	46%	18%	4%	32%	100%

1 Includes 1 case of penicillamine induced myasthenia gravis

Table III. Equivocal test results in myasthenia subjects expressed as the ratio of the number of equivocal results to the total number of patients tested

	AchR-antibodies	Edrophonium	EMG
Ocular MG	0/22	2/19	0/15
	0%	10%	0%
Generalised MG	0/55	2/28	2/29
	0%	7.1%	6.9%

Table IV. Equivocal test results in patients not diagnosed as myasthenia gravis expressed as the ratio of the number of equivocal results to the number of patients tested

	AchR-antibodies	Edrophonium	EMG
Diagnosis other than MG	0/47	1/15	1/13
	0%	6.6%	7.6%
No diagnosis reached	0/60	4/14	0/10
	0%	28%	0%

Table V. Results of diagnostic tests in patients not diagnosed as myasthenia gravis expressed as the ratio of positive results to the number of patients tested

	AchR-antibodies	Edrophonium	EMG
Diagnosis other than MG	0/47	0/15	0/13
	0%	0%	0%
No diagnosis reached	0/60	0/14	0/10
	0%	0%	0%

Table VI. Diagnostic test results in other myasthenic syndromes. Numerals indicate positive results

Patients (n)	AchR-antibodies	Edrophonium	EMG
Familial MG (1)	0	–	–
Juvenile myasthenia (1)	0	1	–
Penicillamine MG (ocular, 1)	0	1	1
Penicillamine MG (generalised) (1)	1	0	0
Penicillamine Rx (6)	0	–	–

0 = No antibody detected
– = Not tested

Method

The study was carried out by surveying all patients whose serum had been referred to our laboratory for AchR-antibody testing. Clinical details, results of intravenous edrophonium and EMG testing were obtained by questionnaire or personal enquiries directed to referring physicians. Ocular myasthenia gravis was defined by clinical features consistent with ocular myasthenia gravis with at least one positive test (intravenous edrophonium, EMG or AchR-antibody).

Intravenous edrophonium testing was carried out by referring neurologists. No attempt was made to standardise techniques between observers, and the results in most cases were determined by the subjective impression of the examining physician. Equivocal results were those recorded as such at the time of the examination.

EMG test results were those of repetitive stimulation of limb muscles. Where a decremental response was reported the result was classified as positive. When more than one EMG study gave both positive and negative results the response was scored as equivocal.

AchR-antibody studies were carried out as previously reported (Nicholson and Griffiths, 1981).

Results

The diagnostic yield of the 3 tests in ocular and generalised myasthenia gravis is shown in table I. In ocular myasthenia gravis edrophonium testing had the highest yield of positive results. A number of patients with ocular myasthenia gravis had only 1 of the 3 tests (table II). Equivocal edrophonium and EMG results occurred in some myasthenia gravis patients (table III) and in some patients with diagnoses other than myasthenia gravis (table IV).

No false positive results were obtained with any test (table V). However, one patient subsequently diagnosed as having an hysterical weakness had initially a positive EMG result and later 2 negative results. This result has been classified as equivocal. Results for other myasthenia-like syndromes are shown (table VI).

Table VII. Clinical features of patients with a generalised myasthenia-like syndrome without AchR-antibodies

Patient	Clinical details	Test result	
		Edrophonium	EMG
Case 1	Ocular and limb; onset 17y; complete remission 5y since thymectomy	+	-
Case 2	Ocular, bulbar, limb for 10y; onset 30y; thymectomy 1973; pyridostigmine only	+	+

Two patients with generalised myasthenia gravis did not have raised AchR-antibody levels (table VII) as defined above. One patient had been in complete remission for 5 years and had a positive edrophonium test but EMG examination was negative. The second patient had ocular and bulbar myasthenia gravis for 19 years from the age of 30. Since thymectomy the patient was controlled by pyridostigmine alone. This patient had positive edrophonium and EMG tests.

Conclusion

The results of this study reflect the way in which the patients were selected. In particular edrophonium testing was the main method for establishing the diagnosis of ocular myasthenia gravis and the results reflect this fact.

The results for edrophonium and EMG testing possibly could have been improved if the study had been confined to a single laboratory with an interest in myasthenia gravis.

Negative results for AchR-antibody testing effectively exclude generalised myasthenia gravis. The same can be said for edrophonium testing in ocular myasthenia gravis but this reflects the fact that we have defined ocular myasthenia gravis as having a positive edrophonium result.

All tests are needed for full investigation of patients with suspected myasthenia gravis because if one test is negative the other tests may yield a positive result, increasing the diagnostic yield. The EMG results compare favourably with those reported by Horowitz et al. (1975).

Other authors have diagnosed myasthenia gravis (for the purpose of comparing AchR-antibody testing) by clinical features together with positive edrophonium and/or EMG results. This approach may not be correct as some neuromuscular defects, other than myasthenia gravis, can have positive edrophonium tests and decremental responses to repetitive stimulation (Swift, 1980). Because of this growing group of neuromuscular disorders it may become necessary to redefine myasthenia gravis as a disease with both the clinical features of myasthenia gravis and AchR-antibodies. The definition could be readily applied to the diagnosis of generalised myasthenia gravis but further investigations are needed to define the disease process in patients with clinical ocular myasthenia who do not have AchR-antibodies.

Summary

Results of 3 tests, intravenous edrophonium chloride, EMG, and acetylcholine receptor antibody testing, were compared in patients with generalised and ocular myasthenia gravis. None of the 3 tests was positive in any patient with a diagnosis other than myasthenia. However, equivocal results were obtained with edrophonium and EMG testing in some patients with myasthenia gravis and in patients with other diseases.

It is concluded from this survey that antibody and edrophonium testing were equally efficient in detecting generalised myasthenia gravis. Edrophonium testing was superior in ocular myasthenia gravis. Although the yields from each test varied, all 3 tests were needed for the evaluation of some myasthenia gravis patients as each test may provide additional information.

References

Horowitz, S.H.; Genkins, G.; Kornfeld, P. and Papatestas, A.: Electrophysiologic diagnosis of myasthenia gravis and the regional curare test. Neurology (abstract) 25: 386 (1975).

Lefvert, A.K.; Bergstrom, K.; Matell, G.; Osterman, P.O. and Pirskanen, R.: Determination of acetylcholine receptor antibody in myasthenia gravis: clinical usefulness and pathogenetic implications. Journal of Neurology, Neurosurgery and Psychiatry 41: 394-403 (1978).

Lindstrom, J.M.; Seybold, M.E.; Lennon, V.A.; Whittingham, S. and Duane, D.D.: Antibody to acetylcholine receptor in myasthenia gravis: Prevalence, clinical correlates and diagnostic value. Neurology 26: 1054-1059 (1976).

Nicholson, G.A. and Griffiths, L.R.: Acetylcholine receptor antibodies in the diagnosis and management of myasthenia gravis; in Tryer and Eadie (Eds) Clinical and Experimental Neurology, Vol. 18, pp.61-69 (ADIS Health Science Press, Sydney 1981).

Ozemir, C. and Young, R.R.: The results to be expected from electrical testing in the diagnosis of myasthenia gravis. Annals of the New York Academy of Sciences 274: 203-223 (1976).

Sanders, D.B.: SFEMG in myasthenia gravis. Muscle and Nerve 4: 253 (1981).

Stalberg, E.: Clinical electrophysiology in myasthenia gravis. Journal of Neurology, Neurosurgery and Psychiatry 43: 622-633 (1980).

Swift, T.R.: Disorders of neuromuscular transmission other than myasthenia gravis. Muscle and Nerve 4: 334-353 (1981).

Hormonal Influence on Water Permeability across the Blood-Brain Barrier

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The blood-brain barrier is a highly complex membrane which serves to regulate the internal environment of the brain, maintaining it within narrow homeostatic limits. Some substances are freely or highly permeable across this barrier while others are impermeable or relatively impermeable. It has been traditionally believed that water is freely permeable, being subject only to hydrostatic and osmotic forces. Experimental work over the past decade, however, has revealed that the situation is in fact much more complex and that the barrier, under neural and hormonal influences, may function in a dynamic fashion in order to regulate its own water permeability (Raichle et al., 1975, 1978).

Steroid hormones are known to influence brain water content. Zuckerman (1950) showed that ethinyloestradiol increases brain water content in rats, and dexamethasone has well-recognised efficacy in treating some types of brain oedema. We have used a recently described technique (McCulloch and Angerson, 1981) for measuring the rate of flux of water across the blood-brain barrier (PS H_20), in order to investigate whether steroid hormone manipulations influence water permeability, whether such changes are regional and whether brain water content changes.

Methods

Drug Administration

Group 1

Young mature female Sprague-Dawley rats were given dexamethasone 2 μg/ml in their drinking water for 3 weeks prior to determination of PS H_20.

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Group 2

These rats were treated as for group 1 but dexamethasone was abruptly withdrawn 3 days prior to determination of PS H_20. Control rats were allowed ordinary drinking water.

The first regime was designed to investigate the effects of exogenously administered steroid while the second was designed to look at the effects of abrupt steroid withdrawal and to create a state of relative adrenal insufficiency.

Group 3

Rats were given an intramuscular bolus of 0.1 μg ethinyloestradiol in arachis oil 20 hours prior to the experiment. Control rats received an injection of vehicle alone.

Experimental Procedure

Under light halothane and nitrous oxide anaesthesia the femoral arteries and veins were cannulated in each leg and the hindquarters immobilised in a plaster cast. Recovery time of 2 hours was allowed while blood pressure and blood gases were monitored.

Two diffusible tracers 40 μCi titrated water and 20 μCi ^{14}C-iodoantipyrine were infused simultaneously and multiple blood samples taken over 60 seconds. The rat was then decapitated, the brain dissected into regions and solubilised. The amount of each tracer in both the blood and brain was measured by the liquid scintillation counter enabling calculation of cerebral blood flow (CBF) and water permeability (PS H_20) in specific brain regions.

Brain water content was determined in parallel groups of animals by measurement of wet and dry weights.

Theory

The diffusional movement of an agent from blood into brain is described by the equation developed by Kety (1951):

$$Ci(T) = \lambda K \int_0^T Ca(t)\, e^{-K(T-t)}\, dt \qquad (1)$$

where T = kill time, t = variable time, Ci = tissue concentration, Ca = arterial concentration, λ = brain:blood partition coefficient and K is a constant which varies with tissue blood flow (F), permeability across the barrier (P) and the surface area of exchange (S).

The factor K is also defined as:

$$K = \frac{F}{\lambda}\,(1 - e^{-PS/F}) \qquad (2)$$

Table I. The effect of dexamethasone on cerebral blood flow (CBF) and rate of flux of water (PSH_20) across the blood-brain barrier of rats. Values expressed as ml/100g/min

Experimental group (n)	Cerebral cortex		Pons		Cerebellum	
	CBF	PSH_20	CBF	PSH_20	CBF	PSH_20
Controls (5)	111 ± 8	262 ± 16	84 ± 5	188 ± 3	74 ± 9	202 ± 24
Continuous dexamethasone (5)	110 ± 6	174 ± 14[1]	76 ± 3	155 ± 22	76 ± 3	131 ± 20*
Dexamethasone discontinued (5)	128 ± 19	322 ± 15[2]	89 ± 10	263 ± 25	83 ± 5	237 ± 23

Results are means ± SEM (standard error of the mean).
1 $p < 0.01$
2 $p < 0.05$

By using a tracer such as ^{14}C-iodoantipyrine which is freely permeable across the barrier, $e^{-PS/F} \rightarrow 0$, and equation 2 can be simplified to:

$$K = \frac{F}{\lambda}$$

Hence F, tissue blood flow, may be calculated since the constant K can be derived from equation 1 and λ is known experimentally. Once tissue blood flow has been derived, then equation 2 may be solved for the PS product of the second agent, that is, water.

Statistics

Mann-Whitney U tests were used to evaluate the significance of observed changes in CBF and PS H_20.

Results

Table I shows that although 3 weeks' treatment with dexamethasone did not alter CBF, it produced significant changes in PS H_20 in the cerebral cortex. This was decreased in rats treated continuously but increased in rats from whom treatment had been withdrawn. PS H_20 in deeper structures and in the brainstem changed in a similar direction but was significant only in the cerebellum of the continuously treated rats.

Table II shows that a single dose of ethinyloestradiol markedly increased PS H_20 in cerebral cortex without affecting CBF.

Water content of the cerebral cortex was increased in rats from whom dexamethasone had been withdrawn and in those that received ethinyloestradiol (81.1 ± 0.4%, 80.1 ± 0.1% versus 79.2 ± 0.2% in controls).

Table II. The effect of ethinyloestradiol on cerebral blood flow (CBF) and rate of flux of water (PSH_20) across the blood-brain barrier of rats. Values expressed as ml/100g/min

Experimental group (n)	Cerebral cortex		Pons		Cerebellum	
	CBF	PSH_20	CBF	PSH_20	CBF	PSH_20
Controls (5)	125 ± 8	190 ± 16	95 ± 5	175 ± 18	97 ± 10	199 ± 25
Ethinyloestradiol (5)	133 ± 5	369 ± 25[1]	96 ± 4	260 ± 12[2]	92 ± 5	205 ± 10

Results are means ± SEM (standard error of the mean)
1 $p < 0.001$
2 $p < 0.01$

Summary and Conclusions

We have shown that steroid manipulations may influence the rate of flux of water across the blood-brain barrier. Such changes are regionally variable and are best seen in the cerebral cortex. Administration of dexamethasone produced decreased water permeability while withdrawal of dexamethasone and ethinyloestradiol resulted in increased permeability. Increased water content in cerebral cortex was demonstrated after steroid withdrawal and ethinyloestradiol administration.

We believe that these experimental findings may have relevance in the clinical situation and may help in understanding the pathogenesis of some types of brain oedema. One such example is benign intracranial hypertension where brain swelling is seen typically in young obese females and is also associated with the contraceptive pill, pregnancy and corticosteroid withdrawal.

References

Ketys, S.S.: The theory and applications of the exchange of inert gas at the lungs and tissues. Pharmacological Reviews 3: 1-41 (1951).

McCulloch, J. and Angerson, W.: Regional water permeability in the CNS of conscious rats. Journal of Cerebral Blood Flow and Metabolism 1 (Suppl. 1): 377-378 (1981).

Raichle, M.E.; Hartmann, B.K.; Eichling, J.O. and Sharpe, L.G.: Central nonadrenergic regulation of cerebral blood flow and vascular permeability. Proceedings of the National Academy of Sciences of the United States of America 72: 3726-3730 (1975).

Raichle, M.E.; Grubb, R.L. and Eichling, J.O.: Central neuroendocrine regulation of brain water permeability; in Cerebral Vascular Smooth Muscle and its Control. Ciba Foundation Symposium 56: 219-276 (Elsevier, Amsterdam 1978).

Zuckerman, S.; Palmer, A. and Hausen, D.A.: The effect of steroid hormones on the water content of tissues. Journal of Endocrinology 6: 261-276 (1950).

Myelopathy Associated with Decompression Sickness: A Report of Six Cases

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The neurological complications of decompression sickness (dysbarism) are many and varied (table 1). The spinal cord is the site of predilection in divers, but focal or diffuse cerebral involvement as well as peripheral nerve lesions may also occur (Aita, 1972; Edmonds et al., 1981). There have been few detailed clinical studies of divers who have suffered such complications (Peters et al., 1977) and relatively few pathological studies in survivors.

Details are presented of 6 divers who developed spinal cord damage as a complication of decompression sickness, including 3 who were re-examined after intervals of 3 to 7 years after the acute episode and 1 in whom the spinal cord was examined pathologically.

Case Reports

Case 1

A 34-year-old scuba diver made an ascent from a dive of 20 to 25 minutes duration at a depth of 100ft on 7.6.76. A few minutes later he developed pain and a tight sensation around the mid-chest with shallow breathing. By the time of admission to hospital his symptoms had disappeared but he was placed in a compression chamber and pressurised to the equivalent of 60ft. He was subsequently decompressed and remained symptom free. Later the same day, he developed numbness in the sole of the right foot and weakness in both legs and was unable to stand. Examination showed an asymmetric paraparesis, the left leg being weaker than the right, and patchy impairment of pain sensation over the right leg and foot. He was given a therapeutic recompression, including oxygen, following which his legs felt stronger. The leg weakness improved progressively over the course of the next month.

When reviewed in January 1980, muscle power, tone and coordination in the lower limbs

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Table I. Neurological manifestations of decompression sickness

Cerebral	Cerebellar	Brain stem	Spinal Cord	Peripheral nervous sytem
Headache Delirium Convulsions Coma Focal deficits Raised intra-cranial pressure Permanent mental impairment	Ataxia Incoordination Dysarthria Nystagmus	Cranial nerve palsies Pupillary abnormalities	Segmental pain, paraesthesiae Paraparesis (plegia) Urinary retention	Radiculopathy Neuropathies

were normal but the deep tendon reflexes in both legs were pathologically brisk with sustained clonus at the ankles and knees and bilateral Babinski responses. Sensory testing showed minimal impairment of joint position sense at the toes in both feet. Other findings included brisk snout and palmomental reflexes. It was concluded that he had probably sustained ischaemic cord damage in the thoracic region.

Twelve days following this review, he met with a violent death unrelated to diving. Pathological examination of the spinal cord showed patchy damage compatible with a previous ischaemic event in the dorsal and lateral columns involving the corticospinal, spinocerebellar and spinothalamic tracts, particularly between the levels of C7 and T4 with secondary ascending and descending tract degeneration (Palmer et al., 1981).

Case 2

In August 1976 a 36-year-old scuba diver made a rapid ascent from a depth of 95ft and immediately developed pain and paraesthesiae around the trunk and in both lower limbs. On the preceding 2 days he had made dives to depths of 130 and 120ft followed on each occasion by an uneventful decompression. His symptoms subsided but on the following morning his legs were completely paralysed and he felt numb up to the level of the rib margin on both sides. He subsequently developed retention of urine. At this stage he received therapeutic recompression and subsequent decompression over 2 days. On leaving the compression chamber he was able to walk without support but his gait was ataxic. Sensory testing showed impaired appreciation of light touch and pinprick to the level of the groin on the left side. Bladder function and lower limb weakness continued to improve over the next week and more gradually thereafter.

When reviewed in October 1979, he still complained of urgency of micturition and occasional incontinence of urine, stiffness and nocturnal flexor spasms in the legs and some residual subjective disturbance of sensation in the legs. Examination showed hyper-reflexia in both lower limbs (left more than right) with bilateral Babinski responses and absent superficial abdominal reflexes. Sensory testing showed mildly impaired light touch and temperature sensation in both legs with preservation of other sensory functions.

It was concluded that he had probably sustained ischaemic damage in the mid-thoracic region of the cord as a result of the decompression sickness in August 1976.

Case 3

In 1972 a 40-year-old scuba diver spent about 90 minutes at a depth of 40 feet followed 4 hours later by a further dive to 100ft for approximately 30 minutes. On ascent from this depth he was unable to move his legs. He felt numb to the level of the hips and could not pass urine. On the following day he was unable to move his legs at all. Therapeutic recompression was carried out and he was treated with adenocorticotrophic hormone (ACTH). The patient started to improve while in the decompression chamber and subsequently he improved progressively over the next 6 months. When re-examined in July 1977, there was no residual weakness but

the deep tendon reflexes were pathologically brisk in both legs with the exception of the left ankle jerk which was absent. There was clonus at the right ankle, bilateral Babinski responses and absent superficial abdominal reflexes. Sensory testing showed impaired appreciation of pinprick distally in the left leg to a level just below the knee.

It was concluded that the patient had suffered spinal cord damage probably involving the mid or lower thoracic region of the cord.

Case 4

In June 1979 a 22-year-old scuba diver made an ascent from a depth of 20 to 30ft. Almost immediately he experienced severe frontal headache, stabbing pain in the left chest and weakness of the legs. He subsequently also complained of dizziness when he moved his head. Examination showed severe paraparesis with depression of the deep tendon reflexes in the legs with the exception of the right knee jerk which was brisk, equivocal plantar responses, absent superficial abdominal reflexes and impairment of all sensory functions in both legs.

After therapeutic recompression, his headache and dizziness went and the weakness and sensory disturbance in the lower limbs had improved considerably. The tendon reflexes could now be elicited and the plantar responses were flexor. Examination 2 days later showed weakness of pyramidal distribution in the right leg with symmetrical tendon jerks, flexor plantar responses, and depressed superficial abdominal responses on the right side. Sensory testing showed impaired appreciation of pinprick and temperature over the right leg and trunk to the level of T5 together with impaired appreciation of vibration sense in the right leg. A further examination 2 months later showed only minimal residual pyramidal tract type of weakness and hyper-reflexia in the right leg with flexor plantar responses, depressed superficial abdominal reflexes and impaired appreciation of pinprick and vibration sense below the level of the right knee with preservation of other sensory modalities.

It was concluded that he had suffered ischaemic damage to the mid-thoracic region of the cord, possibly as a result of air embolism due to pulmonary barotrauma.

Case 5

On 10.8.78 a 34-year-old professional diver made a dive to a depth of 110ft in Dubai for a period of 70 minutes. Two days later he made a further dive to 160ft for 25 minutes. About 30 minutes later he noted numbness of the right little finger which persisted. Two days later during a 9-hour jumbo jet flight to London, he developed pain and paraesthesiae in the legs and by the end of the flight he noted weakness in the legs and difficulty in walking. A few hours later he collapsed and was unable to move either leg. Examination showed a severe paraparesis with depressed deep tendon reflexes in both legs and absent superficial abdominal reflexes. There was also weakness of grip in both hands, particularly the right. Pain sensation was impaired over both legs, particularly below the level of the knees.

Therapeutic recompression resulted in some improvement. He continued to improve thereafter and when seen 1 month later he considered that he had recovered to approximately 90% of normal. Examination at this time showed mild pyramidal tract type of weakness and hyper-reflexia in both legs with flexor plantar responses, impairment of all sensory modalities in the right leg and over the ulnar border of the right hand and medial border of the right forearm with milder impairment over the rest of the arm and normal sensation over the trunk. The 2 point discrimination threshold over the right little finger was 5cm compared with 4mm over the index finger. The only other sensory abnormality was mild impairment of joint position sense at the left hallux.

It was concluded that he had sustained multifocal cord damage in the cervical and lumbar regions. Psychometric testing 1 month later suggested that there may also have been some cerebral involvement: the verbal IQ was 96, performance IQ 97 (average). There was poor learning ability, poor visual associative reasoning and mild impairment in visual perceptual-motor ability suggesting some deterioration in right hemisphere function.

Case 6

In February 1979 a 29-year-old professional diver made an emergency ascent from a depth of 100ft. This was followed by a surface decompression procedure at the end of which he de-

veloped a dull ache around the left elbow joint which persisted for about 12 hours. On the following day while on board a jet at 36,000ft, he developed paraesthesiae in the left hand which persisted until the end of the flight. He dived on the following day and 1 hour after his last dive, he again developed pain in the left elbow and around the waist, and numbness around both ankles. Therapeutic recompression led to a resolution of his symptoms but the pain recurred on leaving the decompression chamber. The procedure was therefore repeated and he was left with only a mild intermittent pain in the left elbow and wrist and subjective sensory disturbance over the front of the right leg.

Neurological examination in April 1979 showed mild loss of dexterity of the dominant right hand, instability when standing on the right leg, and increased deep tendon reflexes in the right leg with no other significant abnormalities. It was concluded that he had suffered mild spinal cord damage in the cervical region as well as a 'limb bend' in view of the pain in the left elbow joint.

Discussion

Of the 6 cases, 2 were professional deep sea divers, while the other 4 cases were casual scuba divers. This distinction is of some relevance as the risk of decompression sickness may well be different in the 2 groups. First, it is known that decompression sickness is less likely to occur in those who dive regularly. On the other hand, repeated dives within 24 hours (as in Cases 2 and 3) are known to increase the likelihood of decompression sickness. Secondly, poorly controlled rates of ascent favour the development of decompression sickness and are more likely to occur in inexperienced casual divers than in professionals (Pearson and Leitch, 1979).

The time of onset and subsequent evolution of neurological symptoms in the present cases was variable. In Case 3 paralysis of the legs had developed by the time he reached the surface, while in Cases 1, 2 and 4, symptoms developed within a few minutes, and in Cases 5 and 6, 30 to 60 minutes after completion of the last dive. This is in accord with previous reported series in which most cases of decompression sickness presented within 6 hours of the dive, although a minority were delayed for up to 24 hours or even longer (Edmonds et al., 1981). The evolution of symptoms in Cases 1, 2, 5 and 6 was of particular interest. In Cases 1, 2 and 5 the development of the myelopathy was biphasic, while in Cases 5 and 6, new symptoms developed during the course of a jet flight, presumably because of exposure to subatmospheric pressures.

The present cases illustrate a number of anatomical features of the myelopathy associated with decompression sickness. As pointed out by previous authors (Haymaker, 1957; Aita, 1972; Edmonds et al., 1981) the spinal cord may be affected at various levels but the cervical and thoracic regions are most frequently involved, the brunt of the damage falling upon the lateral and posterior columns. In Cases 1 to 4, the clinical findings pointed to a localised area of involvement in the mid- or lower thoracic cord, while in Cases 5 and 6, focal involvement at more than one level seemed likely. Of interest in Cases 4 and 5 was the finding of ipsilateral impairment of spinothalamic (pain and temperature) and posterior column (vibration and tactile) sensory functions in the same limb, suggesting a lesion in the dorsal root entry zone over a number of segments.

In some cases, segmental pain or paraesthesiae were a feature and again suggested involvement of sensory fibres in the root entry zone, although the possibility of radicular involvement could not be excluded.

Conclusion

The present cases indicate that the prognosis for functional recovery after spinal decompression sickness is optimistic following the institution of therapeutic recompression/decompression regimes. However, the findings in Cases 1, 2 and 3 who were re-examined after intervals of 3.25 to 7 years, show that recovery is not necessarily complete and that contrary to previous statements in the literature (Aita, 1972), there may be permanent neurological sequelae. Moreover, an unexpected degree of permanent cord damage involving the lateral and posterior columns was found in Case 1 who died from an unrelated cause 3.5 years after the acute episode. Similar neuropathological findings were described by Haymaker (1957).

Decompression sickness is thought to be caused by the liberation of gas bubbles from a soluble phase into the body tissues and fluids (Edmonds et al., 1981). Other factors which may play a part include air embolism, when pulmonary barotrauma and alveolar rupture occurs, coalescence of lipid macromolecules and formation of lipid emboli, hypovolaemia, platelet aggregation and release of vasoactive amines (Elliott and Hallenbeck, 1975). Although the development of spinal cord lesions has been attributed to venous obstruction by coalescing bubbles by some workers (Hallenbeck et al., 1973; Cockett et al., 1979), the pathological findings in man (Slager, 1968) and in experimental decompression sickness in the goat (Palmer et al., 1976, 1978) suggest that intra-arterial bubble formation and arterial micro-embolism are the major factors responsible. The findings in the present cases are quite compatible with the effects of arterial insufficiency on the spinal cord. The maximal site of involvement in the mid- or low thoracic region of the cord in 4 of the present cases, suggests a critical reduction in spinal cord blood flow with maximal effects on these watershed areas of the cord which constitute arterial border zones (Zülch and Schumacher, 1970). A comparable distribution of lesions within the watershed regions of the cord was found in the experimental model of decompression sickness in the goat (Palmer et al., 1976).

Summary

Four scuba divers and 2 professional deep sea divers developed spinal cord symptoms due to decompression sickness. Symptoms developed during or immediately after ascent in 4 cases and were delayed in 2. In 2 cases new symptoms appeared during a jet flight. In 4 cases paraparesis was associated with a sensory level in the mid or low dorsal region indicating the thoracic cord as the major site of involvement. In the other 2 cases the clinical findings were suggestive of

combined lesions in the lower cervical and lumbar cord. Therapeutic recompression led to improvement in each case. Three cases who were re-examined after intervals of 3 to 7 years each showed residual corticospinal and minor sensory signs. One of these cases met with a violent death 3.5 years after the acute episode; examination of the cord showed multifocal white matter degeneration in the posterior and lateral columns between C7 and T4 with secondary ascending and descending tract degeneration. The mechanism of spinal cord damage in decompression sickness is discussed.

References

Aita, J.A.: Neurologic manifestations of dysbarism: in Vinken and Bruyn (Eds) Vascular Diseases of the Nervous System, Handbook of Clinical Neurology, Vol. 12, pp.665-676 (North Holland Publishing Co., Amsterdam 1972).

Cockett, A.T.K.; Pauley, S.M.; Zehl, D.N.; Pilmanis, A.A. and Cockett W.S.: Pathophysiology of bends and decompression sickness. Archives of Surgery 114: 296-301 (1979).

Edmonds, C.; Lowry, C. and Pennefather, J.: Decompresion sickness; in Diving and Subaquatic Medicine, pp.103-124 (Diving Medical Centre Publication, Mosman, N.S.W., 1981).

Elliott, D.H. and Hallenbeck, J.M.: The pathophysiology of decompression sickness; in Bennett and Elliott (Eds) The Physiology and Medicine of Diving and Compressed Air Work, 2nd ed. pp.435-455 (Balliere, Tindall 1975).

Hallenbeck, J.M.; Bove, A.A. and Elliott, D.H.: The bubble as a non-mechanical trigger in decompression sickness; in Ackles (Ed) Proceedings of a Symposium on Blood Bubble Interaction in Decompression Sickness, pp.129-139 (Defence Board, Department of National Defence, Toronto 1973).

Haymaker, W.: Decompression sickness; in Lubarsch et al. (Eds) Handbuch der Speziellen Pathologischen Anatomie und Histologie. Nervensystem, pp.1600-1672 (Springer-Verlag, Berlin 1957).

Palmer, A.C.; Blakemore, W.F. and Greenwood, A.G.: Neuropathology of experimental decompression sickness (dysbarism) in the goat. Neuropathology and Applied Neurobiology 2: 145-156 (1976).

Palmer, A.C.; Blakemore, W.F.; Payne, J.E. and Sillence, A.: Decompression sickness in the goat: nature of brain and spinal cord lesions at 48 hours. Undersea Biomedical Research 5: 275-286 (1978).

Palmer, A.C.; Calder, I.M.; McCallum, R.I. and Mastaglia, F.L.: Spinal cord degeneration in a case of 'recovered' spinal decompression sickness. British Medical Journal 283: 888 (1981).

Pearson, R.R. and Leitch, D.R.: Treatment with air or oxygen/nitrogen mixture in decompression illness in the Royal Navy. Journal of the Royal Navy Medical Services 65: 53-62 (1979).

Peters, B.H.; Levin, H.S. and Kelly, P.J.: Neurologic and psychologic manifestations of decompression illness in divers. Neurology (Minneapolis) 27: 125-127 (1977).

Slager, U.: in Minckler (Ed) Pathology of the Nervous System Vol. 1, pp.979-984 (McGraw-Hill, New York 1968).

Zülch, K.J. and Schumacher, R.K.: The pathogenesis of 'intermittent spinovascular insufficiency' ('spinal claudication of Dejerine') and other vascular syndromes of the spinal cord. Vascular Surgery 4: 116-136 (1970).

The Hypereosinophilic Syndrome

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The physiology and function of the eosinophil is poorly understood. It is produced in the bone marrow where it shares a common stem cell with neutrophils and monocytes. Its kinetics are probably similar to those of the neutrophil and the association with allergies and atopic conditions has been recognised since the earliest descriptions of the cell.

A variety of other conditions show eosinophilia including parasitic infections, drug reactions, autoimmune diseases, malignancies, blood dyscrasias and infectious diseases. A rare benign familial eosinophilia has also been reported. After adequate investigation most individuals with eosinophilia are found to have one of the above diseases, but there remains a small group in whom the aetiology cannot be determined. Hardy and Anderson (1968) described these patients with idiopathic eosinophilia and widespread eosinophilic tissue infiltration under the term, the hypereosinophilic syndrome (HES). The review by Chusid et al. (1975) revealed that the cardiovascular, haemopoietic, pulmonary and nervous systems were most often involved with hepatic, dermatological, gastrointestinal and renal abnormalities being less frequently encountered. The syndrome includes a continuum of disease from the asymptomatic patient with skin and heart involvement at one end to the much debated entity of eosinophilic leukaemia at the other (Kazmierowski et al., 1978).

Löffler's endocarditis, disseminated eosinophilic collagen disease, Löffler's syndrome with cardiac involvement, idiopathic eosinophilia and eosinophilic leukaemia are all part of the spectrum of HES.

Chusid et al. (1975) analysed 14 cases, 2 of whom had a peripheral neuropathy presumed to be due to eosinophilic infiltration of peripheral nerves, but no pathological material was reported. Six other patients had symptoms or signs of central nervous system disease including seizures, hemiparesis, spastic quadraparesis, and abnormal EEGs.

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Case Report

A 26-year-old woman was admitted to hospital in March 1981 under the orthopaedic surgeons for investigation of lower limb paraesthesiae and a left foot drop. She had been in good health in the past apart from a 2-year history of asthma. Her sister and son also suffered from asthma.

Three months before admission she developed pins and needles in the outer border of the right root which gradually subsided over a week. She then became aware of a similar disturbance in the left foot which spread into the dorsum and sole, and the lateral aspect of the left calf. A month later she experienced weakness in the left foot which she first noticed when she was unable to depress the clutch while driving her car. The weakness gradually became worse but remained static in the week before presentation. Back, buttocks and posterior thigh pain as well as calf cramps were also troublesome.

She was a healthy-looking young woman with a normal general examination. Neurological abnormalities were confined to the lower limbs, where she displayed severe weakness of the left foot with only a flicker of movement in lateral popliteal innervated muscles, grade 2/5 weakness of the long toe flexors and plantar flexors of the left foot and 4-/5 weakness of the invertors. Proximal power in the left leg and power in the right lower limb were normal. The knee jerks were brisk, the right ankle jerk was preserved and the left absent. Sensory impairment to pain, light touch and temperature was present in sciatic nerve territory on the left and below the mid-dorsum of the foot on the right. There was no thickening of peripheral nerves.

After a normal myelogram she was seen by the neurology service and considered to have a mononeuritis multiplex. Investigations showed a white cell count of 11,000 with 50% eosinophils, an ESR of 11 and a normal multiple biochemical analysis. Hypogammaglobulinaemia was found on one occasion but serum immunoglobulins and complement studies were normal. Urine analysis including examination for casts was negative and a chest radiograph showed some peribronchial thickening but no infiltrates. Electromyography revealed evidence of complete or almost complete denervation in lateral and medial popliteal innervated muscles in the left leg with normal muscle sampling on the right. Right medial and lateral popliteal maximum motor conduction velocities were 39 and 44 msec respectively, the right sural sensory action potential was small and the left absent.

In the bone marrow aspirate there was a normal myeloid/erythroid ratio of 3 : 1 with 19% eosinophilia and absent iron stores. It was suggested that this might be due to a connective tissue disorder or a drug effect.

The significance of the eosinophilia was not fully appreciated, but because of an exacerbation of the patient's asthma she was given a single intravenous dose of hydrocortisone and 3 days later the eosinophilia had fallen to 5% of the total WCC. She was discharged from hospital on a reducing regime of oral prednisolone (given for her asthma) but over the next month there was no improvement in her neurological state and she was therefore readmitted for plasmapheresis. She received eight 3L exchanges over 2 weeks, and over the next 2 months there was a little improvement in the muscle grades in the left foot.

She re-presented in August 1981 with a 6-week history of paraesthesiae in the right sciatic nerve territory accompanied by mild weakness in the right foot. She had also noticed intermittent numbness in a right median distribution and for the previous 2 months had been generally unwell with dyspnoea, weight loss, nausea, anorexia and persistent bloody diarrhoea.

On examination she looked unwell and had numerous splinter haemorrhages under the nails of both hands with vasculitic changes on the soft palate, lips and lateral aspects of the feet. She had a tachycardia, a blood pressure of 100/65, and a loud pericardial friction rub, the remainder of the chest being normal. There was bilateral submandibular and cervical lymphadenopathy but no enlargement of the liver and spleen. The neurological examination was essentially unchanged except for sensory loss in the right sciatic and median nerve territories with some distal weakness in the right foot.

Further investigation revealed a white cell count of 20,800 with 55% eosinophils, an ESR of 26, a mildly raised alkaline phosphatase and lactate dehydrogenase (LDH) but otherwise normal biochemistry. The serum electrophoretic pattern showed increased α-2, β and γ globulins with depressed albumin. The IgE was increased at 615 units/ml ($N < 250$). C3, C4 and total

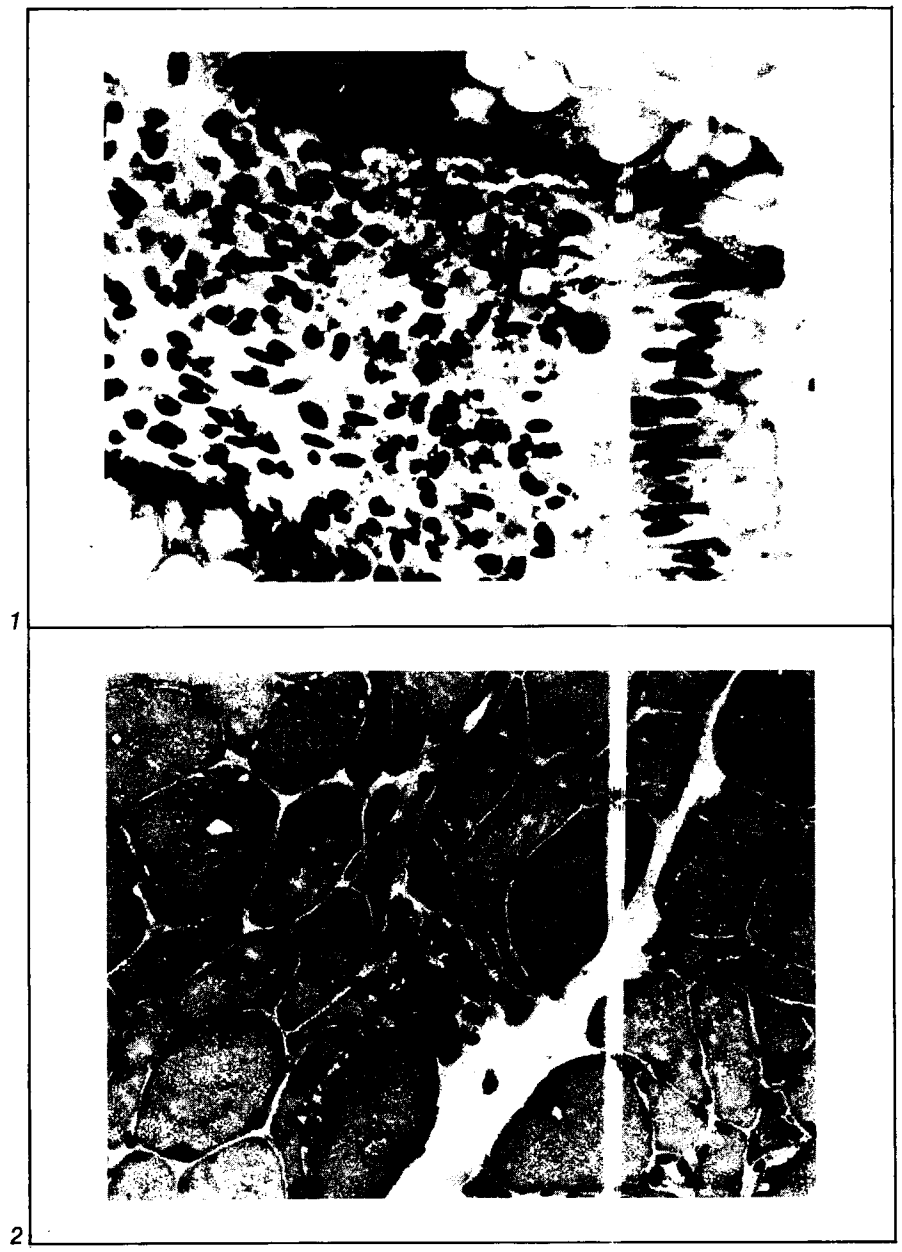

Fig. 1. Eosinophilic infiltration in the rectum. (Haematoxylin and eosin X 940)

Fig. 2. Small group atrophy and scattered small angular fibres in the gastrocnemius. (Haematoxylin and eosin X 750)

haemolytic complement were normal and several cultures of faeces for ova, cysts and parasites were negative. The chest radiograph was also normal, the ECG showing a sinus tachycardia. An echocardiogram showed reduced mobility of the left posterior ventricular wall and it was noted that the pericardium moved with the epicardium indicating adhesions between them.

A radionuclide cardiac scan showed an injection fraction of 37% (N 65 to 83%). Upper and lower gastroenterological endoscopy revealed widespread patchy ulceration in the prepyloric region, duodenal loop, rectum and sigmoid colon with biopsies of these regions showing eosinophilic gastroenteritis (fig. 1).

The patient was treated with 75mg prednisolone daily and within 24 hours the eosinophil count fell to zero. The dose was gradually reduced and at the time of discharge a dose of 40 mg/day maintained the eosinophil count at 1%. The evidence of vasculitis disappeared over 2 weeks, the pericardial friction rub resolved and the gastrointestinal symptoms settled. The cardiac injection fraction increased to 64%. A biopsy of the right gastrocnemius muscle was performed which showed features of mild neurogenic atrophy with scattered small angular fibres and a few foci of small group atrophy (fig. 2). There was no evidence of interstitial inflammation or arteritic change. Studies of the right sural nerve revealed a reduced number of myelinated nerves (2,580 fibres/sq mm) N 6,000 to 10,000) with some fibres showing obvious myelin breakdown associated with axonal degeneration. No interstitial inflammatory infiltrate or arteritis was present (fig. 3).

Following discharge from hospital the steroid dose was gradually reduced to 15 mg/day on an alternate day regimen.

In February 1982 on 30mg prednisolone on alternate days, she developed an erythematous maculopapular facial rash associated with some vesiculation. This responded partially to hydrocortisone cream. In mid-April 1982 on 25mg prednisolone on alternate days the patient had an exacerbation of her asthma with a productive cough of bloodstained sputum which contained

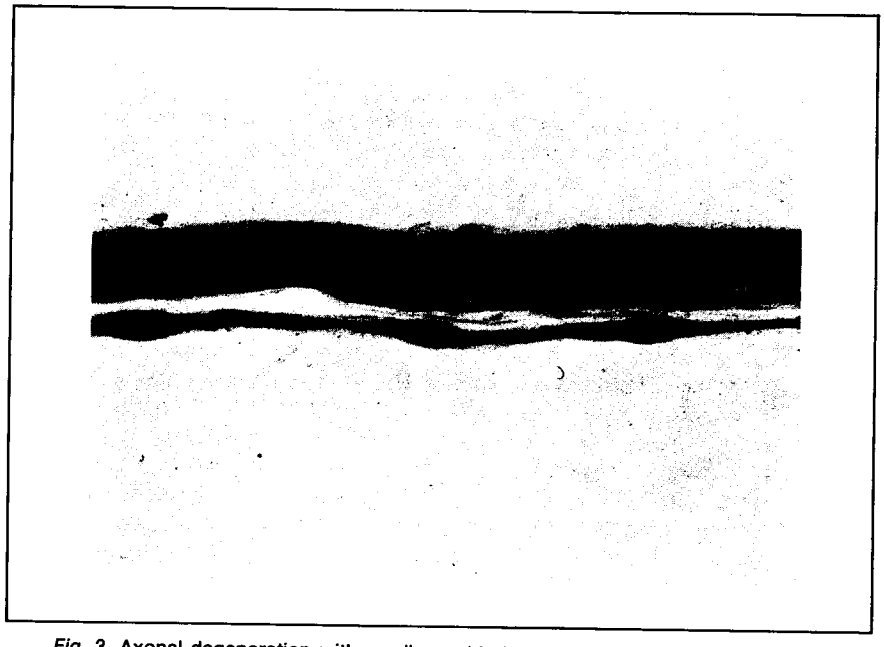

Fig. 3. Axonal degeneration with myelin ovoids in teased fibre preparation of the sural nerve. (Actual mag. 937.5)

numerous eosinophils. The eosinophils had increased to 6% of the total white cell count. The mononeuropathy multiplex has shown a slow but steady improvement.

Discussion

The case under discussion satisfies the criteria for the diagnosis of HES as outlined by Chusid (1975):

1. A persistent eosinophilia of 1500 eosinophils/mm^3 for longer than 6 months, or death before 6 months associated with the signs and symptoms of hypereosinophilic disease.
2. No known cause for eosinophilia.
3. Widespread tissue infiltration with eosinophils.

While the absolute eosinophil values in our patient were not strictly greater than 1500 for 6 months, as there were levels of 650 and 1300 early in the disease, the first occurred within 3 days of intravenous cortisone and the second during plasmapheresis. It is interesting to speculate on the adjunctive role of plasmapheresis in this patient as Ellman et al. (1974) reported a young woman with myocarditis, myositis, vasculitis, and severe eosinophilia following sulfisoxazole, who made no response to steroids but responded dramatically to leukopheresis.

No cause for the eosinophilia was found in our patient and there was definite evidence of eosinophilic infiltration in the gut with probable involvement of the heart, lung, peripheral nerves, and lymph nodes. The combination of asthma, mononeuropathy multiplex and eosinophilia suggests a diagnosis of an arteritis of the polyarteritis nodosa type (PAN).

Fauci (1978) in his review of the spectrum of vasculitis divides the PAN group of systemic necrotising vasculitides into classic PAN, allergic granulomatosis and the overlap syndromes. In classic PAN allergic histories are uncommon as is eosinophilia with tissue infiltration. The absence of hypertension, renal involvement (although no biopsy was performed) and arthralgias would be against this diagnosis in our patient. However, she does share many of the clinical features present in the entity of allergic granulomatosis described by Churg and Strauss (1951). They reviewed the case records and histopathology of 13 postmortem cases, 9 female and 4 male, all of whom presented with severe asthma, fever and eosinophilia and had widespread eosinophilic infiltration of organs. Pathologically the prominent feature was that of a granulomatous reaction in connective tissue and blood vessel walls. Careful search of the vessels and connective tissues in the biopsy specimens of nerve, gut and muscle in the described patient failed to show any inflammatory reaction. Nevertheless, during the acute phase of the patient's illness there was clinical evidence of a vasculitis and while this has not been emphasised as being part of the HES spectrum, in a recent Case Record in the New England Journal of Medicine (1980) of a young woman with asthma and eosinophilic myocarditis there was also presumptive evidence of vasculitis at one stage of her illness.

In the analysis by Chusid et al. (1975) of 14 cases, 1 man who had asthmatic symptoms, pulmonary infiltrates and eosinophilic infiltration of the lung, liver,

lymph nodes and vessels, Churg's granulomatosis was considered to be the most likely diagnosis. Perhaps this disease can also be embraced within the HES spectrum.

The HES shows a male predominance (9 : 1) with a mean age of onset of 38 years. Historically it has been associated with significant morbidity and high mortality figures (Chusid's 3-year survival rate of 12%). Recently, however, Parrillo (1978) in a prospective study of 26 patients, 21 of whom required treatment with steroids or hydroxy urea for progressive disease, reported a 96% 3-year survival rate, even though 12 patients had poor prognostic indicators including a white cell count of 90,000 to 100,000 myeloblasts in the peripheral blood and congestive cardiac failure. Certain characteristics emerged from his study which were found to be of value in predicting responses to steroid therapy. The presence of angioedema, raised serum IgE levels and a prolonged eosinopenic response to a single prednisolone dosage indicate a favourable response to steroids. Our patient demonstrates the latter 2 characteristics and has clearly responded well to prednisolone.

The usual cause of death is cardiac in origin. Fallon (1980) suggests that there are various stages of cardiac involvement with initial eosinophilic infiltration of the myocardium, necrosis of myocytes and possible arteritis followed by formation of mural thrombi in the ventricular outflow areas and later fibrosis of the endomyocardium in the same region.

The role of the eosinophil in cardiac damage is uncertain. Eosinophils in the HES are frequently abnormal showing increased vacuolation and degranulation and a higher percentage have surface receptors for the Fc portion of the IgG molecule (Parrillo, 1978) and therefore might be activated and become more capable of damaging tissue.

Jaski (1978) described a 69-year-old man with a large cell carcinoma of the lung with marked eosinophilia and cardiac dysfunction. The tumour produced an eosinophil chemotactic factor which may have led to alteration in the eosinophils, possibly contributing to their potential for tissue damage.

Summary

The hypereosinophilic syndrome groups together patients with idiopathic eosinophilia and diffuse organ infiltration with eosinophils. It appears to be a continuum of disease from the asymptomatic patient with skin and heart disease at one end to eosinophilic leukaemia at the other.

A case is described of a young woman who presented with asthma, mononeuropathy multiplex and eosinophilia and subsequently developed eosinophilic gastroenteritis, vasculitis and probable myocarditis. The response to prednisolone has been pleasing.

Acknowledgements

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References

Case Records of the Massachusetts General Hospital (Case 18 – 1980). New England Journal of Medicine 302: 1077-1083 (1980).

Churg, J. and Strauss, L.: Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. American Journal of Pathology 27: 277-301 (1951).

Chusid, M.J.; Dale, D.C.; West, B.C. and Wolff, S.M.: The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. Medicine (Baltimore) 54: 1-27 (1975).

Ellman, L.; Miller, L. and Rappeport, J.: Leukopheresis therapy of a hypereosinophilic disorder. Journal of the American Medical Association 230: 1004-1005 (1974).

Fallon, J.T.: Case records of the Massachusetts General Hospital (case 18-1980). New England Journal of Medicine 302: 1077-1083 (1980).

Fauci, A.S.: The spectrum of vasculitis. Clinical, pathologic, immunologic and therapeutic considerations. Annals of Internal Medicine 89: 660-676 (1978).

Hardy, W.R. and Anderson, R.E.: The hypereosinophilic syndromes. Annals of Internal Medicine 68: 1220-1229 (1968).

Jaski, B.E.; Goetzl, E.J.; Said, J.W. and Fishbein, M.C.: Endomyocardial disease and eosinophilia. Circulation 57: 824-826 (1978).

Kazmierowski, J.A.; Chusid, M.J.; Parrillo, J.E.; Fauci, A.S. and Wolff, S.M.: Dermatologic manifestations of the hypereosinophilic syndrome. Archives of Dermatology 114: 531-535 (1978).

Parrillo, J.E.; Fauci, A.S. and Wolff, S.M.: Therapy of the hypereosinophilic syndrome. Annals of Internal Medicine 89: 167-172 (1978).

Concentric Sclerosis

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Concentric sclerosis is a demyelinating disease of the cerebral white matter with a characteristic concentric ring arrangement. From 1928 to 1980, 39 cases had been reported in the literature. Four cases have been observed in China. This paper is a detailed report of 1 of these cases and review of the other 3 cases.

Case Report

The patient, a native of Beijing, was a 40-year-old female teacher. From February 1980, she had been drowsy and confused. On 20.2.80 she was found to have weakness of her right limbs. She laughed inappropriately, made irrelevant comments and spoke repetitively. Subsequently, urinary and faecal incontinence developed. She developed headaches and dysarthria. There was no history of a febrile illness. On 25 and 26.2.80 EEGs showed a slow wave focus in the left anterior temporal region. Echoencephalography on 2 occasions showed no displacement of midline structures. Lumbar puncture revealed a pressure of 160mm water. All other tests done on the CSF were normal. She was admitted to the Capital Hospital on 7.3.80. On examination her temperature was 36.8°C and pulse was 88/minute. Blood pressure was 110/70. She was developed and well nourished. Examination of the head and neck was negative. Heart and lungs were normal. Liver and spleen were not palpable. She was drowsy but easily aroused. She had an incomplete combined type of aphasia. She laughed to herself and spoke stereotypically. Optic fundi were normal. Pupils were equal and reactive to light. No nystagmus was present. Her nasolabial fold was shallower on the right side. There was also a right-sided hemiplegia, hemihypoaesthesia and upgoing plantar response. Abdominal reflexes were not demonstrable and Kernig's sign was negative. There was no neck stiffness. After admission she became more confused, was restless, and vomited twice. She improved after oxygen administration and cerebral dehydrative therapy. Four hours later she suddenly collapsed and died in spite of resuscitative measures.

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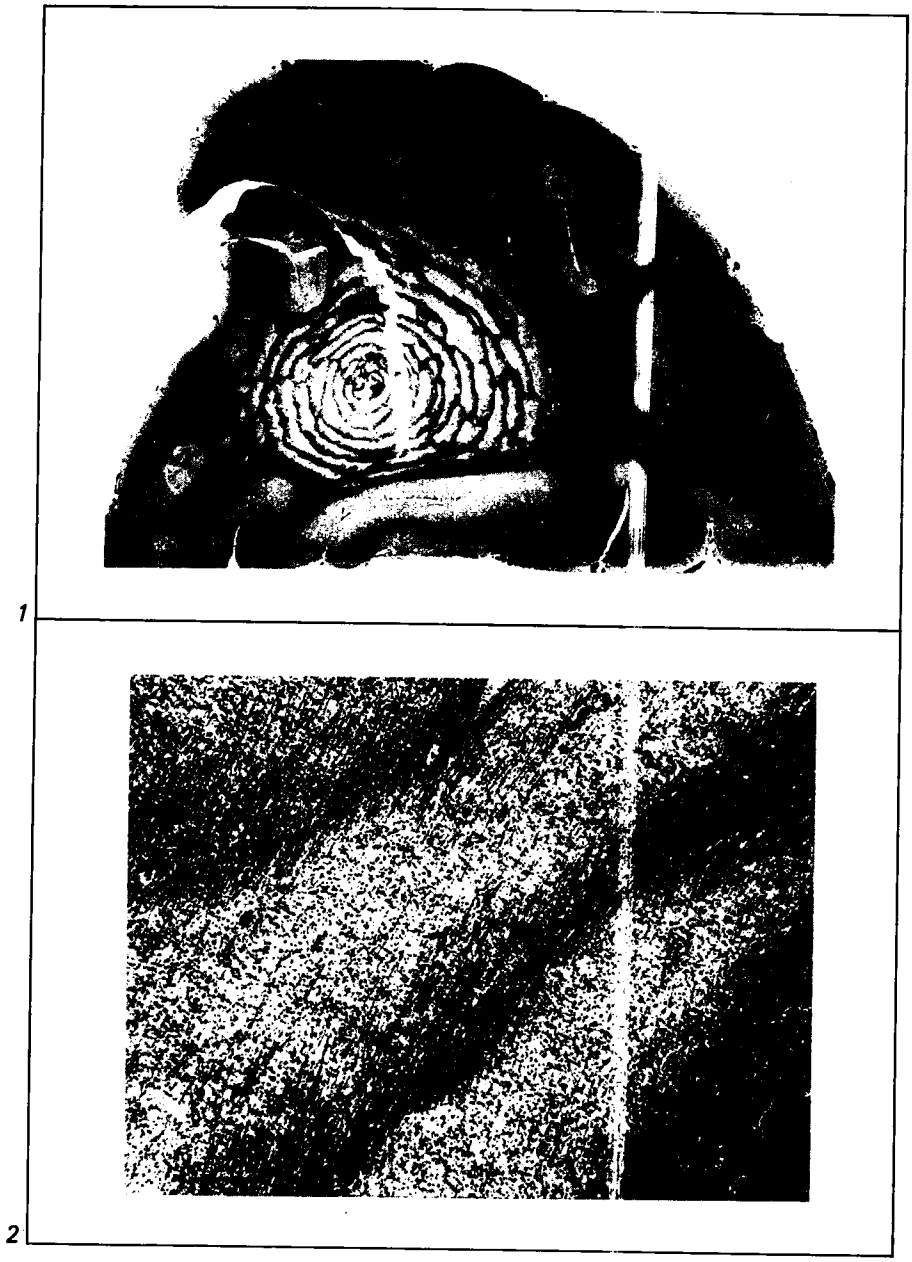

Fig. 1. Concentric sclerosis of white matter of left frontal lobe (Woelcke stain X 1.5).

Fig. 2. Concentric sclerosis of white matter of left frontal lobe (Woelcke stain X 80).

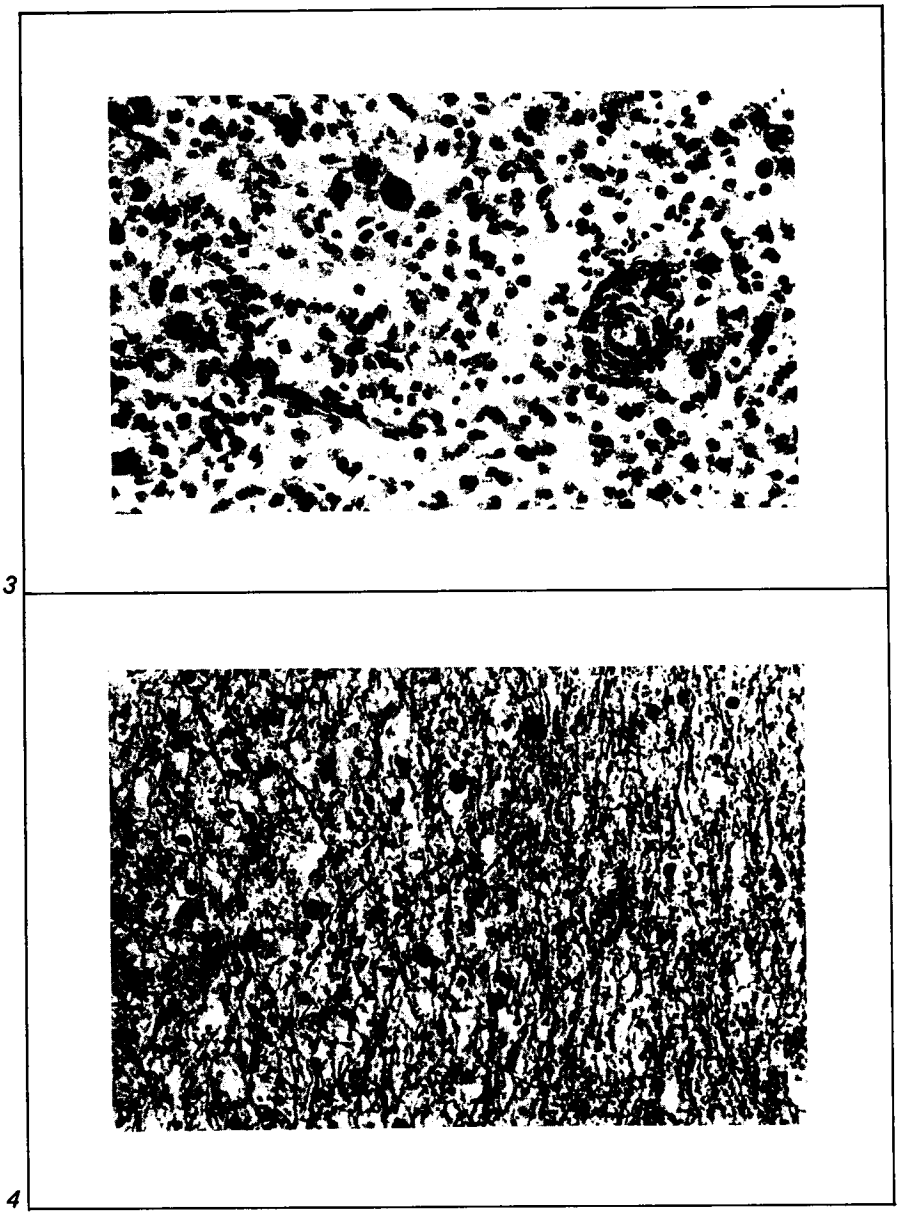

Fig. 3. The demyelinated area of concentric sclerosis showing phagocytes, plump astrocytes and perivascular infiltration with lymphocytes (Nissl stain X 400).

Fig. 4. Concentric sclerosis – left half showing severe demyelination and right half showing relative preservation of myelin. Axis cylinders in both areas were well preserved (Silver impregnation X 400).

Fig. 5. In the relative 'myelin sheath preserved' area of concentric sclerosis showing myelin sheath degeneration, plump astrocytes, loss of oligodendrocytes (embedded in the epoxy resin 618; stained with toluidine blue).

Neuropathological Studies

Postmortem was performed 12 hours after exitus. The brain was fixed in formalin for 2 weeks. Coronal sections were made, and tissues taken and embedded in paraffin and celloidin and stained with Nissl, H + E, van Giesen, Woelcke, Bielschowsky, Cajal and Holzer stains. Sections were also taken from various regions of the white matter and cortex and fixed in 2.5% glutaraldehyde and osmium tetroxide. After washing with buffered barbiturate, they were embedded in epoxy resin. Sections for study by ultramicroscopy were stained with lead nitrite and uranyl acetate and were examined on JEM 100B and H600 electron microscopes. In addition 1μm sections were stained with toluidine blue for light microscopic examination.

Gross Examination

The brain weighed 1332g. The cerebral hemispheres were symmetrical and the cerebral gyri somewhat flattened. There was hyperaemia of the leptomeninges. Bilateral tentorial herniation was evident; more on the left than on the right side. The midbrain was compressed. The cranial nerves and arteries at the base of the brain were normal. The cerebellum and medulla appeared normal.

After sectioning the brain in the coronal plane, concentric rings were evident in the white matter. The concentric rings in the left anterior frontal white matter measured 3.0 x 2.5 x 2.0cm (fig. 1) and on the right side 2.5 x 2.0 x 2.0cm. The rings in the left superior frontal white matter measured 3.5 x 2.5 x 4.0cm and on the left temporal white matter 2.0 x 1.5 x 2.0cm. There was obvious swelling of the brain and the corpus callosum was thickened. The lateral ventricles were small, and the third ventricle was merely a narrow slit and was displaced by about 0.5cm to the right side. The abnormal white matter was softened. There was no hyperaemia or haemorrhage. The cerebellum and brain stem appeared normal.

Light Microscopy

The leptomeninges and subarachnoid space showed a mild degree of perivascular infiltration by lymphocytes and plasma cells. The cerebral cortex was normal. There was no obvious change in the cortical neurones. In the white matter, the concentric rings were related to alternating bands of complete demyelination and partial preservation of myelinated fibres (fig. 2). In the demyelinated bands, the oligodendrocytes were lost or markedly reduced in number and

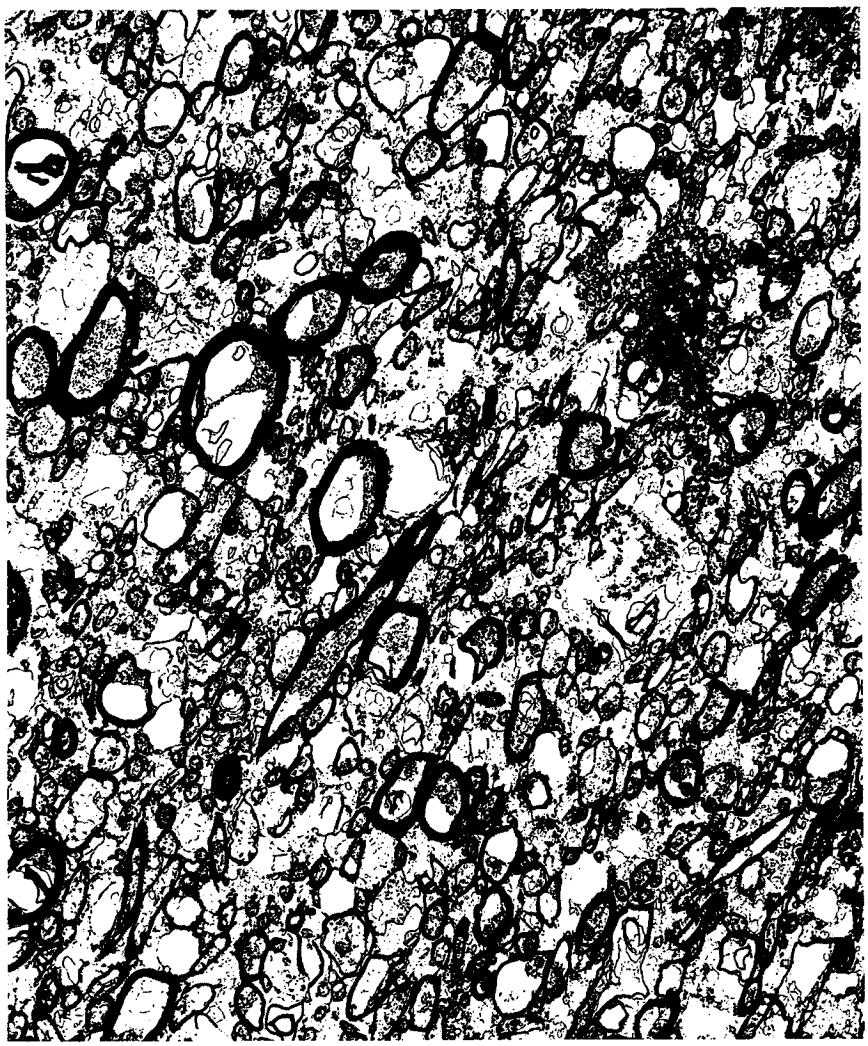

Fig. 6. Apparently unaffected white matter of right frontal lobe, showing preservation of myelin sheaths and vacuolation in axis cylinder (embedded in epoxy resin 618; stained with lead nitrate and uranyl acetate X 3000).

myelin sheaths were broken down. Together with the demyelination there were accumulations of large numbers of phagocytes and scattered plump reactive astrocytes (fig. 3). Around the small vessels, there were lymphocytic infiltrates and Cajal stains revealed protoplasmic astrocytes. Holzer stain showed no gliosis. Silver impregnation methods showed some tortuous but generally well-preserved axis cylinders (fig. 4). In the bands where the myelinated fibres were relatively well preserved, oligodendrocytes were reduced in number, but astrocytes were more abundant (fig. 5) and myelin sheaths were swollen. There was perivascular lymphocytic infiltration but no phagocytic response. In the white matter without the concentric rings, myelinated fibres and oligodendrocytes showed no significant change. However, lymphocytic infiltration around small vessels was present and some even formed perivascular cuffs. No inclusion bodies were seen in the cortical neurones or in oligodendrocytes of the white matter with and without concentric rings. Apart from perivascular lymphocytic infiltrates, no abnormalities were seen in the cerebellum, midbrain, pons and medulla. Some ischaemic change was noted in the neurones of the Sommer's sector of Ammon's horn. The cerebral aqueduct, choroid plexus and ependymal lining were normal.

Electron Microscopic Findings

In the white matter without concentric rings, the structure of the myelin sheaths remained intact (figs 6,7). The nuclear membrane of oligodendrocytes was well demarcated but the cytoplasm was hyperchromatic and vacuolated. The fine cytoplasmic organelles were partially lost. Some myelin sheaths showed degeneration.

In the white matter with concentric rings, changes were very characteristic, particularly where the band of myelin was preserved:

a) Myelin sheath degeneration without distinct thickening of lamellation and irregular contraction of the sheaths. Vacuoles were found inside axis cylinders (fig. 8).

b) Degeneration of oligodendrocytes with splitting of the lamellae at the periphery.

c) Fragments of myelin sheaths were found in the cytoplasm of phagocytes (fig. 9). Some phagocytes had processes extending into the myelinated fibres.

d) Endothelial cells of small blood vessels became hyperplastic causing narrowing of the lumen and thickening of the basal lamina.

Discussion

Concentric sclerosis is a rare disease with unusual but characteristic pathological changes. Balo in 1928 first observed the pathological picture in a man of 23 years, who died 14 weeks after the onset of symptoms, and named the condition 'concentric periaxial encephalitis'. The name of concentric sclerosis was given by Hallervorden and Spatz in 1933. Courville (1975) analyzed 36 cases collected from the literature, and stated that only 20 of these could be diagnosed as concentric sclerosis, while the others were cases of disseminated and diffuse sclerosis.

From 1928 to 1980, 39 cases of concentric sclerosis have been reported in the literature. Four cases have been observed in China and their clinical and pathological features are listed in table 1 (Lin and Liu, 1980; Zhou, 1981). The

Fig. 7. Same as fig. 6 but magnified X 80,000.

Fig. 8. Same as fig. 5 showing degeneration of myelin sheaths (X 14,400).

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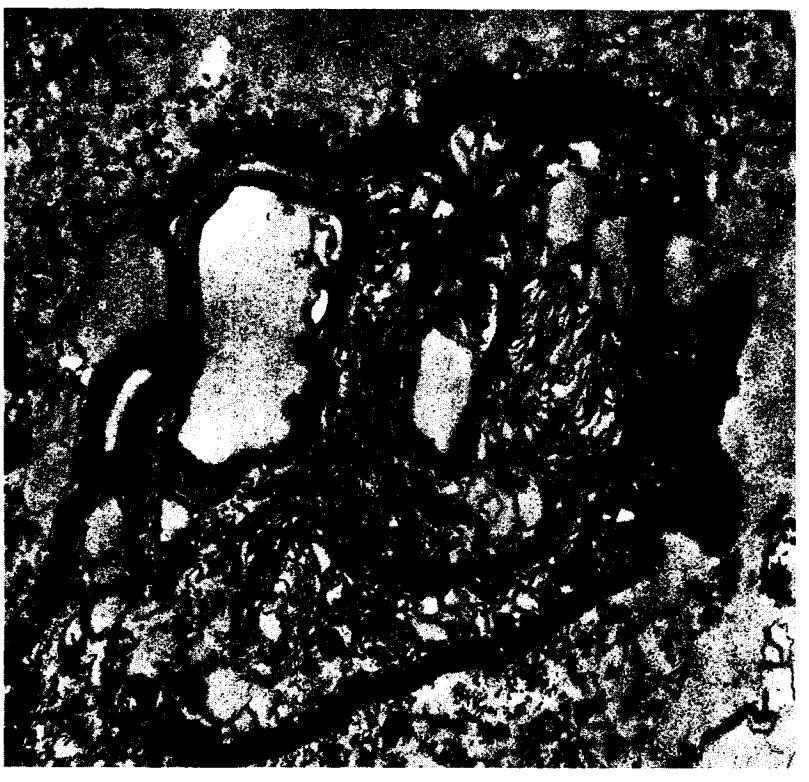

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age of onset ranges from 24 to 40 years. The principal features were: drowsiness, altered mental state, stupor, hemiplegia with or without aphasia, pyramidal signs, and urinary and faecal incontinence. The intracranial pressure as measured at lumbar puncture was normal. In the CSF, there were 6 to 8 leucocytes/cm. Other CSF investigations were normal. These patients died within 20 to 70 days after the onset of symptoms. Clinical features, such as the acute or subacute onset and short course of the disease were similar to those reported by Courville (1975).

Concentric rings of demyelination in the white matter of these 4 cases were evident at postmortem. This concentric ring pattern is the hallmark of the disease and arises as the result of alternating bands of demyelination and preservation of the myelin sheaths. In the demyelinated band, the axis cylinders are mildly affected and there is accumulation of a large number of phagocytes. The oligodendrocytes are reduced or lost. A small number of plump astrocytes are present. There is perivascular infiltration with lymphocytes and plasma cells. No gliosis is seen. In the dark (preserved) band of concentric rings the myelin sheaths appear to be normal by light microscopy. However, as shown here, perivascular infiltration, increased numbers of astrocytes and reduced numbers of oligodendrocytes can be observed. Changes in the myelin sheaths can be seen by electron microscopic examination. The presence of these changes in alternating degenerative bands and preserved bands of myelinated fibres appears to be quantitative rather than qualitative. The more severe effect on the myelin sheaths rather than on axis cylinders indicates a demyelinating process. It is possible that Balo's

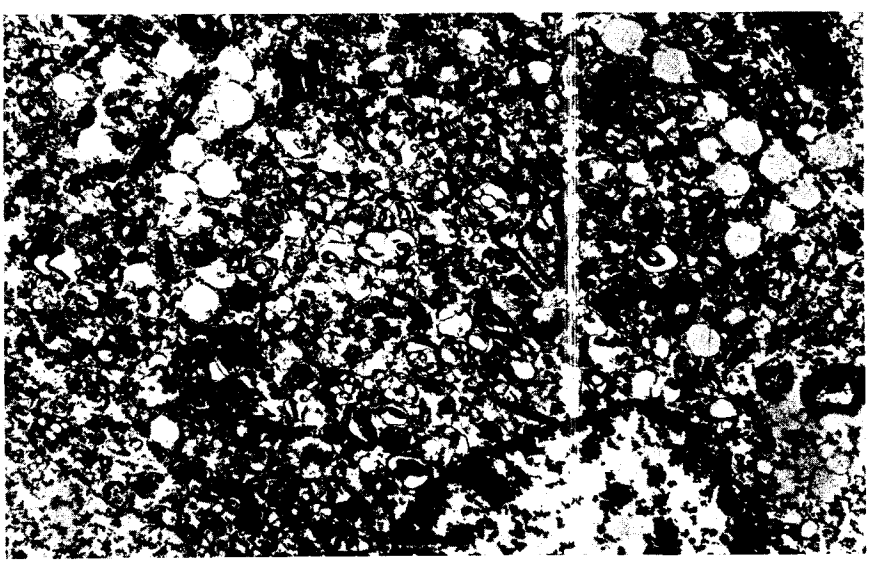

Fig. 9. Severe demyelinated area of concentric sclerosis showing severe demyelinated area with many phagocytes, much (engulfed) phagocyted material containing pieces of degenerated myelin (X 20,000).

Table I. Summary of clinical and pathological findings in concentric sclerosis

Case (No.)	Sex	Age (years)	Duration of illness (days)	Symptoms and signs	Pathological findings
1	F	40	31	Drowsiness, altered mental state, right hemiplegia with aphasia, urinary incontinence	Concentric rings of demyelination in the white matter of both cerebral hemispheres
2 (3)	F	40	70	Common cold, drowsiness, altered mental state, stupor, urinary incontinence, decerebrate rigidity, bilateral pyramidal tract signs	
3 (3)	M	24	20	Drowsiness, altered mental state, right hemiplegia with dysphasia, bilateral pyramidal tract signs	
4 (4)	F	40	50	Drowsiness, altered mental state, urinary incontinence, confused decerebrate rigidity	

disease is a variant of disseminated sclerosis of the acute type (Curie et al., 1970; Lewis, 1976; Oppenheimer, 1976; Lin and Liu, 1980; Harper, 1981).

With regard to the pathogenesis of the condition, inclusion bodies were not found by light microscopy, and viral particles were not detected by electron-microscopy. The fact that there is marked degeneration of myelin sheaths and reduced numbers of oligodendrocytes in the white matter of both bands of relatively intact and demyelinated concentric rings, suggests that oligodendrocytes could be the cells primarily affected. This is followed by degeneration of myelin sheaths and phagocytosis which is the same type of histopathological process (Lewis, 1976) as seen in disseminated and diffuse sclerosis. The acute onset, rapid progress and the severe changes in the myelin sheaths in this disease all suggest an ischaemic or anoxic tendency to which oligodendrocytes are especially sensitive (Courville, 1964). It remains to be seen whether this effect on the oligodendrocytes could lead to development of concentric sclerosis.

References

Balo, J.: Encephalitis periaxiales concentrica. Archives of Neurology and Psychiatry 19: 242 (1928).

Courville, C.B.: Concentric sclerosis; in Vinken and Bruyn (Eds) Handbook of Clinical Neurology, Vol. 9, pp.437-451 (North Holland Publishing Company, Amsterdam 1975).

Courville, C.B.: Pathogenesis of concentric ring formation of Balo's concentric sclerosis. Journal of Neuropathology and Experimental Neurology 23: 205 (1964).

Curie, S.; Roberts, A.H. and Urich, H.: The nosological position of concentric lacunar leukoencephalopathy. Journal of Neurology, Neurosurgery and Psychiatry 33: 131-137 (1970).

Grcevic, N.: Concentric lacunar leukoencephalopathy. Archives of Neurology 2 (3): 226-273 (1960).

Hallervorden, J. and Spatz, H.: Über der konzentrische sklerose und die physikalisch-chemischen Faktoren bei der Ausbreitung von Entmarkung-sprozessen, Archiv für Psychiatrie und Nervenkrankheiten 98: 641-701 (1933).

Harper, C.G. (Ed): Acute central nervous system disorder mimicking stroke. Medical Journal of Australia: 136-138 (1981).

Lewis, A.J.: Mechanisms of Neurological Disease pp.402-406 (Little Brown and Company, Boston 1976).

Lin, S.H. and Liu, D.-S.: Concentric sclerosis. Journal of Diseases of the Nervous System and Psychiatry 6 (1): 1-6 (1980).

Oppenheimer, D.R.: Demyelinating diseases, in Blackwood and Corsellis (Eds) Greenfield's Neuropathology, 3rd ed, pp.479-480 (Edward Arnold Publishers Ltd, London 1976).

Zhou, J.M.: Concentric sclerosis. Chinese Journal Neurology and Psychiatry 13 (2): 114, 1981.

Amoebic Meningitis Also Occurs in NSW

*P.G. Procopis, J. Stuart and A. Kan**

Although primary amoebic meningo-encephalitis was first described in Australia in 1965 (Fowler & Carter, 1965) the condition has not previously been described in New South Wales.

Case Report

A 3-year-old boy presented to the Manning River District Hospital with a 2-day history of abdominal pain, nausea and fever which progressed to drowsiness, anorexia and vomiting. On admission he was noted to be febrile, drowsy and had neck stiffness. Examination of the CSF showed 1200 white cells/mm^3 of which 90% were polymorphonuclear. The glucose was 4.6 was 4.6 μmol/L, and protein 2.1 g/L. No organisms were present on Gram stain and no growth occurred subsequently on routine culture. Treatment began with intravenous ampicillin. The next day, however, his condition was worse and chloramphenicol was added to the treatment regimen. The next day episodes of opisthotonos, intermittent apnoea and some convulsive movements occurred. He was given mannitol and a loading dose of phenytoin intravenously and transferred to the Royal Alexandra Hospital for Children, Sydney.

On arrival, he was unconscious, unresponsive to painful stimuli, and was hyperventilating. The right pupil was larger than the left but both reacted to light. The optic fundi were normal. No focal neurological signs were present.

Blood gases indicated a compensated metabolic acidosis. Serum electrolytes were compatible with the syndrome of inappropriate antidiuretic hormone secretion, the sodium being 121 mmol/L, serum osmolality 280 mOsm/kg and urine osmolality 490 mOsm/kg.

During a CT scan he had a cardiac arrest from which he was successfully resuscitated. Treatment was started with vidarabine. Suspected intracranial hypertension was treated with hyperventilation after curarisation, dexamethasone and intermittent mannitol. A ventricular catheter was inserted for intracranial pressure monitoring and a brain biopsy was performed at the same operation. No evidence of Herpes simplex encephalitis was found on immunofluorescence or histological examination of the biopsy.

His condition continued to deteriorate and he died 4 days after the onset of the illness.

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CT Scan

The CT scan findings in this case have been previously described (Lam et al., 1982) and consisted of obliteration of the ambient, interpeduncular and quadrigeminal cisterns but with marked enhancement of these cisterns after administration of intravenous contrast medium. There was also marked contrast enhancement of the sulci and adjacent grey matter.

EEG Findings

The EEG (fig. 1) showed marked bilateral slowing but with high voltage periodic sharp waves with areas of suppression after the sharp waves in the left temporal region. These conformed to the pattern of periodic lateralised epileptic discharges. Because of this finding Herpes simplex encephalitis was suspected.

Postmortem Findings

Macroscopically the brain showed mild swelling and meningeal exudate. The exudate was most obvious over the ventral surface of the brain stem and the inferior aspect of the cerebellum. Histologically, pyogenic meningitis with inflammation of the superficial cortex and focal cortical necrosis was present. Numerous organisms morphologically identical to the amoeba *Naegleria fowleri* were present in the meninges, superficial brain substance and fourth ventricle. Amoebae were also present in perivascular spaces deep in the cerebral cortex without any inflammatory reaction. The amoebae gave a positive reaction to immunofluorescent staining to a titre of 1:1024 against the 'Morgan' strain of *N. fowleri.*

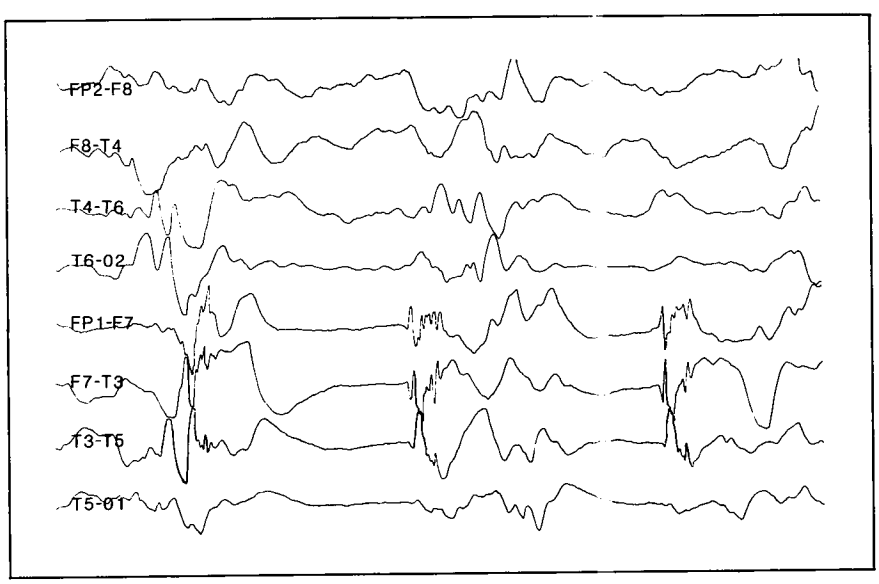

Fig. 1. EEG showing bilateral slowing and periodic lateralised epileptiform discharges over the left temporal region.

Epidemiological Study

Four days before becoming ill, the child had been swimming in a pool in a town outside Sydney. Water samples from the pool and filter were examined and strains of amoebae identified as *Naegleria fowleri* were isolated from both the pool and filter water. Similar organisms were also isolated from the river from which the town water was drawn.

Discussion

Since the original description of acute amoebic meningo-encephalitis in South Australia by Fowler and Carter in 1965, over 100 cases of the disease have been described from all over the world. The disease is contracted by swimming in contaminated water and the amoebae are believed to reach the brain via the nasopharynx and olfactory fibres. The CSF shows changes of acute pyogenic meningitis but without any organisms being identifiable on Gram stain and no growth occurs on culture. If the disease is suspected, however, the amoebae may be seen on microscopy of fresh, unrefrigerated CSF.

The EEG changes in this condition have not been previously described. Most of the cases in the Adelaide series did not have EEGs (Carter, R.F., personal communication, 1981) although one recent case showed severe generalised changes with no focal features (Manson, J., personal communication, 1981). The changes in the present case indicated acute cortical infarction and for this reason a clinical diagnosis of Herpes simplex encephalitis was strongly considered.

The CT scan changes indicated an acute inflammatory reaction of the cerebral cortex and basal arachnoiditis. These findings have been reported in detail elsewhere (Lam et al., 1982).

Most reported cases of primary amoebic meningo-encephalitis have been fatal, although 4 patients who have recovered from the illness have been described. All these cases have been treated with amphotericin-B and the most recent patient was treated with miconazole and rifampicin as well (Seidel et al., 1982). Such reports of successful treatment underline the necessity for suspecting the disease and undertaking specific examination of fresh CSF in cases of pyogenic meningitis when no organisms are isolated. This applies particularly during the summer months.

Summary

The clinical, pathological and laboratory findings of a 3-year-old boy with proven primary amoebic meningo-encephalitis are described. The EEG showed changes of acute cortical necrosis lateralised to one temporal lobe and was similar to that described with Herpes simplex encephalitis. CT scan findings indicated acute cortical inflammation and basal arachnoiditis. The disease should be suspected in the context of acute pyogenic meningitis when no organisms are isolated. Treatment with amphotericin-B, miconazole and rifampicin has been effective in previously reported patients.

Acknowledgements

Miss M. Nugent and Mrs D. Buckley gave invaluable technical assistance.

References

Fowler, M. and Carter, R.F.: Acute pyogenic meningitis probably due to *Acanthamoeba* sp.: a preliminary report. British Medical Journal 2: 740-742 (1965).

Lam, A.H.; De Silva, M.; Procopis, P.; and Kan, A.: Primary amoebic (Naegleria) meningo-encephalitis. Journal of Computer Assisted Tomography 6: 620-623 (1982).

Seidel, J.S.; Harmatz, P.; Visvesvara, G.S.: Cohen, A.; Edwards, J. and Turner, J.: Successful treatment of primary amoebic meningo-encephalitis. New England Journal of Medicine 306: 346-348 (1982).

Encephalitis in Infectious Mononucleosis

*D.H. Todman**

Infectious mononucleosis has been associated with a wide range of nervous system complications including encephalitis, meningitis, optic neuritis, transverse myelitis, Bell's palsy and polyneuritis. Generally the encephalitis associated with infectious mononucleosis is a relatively benign, self limited disorder and while fatal cases have been recorded the prognosis for full recovery is good. The onset of neurological symptoms is usually at the height of the infection and associated with the fever, lymphadenopathy and pharyngitis which are the cardinal systemic manifestations of the disease. However, on occasions the encephalitis may be the heralding or sole manifestation of infectious mononucleosis (Silverstein et al., 1972).

While it has long been assumed that infectious mononucleosis is a viral infection, it is only comparatively recently that the link with Epstein-Barr virus has been established. Epstein, Achong and Barr (1964) identified particles resembling herpes virus in tissue cultures of biopsies from patients with Burkitt's lymphoma. An indirect immunofluorescent antibody to this virus was subsequently developed by Henle and Henk (1966) who detected high antibody titres in patients with Burkitt's lymphoma and also infectious mononucleosis. Epidemiological studies of seroconversion have confirmed Epstein-Barr virus as the aetiological agent in infectious mononucleosis, though its role in the pathogenesis of Burkitt's lymphoma is uncertain.

A positive Paul-Bunnell-Davidsohn (PBD) test is strong presumptive evidence of infectious mononucleosis and false positive titres are rare. The PBD test is frequently negative in children, however, and in about 10% of adults with infectious mononucleosis (Carter and Penman, 1969). Specific Epstein Barr virus serology detecting various virus related antibodies is a more reliable guide to infection with this agent and may allow a definite diagnosis to be made in cases with a negative PBD test.

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Table I. Serological tests for infectious mononucleosis, including specific Epstein-Barr virus antibody titres in paired sera and in CSF

Test	Case 1	Case 2	Case 3
Paul-Bunnell-Davidsohn	Negative	Negative	Negative
VCA-IgG acute	80	320	160
convalescent	640	640	640
VCA-IgM acute	80	160	80
convalescent	80	80	40
Spinal fluid VCA-IgG	10	10	10
EA (Anti-D) acute	160	80	80
convalescent	10	10	10
EBNA acute	0	0	0
convalescent	10	10	10

VCA = viral capsid antigen; EA = early antigen; EBNA = Epstein-Barr nuclear antigen.

The present study analyses 3 adult cases of presumed encephalitis complicating infectious mononucleosis in which the PBD tests were negative and the diagnosis was established by specific Epstein-Barr virus serology.

Methods

The patients were investigated and treated at the Department of Neurology, Royal Brisbane Hospital. The PBD test and determination of specific IgG and IgM to viral capsid antigen (VCA) and antibodies against early antigen (EA anti-D) and Epstein-Barr nuclear antigen (EBNA) were performed as described elsewhere (Lennette and Schmidt, 1979).

Case Reports

A summary of the serological studies is presented in table I.

Case 1

An 18-year-old student was brought to the hospital emergency department in a deeply unconscious state with a high fever. Two weeks earlier he had developed symptoms of sore throat and neck ache associated with cervical lymphadenopathy and despite a negative PBD test at this time the illness was regarded as infectious mononucleosis and he was treated symptomatically. The symptoms settled in 7 days. However, after 10 days he complained of lethargy and headaches and on the day prior to admission a tonic-clonic seizure was observed. A blood film revealed 22% atypical lymphocytes in a total white cell count of 9.2 x 10^9/L, while lumbar spinal fluid examination showed a normal opening pressure, 30 mononuclear leukocytes/mm^3 and a protein of 0.63 g/L. The electroencephalogram demonstrated diffuse high voltage delta activity with loss of normal rhythms, and a CT head scan was normal. Phenytoin and dexamethasone were administered and an improvement in his conscious state followed within 48 hours. One week after presentation there was no evidence of any neurological deficit.

Case 2

A 25-year-old school teacher was referred because of cerebellar ataxia. Ten days earlier she experienced myalgia with a low grade fever and headache. Five days after the onset, marked incoordination of gait with vertigo and dysarthria developed. Clinical examination confirmed the signs of cerebellar ataxia. However, there were no other neurological signs and no fever, pharyngeal infection or lymphadenopathy. A blood film examination was normal and an electroencephalogram showed a diffuse excess of theta activity with some retention of normal rhythms. The lumbar spinal fluid pressure was normal and analysis revealed 20 mononuclear leukocytes/mm^3 and a protein concentration of 0.61 g/L. A CT head scan revealed no abnormality. The symptoms of ataxia and vertigo lasted for 2 weeks and were followed by complete recovery with supportive treatment only.

Case 3

A 47-year-old truck driver was hospitalised because of a 2-week history of fever, mental confusion and frontal headaches suggestive of raised intracranial pressure. Physical examination revealed a low grade fever, nuchal rigidity and papilloedema but no palatal enanthem or lymphadenopathy. A blood film examination was normal and an electroencephalogram showed a generalised excess of theta activity. The spinal fluid opening pressure was 30cm of CSF and the fluid contained 95 mononuclear leukocytes/mm^3 and a protein concentration of 1.02 g/L. A CT head scan was normal. Although the headache and confusion resolved spontaneously, a low grade fever and papilloedema persisted for 6 weeks. There was no deterioration in visual acuity and complete recovery eventuated.

Discussion

Epstein-Barr virus infection results in the synthesis of serum antibodies directed against a variety of viral antigens, as well as against unrelated antigens found on sheep, horse and beef red cells. The latter are known as heterophile antibodies and lead to sheep or horse red cell agglutination, the basis of the PBD test. There is no cross reactivity between heterophile antibodies and specific antibodies for Epstein-Barr virus.

Approximately 90% of adults with infectious mononucleosis documented by conversion of Epstein Barr virus titres will have a positive PBD test by the end of the third week of illness. The test usually remains positive for 2 to 3 months, though rarely it may be positive for up to a year. A large percentage of children, as well as 10% of adults, will not demonstrate heterophile antibodies throughout the course of the infection (Carter and Penman, 1969).

Epstein-Barr virus antibody titres provide a reliable guide to infection with this agent and may be indicated in heterophile-negative cases and for diagnosis in atypical cases. Antibodies to VCA arise early in the course of infection and are detectable at presentation in the majority. High titres of IgG-VCA are usually present in the first blood sample and a greater than fourfold increase in titre is demonstrable in less than 20%. A significant titre of IgG-VCA persists for life and, unlike the heterophile antibody, a positive serology frequently represents remote past infection. Specific IgM antibodies to VCA are sensitive and specific for infectious mononucleosis, and are generally detected at the time of clinical presentation and remain for an average of 4 months after diagnosis (Evans et al., 1975). Measurement of antibodies against an early antigen, anti-D or anti-R (antigens expressed only during the phase of rapid viral replication), are also

very sensitive though they are difficult to perform and are used mainly as research tools (Henle et al., 1971). Antibodies to EBNA appear late in the course of all cases of infectious mononucleosis and persist for life (Henle et al., 1974).

The 3 cases presented had positive serological evidence of infectious mononucleosis despite negative PBD tests. The detection of VCA-IgM antibodies in the first serum samples, the decreasing EA antibody titres and the development of antibodies to EBNA were diagnostic of a recent infection with Epstein-Barr virus. Evidence of low titres of IgG-VCA in the spinal fluid is consistent with neurological involvement in infectious mononucleosis (Joncas et al., 1974).

The 3 cases described are characteristic of the course of encephalitis that complicates infectious mononucleosis, in that despite the severity of symptoms the prognosis for full recovery is usually good. The mortality and residual morbidity in a large series are reported to be less than 8% and 12% respectively (Carter and Penman, 1969). The encephalitis commonly manifests with cerebellar involvement (Bejada, 1976) as illustrated in Case 2, but may also be global. A precise incidence of encephalitis in infectious mononucleosis is difficult to define though estimates have ranged from 0.37% (Silversides and Richardson, 1950) to 26.5% (Pejme, 1964). The latter study used abnormal CSF parameters as the criterion for diagnosis. Patients with infectious mononucleosis and abnormal CSF findings may have no clinical neurological abnormalities, however. Silverstein et al. (1972) found a 5.5% incidence of clinical neurological involvement in patients hospitalised with various complications of infectious mononucleosis.

A number of authors have suggested that central nervous system disease is not uncommon as the sole or major manifestation of infectious mononucleosis (Bernstein and Wolff, 1950; Silverstein et al., 1972). Similar claims have been made for polyneuritis and Bell's palsy in young patients (Michel et al., 1975). Silverstein et al. (1972) reviewed 15 patients with neurological involvement as the major manifestation of infectious mononucleosis, 10 of whom had evidence of encephalitis. A plea was then made to consider the diagnosis of infectious mononucleosis and perform serological tests in cases of encephalitis, particularly in children and young adults.

The time of onset of nervous system involvement varies in relation to other systemic manifestations of infectious mononucleosis, though most commonly it occurs at the height of infection. In Case 1 the development of encephalitis transpired after clinical resolution of systemic symptoms. This course of the illness suggested that a delayed antibody-antigen reaction may be involved in the pathogenesis of encephalitis. Pathological study of patients who have died with infectious mononucleosis encephalitis has shown a prominent inflammatory reaction in the meninges and in the brain with a perivascular distribution, as well as degenerative changes of ganglion cells in the brain stem and similar changes in the Purkinje cells of the cerebellum (Bergin, 1960; Carter and Penman 1969). The findings of perivenous demyelination in the white matter in some cases of fatal cerebral infectious mononucleosis has led to the suggestion that a post-infection encephalomyelitis may be the result of Epstein-Barr virus infection.

There is no specific treatment for patients with encephalitis complicating

infectious mononucleosis. However, even patients with prolonged periods of coma frequently make a spontaneous recovery. In view of the good prognosis, intensive supportive therapy is recommended to avoid the complications of electrolyte and metabolic disturbances, secondary infection and seizure disorders. Cerebral oedema itself may cause deterioration and on occasion corticosteroids may be necessary for its control. Steroids have been advocated empirically in the treatment of patients with infectious mononucleosis encephalitis. The steroid effect in infectious mononucleosis may be by blocking T-lymphocyte cytotoxicity (Royston, 1975) though this mode of therapy is clinically unproven. The specific antiviral agents adenine arabinoside (Coken-Vann and Dolin, 1977) and phosphonoacetic acid (Summers and Klein, 1976) have been shown to inhibit Epstein-Barr virus *in vitro* and may ultimately play a role in the management of severe disease.

Summary

Three cases of infectious mononucleosis encephalitis are presented in which the aetiological diagnosis was established by specific Epstein-Barr virus serology. Paul-Bunnell-Davidsohn tests were negative in all cases, and characteristic non-neurological features of infectious mononucleosis were present in only one. The 3 cases had blood serological tests diagnostic of a recent infection with Epstein-Barr virus.

The Epstein-Barr virus is one of the more common causes of sporadic encephalitis particularly in young patients and the diagnosis may be considered even in the absence of systemic features of mononucleosis. As there is a substantial false negative rate with the Paul-Bunnell test, confirmation of recent infection may be gained by specific viral serology.

Acknowledgement

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References

Bejada, S.: Cerebellitis in glandular fever. Medical Journal of Australia 1: 153 (1976).

Bergin, J.D.: Fatal encephalopathy in glandular fever. Journal of Neurology, Neurosurgery and Psychiatry. 23: 69-73 (1960).

Bernstein, T.C. and Wolff, H.C.: Involvement of the nervous system in infectious mononucleosis. Annals of Internal Medicine 33: 1120-1138 (1950).

Carter, R.L. and Penman, H.G.: Infectious mononucleosis. Blackwell Scientific Publications (Oxford 1969).

Coker-Vann, M. and Dolin. R.: Effect of adenine arabinoside on Epstein-Barr virus *in vitro*. Journal of Infectious Diseases 135: 447 (1977).

Epstein, M.A.; Achong, B.G. and Barr, Y.M.: Virus particles in cultured lymphoblasts from Burkitt's lymphoma. Lancet 1: 702-703 (1964).

Evans, A.S.; Niederman, J.C. and Cenabre, L.C.: A prospective evaluation of heterophile and Epstein Barr virus specific IgM antibody tests in clinical and subclinical infectious mononucleosis. Journal of Infectious Diseases 132: 546 (1975).

Henle, G. and Henk, W.: Immunofluorescence in cells derived from Burkitt's lymphoma. Journal of Bacteriology 91: 1248 (1966).

Henle, W.; Henle, G. and Niederman, J.C.: Antibodies to early antigens induced by Epstein-Barr virus in infectious mononucleosis. Journal of Infectious Diseases 124: 58 (1971).

Henle, W.; Henle, G. and Horwitz, C.A.: Epstein-Barr specific diagnostic tests in infectious mononucleosis. Human Pathology 5: 551 (1974).

Joncas, J.H.; Chicoine, L.; Thivierge, R. and Bertrand, M.: Epstein-Barr virus antibodies in the cerebrospinal fluid. American Journal of Diseases of Children 127: 282-285 (1974).

Lennette, E.H. and Schmidt, N.J.: Diagnostic Procedures for Viral Rickettsial and Chlamydial Infections, 5th ed. (American Public Health Association, Washington, D.C. 1979).

Michel, R.G.; Pope, T.H. and Paterson, C.N.: Infectious mononucleosis, mastoiditis and facial paralysis. Archives of Otolaryngology 101: 486-489 (1975).

Pejme, J.: Infectious mononucleosis. Acta Medica Scandinavica 413: 1-83 (1964).

Royston, I.; Sullivan, J.L.; Periman, P.O. and Perlin, E.: Cell-mediated immunity to Epstein-Barr-virus-transformed lymphoblastoid cells in acute infectious mononucleosis. New England Journal of Medicine 293: 1159-1163 (1975).

Silversides, J.L. and Richardson, J.C.: Neurological complications of infectious mononucleosis. Canadian Medical Association Journal 63: 138-143 (1950).

Silverstein, A.; Steinberg, G. and Nathanson, M.: Nervous system involvement in infectious mononucleosis. Archives of Neurology (Chicago) 26: 353-358 (1972).

Summers, W.C. and Klein, G.: Inhibition of Epstein-Barr DNA synthesis and late gene expression by phosphonoacetic acid. Journal of Virology 18: 151 (1976).

Hypopituitarism with Arachnoid Cyst

*R.H.C. Rischbieth**

The presence of cysts within the cranial cavity was first described by Richard Bright in 1831. Various authors since then have described intracranial cysts, but the topic was confused by a failure to discriminate between 'porencephalic cysts' which, strictly speaking, are diverticulae extending from the cerebral ventricles to the cortical surface of the brain, and arachnoid cysts, which are formed by reduplication of the arachnoid layer or by a split between the pia and arachnoid, or the dura and arachnoid (Starkman, 1958).

Matson (1969) reviewed the subject, and pointed out that the most common sites of arachnoid cysts were in a Sylvian fissure, or over the convexity of a cerebral hemisphere; posterior fossa cysts, either in the cerebello-pontine angle or posterior to the cerebellar hemisphere or vermis, were much rarer. Marcel Sofer Schreiber was the first Australian author to report primary congenital arachnoid cysts to a meeting of the Australian Pediatric Association in 1959.

Richard Robinson in a series of papers in 1955, 1958, 1964 and in a review article in 1971, described 25 cases of arachnoid cyst, 16 of which were in the Sylvian fissure region, producing the so called temporal lobe agenesis syndrome. He pointed out that frequently the patient presented with headache, less commonly with epilepsy, and that visual field defects, impaired intelligence, or other neurological symptoms or signs were uncommon.

Some patients described in the literature presented after a head injury, which, by provoking haemorrhage into the cyst, had led to a worsening of the headache, at times associated with the presence of papilloedema or sixth nerve palsy. Macrocrania, or asymmetrical enlargement of the middle cranial fossa, could often be palpated. Radiographs showed expansion and/or thinning of the squamous temporal bone and, at times, of the adjacent parietal and frontal bones, with anterior displacement of the greater wing of the sphenoid bone and deviation of the lesser wing, the clinoid processes being spared, though not in Case 1

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Fig. 1. Lateral radiograph of pituitary fossa.

of Oliver (1968). Carotid angiography sometimes revealed the presence of an avascular area in the middle fossa with upward displacement of the middle cerebral artery in the posterior-anterior and lateral view, with forward displacement also in the latter, while air studies failed to show filling of the cyst from the ventricular system, the temporal horn being displaced medially and backwards.

Estimates of the frequency of arachnoid cysts varied between 0.3% (Cassinari, 1960) and 0.4% (Shuangshoti, 1978) of all intracranial space occupying lesions. Robinson's figure of 1% in his series of space occupying lesions possibly reflected his known special interest in the topic. With the advent of computerised axial tomography (CT) of the cranium the discovery of these lesions has been rendered much less traumatic to the patient than was formerly the case, and an increase in the fortuitous diagnosis of such lesions is to be expected. Indeed, at the Queen Elizabeth Hospital in the years 1977 to 1981, 5 cases of arachnoid cyst have been diagnosed amongst a series of 250 intracranial space occupying lesions seen in that period – an incidence of 2%. Two of these lesions, both

situated in the posterior fossa, were described by Purdie and Rischbieth in 1978.

The following patient is presented because of the apparently unique combination of hypopituitary symptoms and signs, and a Sylvian fissure arachnoid cyst.

Case Report

The patient, Miss J.D., was referred at the age of 18 to the Endocrinology Unit of the Queen Elizabeth Hospital in April, 1979, for investigation of primary amenorrhoea associated with obesity of 10 years' duration. Breast development and appearance of axillary and pubic hair had occurred at 13. Despite treatment with thyroxine and later fenfluramine, plus dieting, her weight was 62.7kg, at a height of 150cm unchanged since she was aged 12.

The visual fields were normal (confrontation and perimetry) and the visual acuity was normal in each eye. There was a minimal R. faciobrachial paresis. Thyroid function tests were normal, as were thyroid antibodies, and haematological and routine biochemical screens. Follicle-stimulating hormone (FSH) was 1.4 IU, (normal range 2.9 to 11.6). Luteinising hormone (LH) was normal, as was prolactin (18 ng/L). Total oestrogen was low (< 2 μg/24 hours) indicating little or no ovarian activity. Results of laboratory tests are shown in tables I and II.

Skull radiographs showed marked ballooning of the pituitary fossa, chiefly left-sided with destruction of the L. anterior clinoid process (fig. 1) and of both posterior clinoids, suggesting a large intrasellar tumour; there was slight ballooning of skull vault on the left. The bone age was greater than 14 years. An EEG showed voltage depression over the L. frontal and L. anterior to middle temporal regions. A CT scan (fig. 2) showed a huge intracranial cyst completely occupying the L. middle cranial fossa and replacing the lateral half of the L. frontal lobe, extending

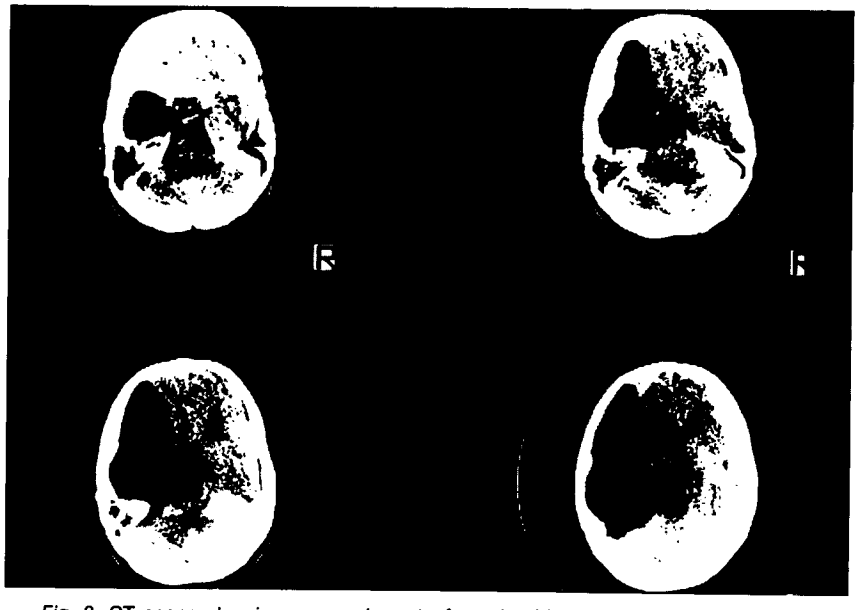

Fig. 2. CT scans showing encroachment of arachnoid cyst on pituitary fossa and displacement of ventricular system to the right.

Table I. Laboratory investigations (I) in primary amenorrhoea and hypopituitarism

Test	Result	Normal range
FSH	1.41 IU	2.9-11.6 IU
LH	2.6 IU	2.0-16 IU
Prolactin	18 ng/L	< 20 μg/L
Pregnanediol	0.9 mg/24 hours	0-0.5
Oestrogens	< 2 μg/24 hours	> -30
Thyroglobulin antibodies	Negative	
Thyroid microsomal AB	Negative	
Thyroid cytoplasmic AB	Negative	
Total thyroxin	129 Nmol/L	
Insulation stimulation	Growth hormone unresponsive	

high into the parietal region and into the pituitary fossa. In April, 1980 the patient was taking ethynodiol-diacetate-mestranol replacement and was having monthly periods. Her weight was 69.6kg. In July, 1980, she weighed 72.5kg and her jaws were wired, with subsequent weight loss. However, she was unable to tolerate this treatment and the wires were removed.

Neurological examination showed no change in the mild faciobrachial paresis with R-sided hyper-reflexia and hypertonia. In September, 1981 she complained of pain and fullness in the L. ear for 6/12 with no deafness, tinnitus, or vertigo. She was very tender over the L. temporomandibular joint. The CT scan was repeated on 12.3.82 and showed no convincing change compared with that of 1979 (fig. 3).

Discussion

The arachnoid cysts of the Sylvian region appear (Starkman, et al., 1958) invariably to be lined with arachnoid. While earlier these were considered to be true cysts, Aicardi and Bauman (1975) and Robinson (1964), comment that it is clinically impossible to distinguish between completely closed cavities, properly named 'cysts', and cavities communicating through a very small orifice with the subarachnoid space, more properly named 'pouches'.

The question arises as to the aetiology of arachnoid cysts. In only a minority is there any evidence of previous trauma or intracranial haemorrhage or inflammation which might have led to failure of fusion of the arachnoid. Robinson (1955) earlier postulated that arachnoid cyst formation was a compensation for the failure of development of the underlying brain of the temporal lobe, pulsa-

Table II. Laboratory investigations (II) in primary amenorrhoea and hypopituitarism

Test	Result
Biochemical screen	Normal
Female karyotype	46 XX
ESR	7
Hb	12.9
Microscopy urine	Normal

tions of the intracranial contents in the infant causing focal thinning and skull enlargement. Dott and Gillingham (1958) postulated pulsations along the cerebral arteries propelling the surrounding fluid in the subarachnoid space. Shuangshoti (1978) emphasised the role of CSF dynamics during fetal development, the choroidal pump-like action influencing the development and patency of the ventricular system, its outlets and the subarachnoid space. He suggested that an aberration of flow during early differentiation of the arachnoid mater could result in the development of a pouch within the arachnoid which may be closed off from the subarachnoid space and entrap fluid. The congenital arachnoid cyst is then formed intra-arachnoidally. Dott and Gillingham (1958) favoured local causes of CSF obstruction and at operation observed CSF being discharged into the cavity of a middle fossa cyst from the interpeduncular cistern by a 2mm orifice synchronously with systole. In 3 patients they noted the close similarity between the patterns of distribution of the cysts and that of major cerebral arteries, the

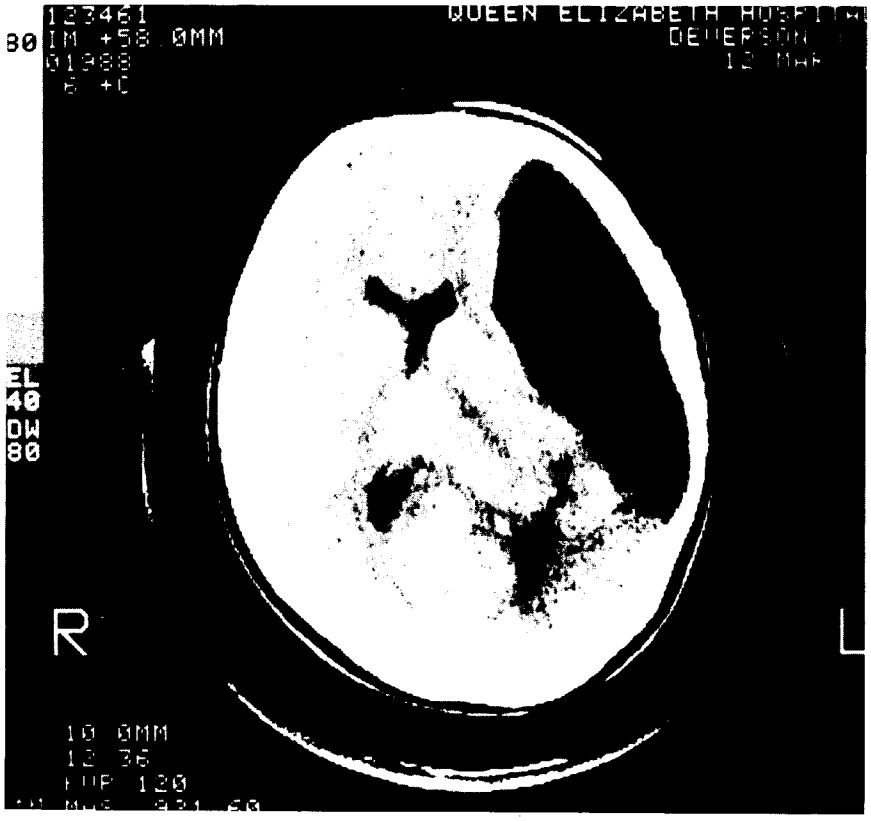

Fig. 3. Essentially unchanged CT scan appearances 3 years later.

fluid collections lying in the course of these vessels. They postulated that pulsations along the cerebral arteries propel the surrounding fluid in the blocked subarachnoid space. Williams and Guthkelch (1974), however, considered that pulsatile energy of arterial origin was far too inefficient to lead to progressive expansion of a pouch. The spinal subarachnoid space is much more sensitive to changes in venous pressure. If the mouth of the pouch is larger than the outlets of the fourth ventricle, then on coughing, sneezing, or straining, fluid would be propelled more easily into the cyst than the ventricles, leading to enlargement of the cyst.

Role of Surgery

Aicardi and Bauman (1975) agree with Matson (1969) and with Robinson (1964) that arachnoid cysts may be complicated by intracranial bleeding, either subdural or intracystic, giving rise to an acute neurological disorder, frequently as the result of trauma which may be quite trivial, but at times spontaneous. This group, and those cysts frequently seen in infancy which, without bleeding, give rise to pressure or localised signs or symptoms, warrant surgery, but many cases remain asymptomatic and some have been discovered by chance in the ninth and tenth decades.

It is proposed to continue close surveillance of the patient discussed, particularly in the light of the L.-sided head pain, with serial CT brain scans, while maintaining oestrogen replacement and dietetic advice, supplemented by counselling in view of the emotional problems associated with the patient's short stature, obesity and endocrine dysfunction.

Summary

Arachnoid cysts, most characteristically situated in the middle cranial fossa, have been described at other situations, in the posterior fossa and in the interpeduncular region.

A case of primary amenorrhoea, obesity, with short stature, proved to be associated with a huge arachnoid cyst involving the L. middle and anterior cranial fossae; and pituitary fossa, producing panhypopituitarism with right faciobrachial paresis, normal visual fields and visual acuity.

No evidence of progress of the lesion has been found after 3 years of observation, and further conservative management with regular CT scanning and oestrogen replacements is proposed.

Acknowledgement

I am grateful to Drs W.G. Tucker and M.R. Sage for radiological assistance and to Dr B.A. Higgins, who referred the patient.

References

Aicardi, J. and Bauman, F.: Supratentorial extracerebral cysts in infants and children. Journal of Neurology, Neurosurgery and Psychiatry 38: 57-68 (1975).

Bright, R.: Serous cysts of the Arachnoid. Reports of Medical Cases, Vol. 2, part 1 (Longmans, London 1831).

Cassinari, V. and Marossero, F.: Infuso L. Le cisti arachnoidal endocraniche. Rivista di Neurologica 30: 138-158 (1960).

Dott N.M. and Gillingham, J.F.: Mechanical aspects of the cerebrospinal fluid circulation – physiological, pathological, surgical; in Ciba Foundation Symposium on the Cerebrospinal Fluid, pp.246-264 (Churchill, London 1958).

Matson, D.D.: Benign intracranial cysts; in Neurosurgery of Infancy and Childhood, pp.179-193 2nd ed. (Charles Thomas Springfield, 1969).

Oliver, L.C.: Primary arachnoid cysts. Report of two cases. British Medical Journal 1: 1147-1149 (1968).

Purdie, G.H. and Rischbieth, R.H.C.: Posterior fossa arachnoid cysts. Clinical and Experimental Neurology. Proceedings of the Australian Association of Neurology. Vol. 15, pp.159-165 (1978).

Robinson, R.G.: Intracranial collections of fluid with local bulging of the skull. Journal of Neurosurgery 12: 345-353 (1955).

Robinson, R.G.: Local bulging of the skull and external hydrocephalus due to cerebral agenesis. British Journal of Radiology 31: 691-700 (1958).

Robinson, R.G.: The temporal lobe agenesis syndrome. Brain 87: 87-106 (1964).

Shuangshoti, S.: Calcified congenital arachnoid cyst with heterotopic neuroglia in wall. Journal of Neurology, Neurosurgery and Psychiatry 41: 88-89 (1978).

Sofer Schreiber, M.: Primary congenital arachnoid cysts. Medical Journal of Australia 1: 802-803 (1959).

Starkman, S.P.; Brown, T.C. and Linell, E.A.: Cerebral arachnoid cysts. Journal of Neuropathology and Experimental Neurology 17: 484-490 (1958).

Williams, B. and Guthkelch, A.N.: Why do central arachnoid cysts expand? Journal of Neurology, Neurosurgery and Psychiatry 37: 1085-1092 (1974).

Diffuse Infiltrating Astrocytoma (Gliomatosis Cerebri) with Twenty-two-year History

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The onset of focal seizures in an adult is usually the expression of disease involving the cerebral cortex (Adams and Victor, 1977) and an indication, in particular, to exclude tumour.

We here report a case where repeated radiological investigations over 22 years, including angiography, pneumoencephalography and computerised tomography (CT), failed to reveal the diffusely infiltrating astrocytoma (gliomatosis cerebri) ultimately found at postmortem.

Case Report

At the age of 28 years a previously well man presented to the Royal Adelaide Hospital for investigation with a 4-year history of focal epilepsy comprising episodes of twitching of the right face, turning of the head and eyes to the right, loss of speech and generalised convulsing. Neurological examination was normal. There was no family history of epilepsy or of an abnormal birth or head injury. Haematological and biochemical investigations were normal. An x-ray of the skull was normal. An EEG showed a mild generalised abnormality. A left carotid angiogram showed a 2mm shift of the anterior cerebral artery to the right. He was treated with anticonvulsants and 1 year later CSF examination and air encephalogram were normal.

The patient was readmitted 12 years later because of an increasing frequency of minor focal seizures involving the right face and arm. The only abnormal finding was that the tendon reflexes were a little brisker on the right than the left side, the plantar responses being flexor. A further EEG again showed a mild generalised abnormality with no focal features. A CT head scan showed a mild asymmetry of the ventricles without any mass effects. A radionuclide scan was normal. The left carotid angiogram was again normal. The treatment was adjusted to include sodium valproate.

The patient was again admitted 4 years later because of frequent right facial twitching, a recurrence of generalised seizures and an alteration in personality with increasing apathy and

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depression. The right plantar response was noted to be extensor at times. The EEG showed only a minor nonfocal abnormality and a further CT head scan (fig. 1) was unchanged. He was then treated for a mixed depressive illness complicating his epilepsy. However, psychometric assessment showed memory impairment and poor performance on tests reflecting frontal lobe function, particularly of the left hemisphere. Over the next year mild extrapyramidal signs were noted and he became increasingly apathetic, withdrawn, immobile and incontinent. Clinically, a cerebral degenerative condition was suspected.

Final admission was precipitated by focal status epilepticus: the patient was drowsy and virtually mute with almost constant minor focal seizures involving the face. The fundi were normal. A mild right hemiparesis was present but tendon reflexes were brisk bilaterally and both plantar responses were extensor. An EEG showed nonfocal theta activity. Sequential CT head scans during the final admission (fig. 2) were reported as normal. The seizure activity was partly controlled with intravenous clonazepam but his conscious state continued to deteriorate and he developed fixed dilated pupils and Cheyne-Stokes respiration with loss of oculocephalic reflexes. Death occurred after 2 days of respiratory support.

Neuropathology

The brain weighed 1555g. Both cerebral hemispheres were swollen, the left more than the right. The posterior part of the left middle frontal gyrus was expanded by a firm, grey-white swelling (15mm). The left uncus was more deeply grooved than the right and there was bilateral cerebellar tonsillar herniation with necrosis of the tonsils. Coronal sections of the cerebral hemispheres showed enlargement of the central white matter of the left cerebral hemisphere which was abnormally firm to palpation (fig. 3). In many areas there was poor demarcation between the cerebral cortex and underlying subcortical white matter, a change most obvious around the left Sylvian fissure and middle frontal gyrus (fig. 4). The corpus callosum was enlarged and showed focal cystic degeneration at the angle of the right lateral ventricle (fig. 5). The adjacent central white matter of the right frontal lobe was of abnormal texture. The central grey matter on both sides was generally enlarged, pale and firmer than normal.

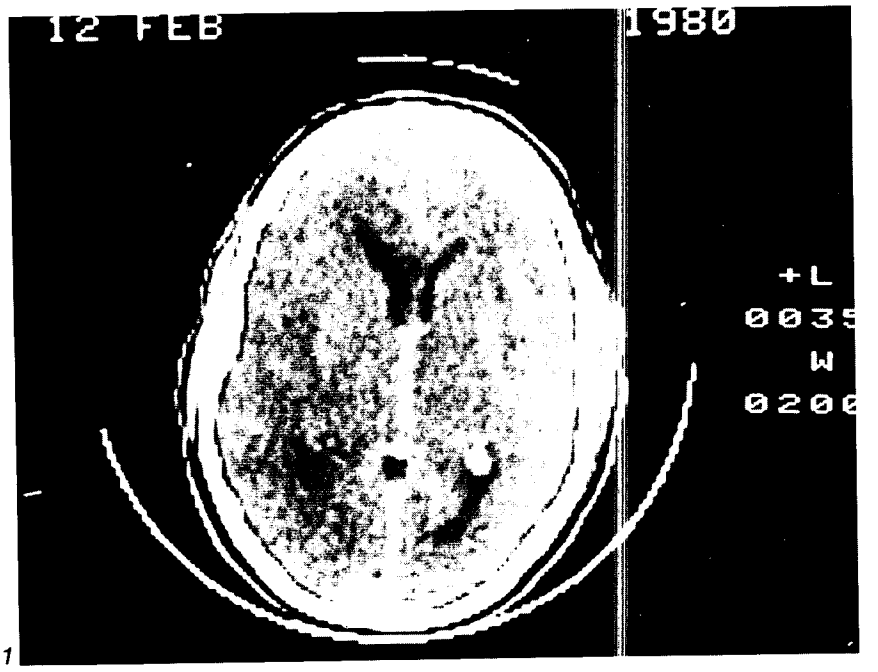
The right hypothalamus and posterior thalamus were disrupted by multiple haemorrhages. The midbrain and pons were larger than normal and cross-section showed massive disruption by multiple secondary haemorrhages which extended into the middle cerebellar peduncles.

Microscopic examination revealed a very extensive infiltrating astrocytoma involving the central white matter of both frontal, parietal and occipital lobes, both internal capsules, the white matter of the left temporal lobe, corpus callosum, anterior commissure, anterior forniceal system and optic chiasm. Numerous areas of cortical invasion were present in both hemispheres with particular involvement of the peri-Sylvian cortex on both sides, the left hippocampus, left middle and inferior frontal gyri, cingulate gyri and right calcarine cortex posteriorly. There was diffuse infiltration of the central grey matter bilaterally including the caudate nuclei, putamina, hypothalamic and thalamic nuclei. The lesion extended down the brainstem to involve the midbrain and rostral pons. Striking features histologically were the relative preservation of the neuronal elements with extensive subpial and cortical infiltration (fig. 6).

The appearance of the tumour cells varied from well-differentiated fibrous astrocytes to small round cells without obvious glial fibril formation. The cellularity also varied in different areas but even in the most cellular areas only occasional mitoses were present. There was no evidence of tumour necrosis, vascular proliferation or multinucleate giant cell formation.

Discussion

Nevin (1938) proposed the name 'gliomatosis cerebri' to describe an unusual type of glial overgrowth of the brain in which there was relative preservation of the underlying neural structures. He regarded the lesion as a 'blastomatous malformation arising upon a congenital developmental defect'. Similar cases have been described employing such terms as 'central diffuse schwannosis' (Foerster



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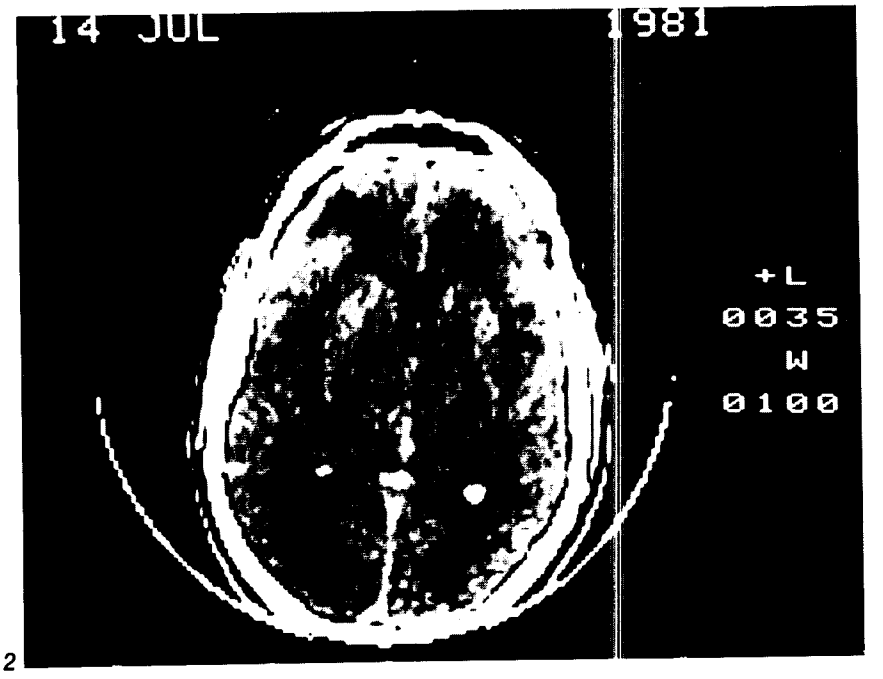

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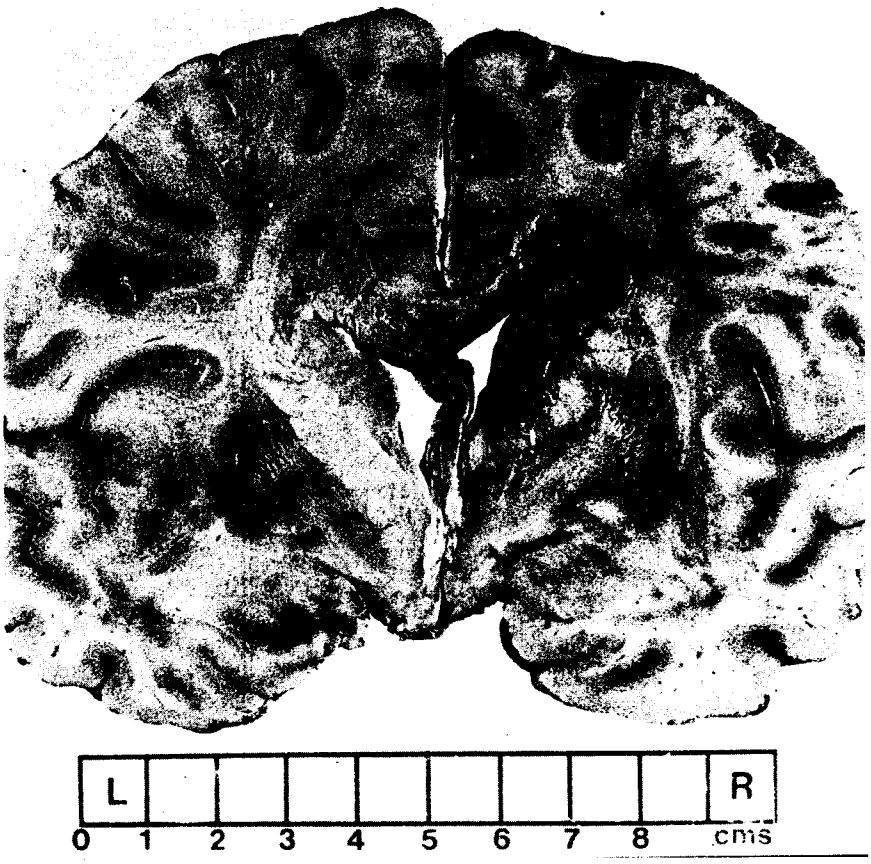

Fig. 3. Coronal section of cerebral hemispheres showing abnormal appearance of the central white matter of the left hemisphere, corpus callosum and right caudate nucleus.

and Gagel, 1934), 'cerebral glioblastosis' (Scheinker and Evans, 1943) and 'patchy blastomatous infiltration of the central nervous system' (Ferraro et al., 1943) reflecting the diversity of opinion regarding the essential nature of this lesion. More recent authors (Malamud et al., 1952; Moore, 1954; Dunn and Kernohan, 1957; Couch and Weiss, 1974) have been unanimous in the opinion that the lesion is a neoplasm arising from multicentric neoplastic transformation of pre-existing astrocytes. Russell and Rubinstein (1977) feel that the lesion merely represents the rarely seen extreme end of the spectrum of diffusely infiltrating astrocytoma.

Fig. 1. CT head scan with contrast (February 1980).

Fig. 2. CT head scan 5 months later, with contrast (July 1981).

The varied clinical presentations of gliomatosis cerebri were described by Couch and Weiss (1974) who reported 4 cases and reviewed 32 cases from the literature. They found that the age of onset varied from 6 to 62 years and the

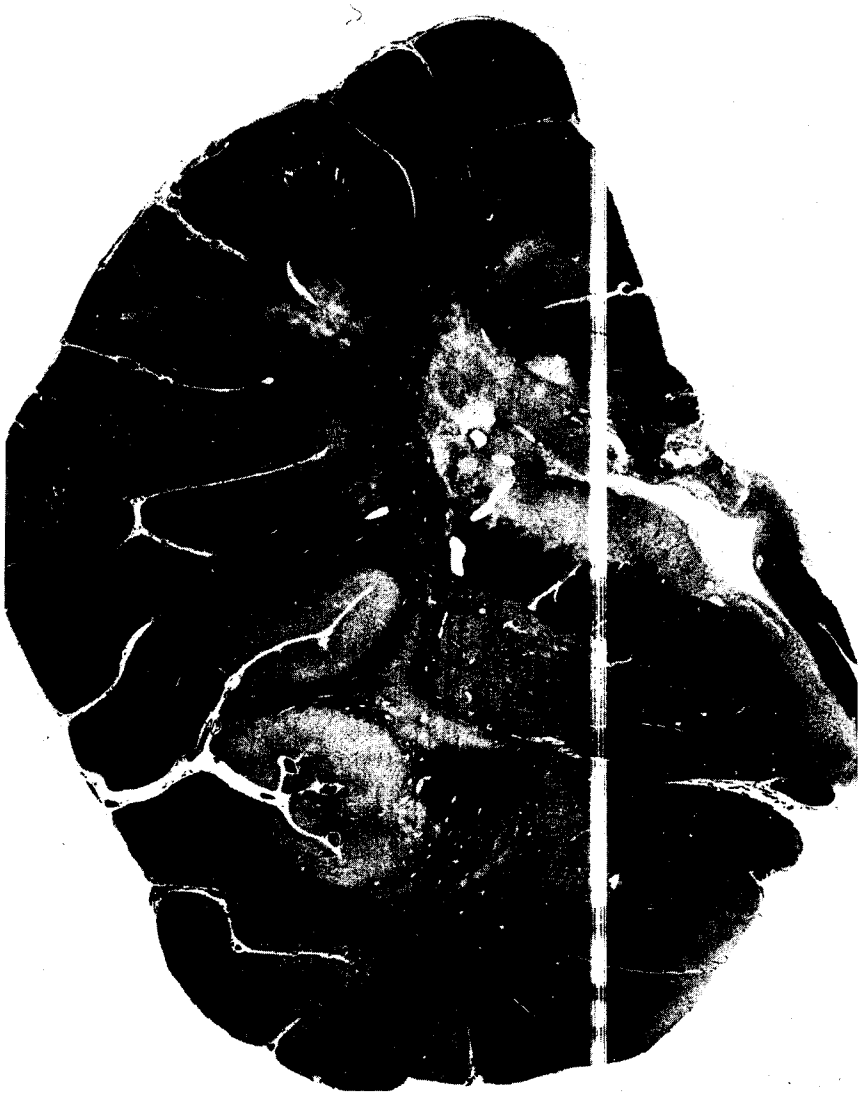

Fig. 4. Coronal section of left cerebral hemisphere showing loss of myelin staining in the central white matter, corpus callosum and infiltration of caudate nucleus, Sylvian cortex, and middle frontal gyrus (Weil X 1½).

interval from initial symptoms to death with diffuse gliomatosis varied from 25 days to 20 years.

Mental and personality change (29 of 36 cases) was the most frequent presentation, followed by hemiparesis (22/36), ataxia (18/36), headache (14/36), visual loss (9/36) and hemihypaesthesia (8/36). Seizures were the initial presentation in 9 of 36 cases and in one patient focal seizures were present for 20 years.

Fig. 5. Coronal section of right cerebral hemisphere showing infiltration of white matter adjacent to corpus callosum, caudate nucleus, internal capsule, Sylvian cortex and cystic degeneration at the angle of the right lateral ventricle (Weil stain X 1½).

As in the present case, Couch and Weiss (1974) found that laboratory investigations (CSF examination, plain x-rays of skull, radionuclide brain scan, angiography, pneumoencephalography and ventriculography) were usually unhelpful and the EEG diffusely abnormal. In the present case, CT head scans frequently repeated over 5 years since 1976 showed only mild persistent asymmetry of the ventricular system. False negative CT head scans for cerebral tumour have been reported (Tentler et al., 1977) but are rare and generally the CT head scan is abnormal at the time of the first examination in about 98% of intracerebral tumours (Claveria et al., 1977).

The present unusual case illustrates some of the difficulties that may still be experienced in diagnosing diffusely infiltrating astrocytomas and warns against the assumption that a negative CT head scan completely excludes this diagnosis.

Summary

The case is described of a man, aged 46 at his time of death, who suffered from focal motor, adversive and generalised seizures for 22 years. He developed a progressive dementia over the last 2 years of his life. Investigation, including angiography and air encephalography early in the course of the illness and repeated CT head scans later, failed to demonstrate any neoplasm. Death occurred abruptly, due to cerebellar tonsillar herniation. At postmortem an extensive diffuse low grade fibrillary astrocytoma infiltrated both cerebral hemispheres, the

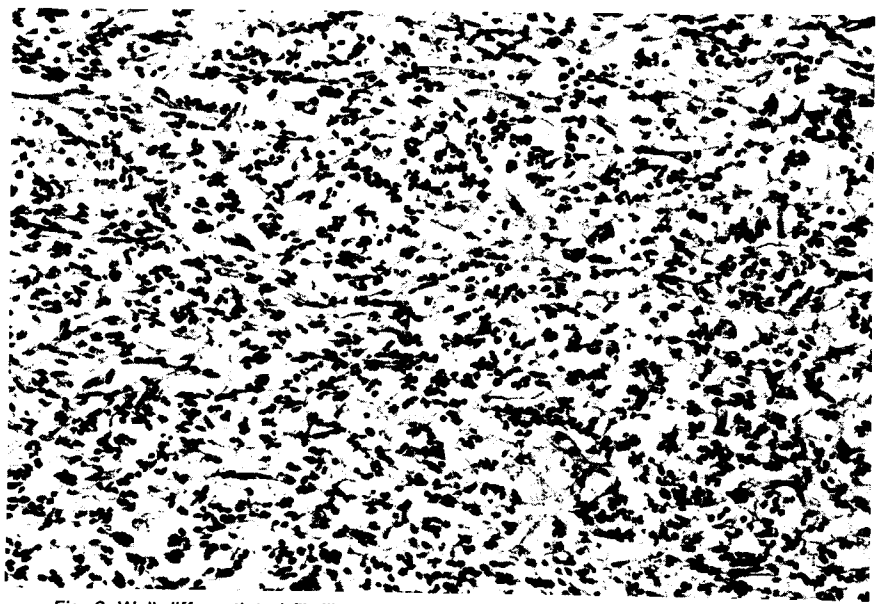

Fig. 6. Well differentiated fibrillary astrocytoma (H&E X 225).

corpus callosum, central grey matter, midbrain and pons. Thus, there was gliomatosis cerebri. Attention is drawn to the exceptional length of the history in this case, the difficulties which may arise in displaying diffusely infiltrating low grade astrocytomas radiologically and to the rare occurrence of gliomatosis cerebri.

References

Adams, R.D. and Victor, M.: Principles of Neurology, pp.211-230 (Blakiston, New York 1977).

Claveria, L.E., Kendall, B.E. and Du Boulay, G.H.: Computerised axial tomography in supratentorial gliomas and metastases; in Du Boulay and Mosley (Eds), First European Seminar on Computerised Axial Tomography in Clinical Practice (Springer-Verlag, Berlin, 1977).

Couch, J.R. and Weiss, S.A.: Gliomatosis cerebri. Report of four cases and review of the literature. Neurology (Minneapolis) 24: 504-511 (1974).

Dunn, J. and Kernohan, J.W.: Gliomatosis cerebri. Archives of Pathology 64: 82-91 (1957).

Ferraro, A.; Jervis, G.A. and Sherwood, W.D.: Patchy blastomatous infiltration of the central nervous system (Patchy schwannosis?). Journal of Neuropathology and Experimental Neurology 2: 207-223 (1943).

Foerster, O. and Gagel, O.: Zentrale diffuse Schwannose bei Recklinghausenscher Krankheit. Zeitschrift für die gesamte Neurologie und Psychiatrie 151: 1-16 (1934).

Malamud, N.; Wise, B.L. and Jones, O.W.: Gliomatosis cerebri. Journal of Neurosurgery 9: 409-417 (1952).

Moore, M.T.: Diffuse cerebrospinal gliomatosis, masked by syphilis. Journal of Neuropathology and Experimental Neurology 13: 129-143 (1954).

Nevin, S.: Gliomatosis cerebri. Brain 61: 170-191 (1938).

Russell, D.S. and Rubinstein, L.J.: Pathology of Tumours of the Nervous System, p.179 (Edward Arnold, Edinburgh, 1977).

Scheinker, I.M. and Evans, J.P.: Diffuse cerebral glioblastosis. Journal of Neuropathology and Experimental Neurology 2: 178-189 (1943).

Tentler, R.L. and Palacios E.: False-negative computerized tomography in brain tumour. Journal of the American Medical Association 238: 339-340 (1977).

Oculopharyngeal Dystrophy: Clinicopathological Study of an Australian Family

P.C. Blumbergs, D. Chin†, D. Burrow†, K.J. Burns‡ and J.P. Rice†*

Oculopharyngeal dystrophy was the term coined by Victor et al. (1962) to describe a distinctive syndrome characterised by the development of slowly progressive ptosis and dysphagia in the late middle life. The familial form, inherited as an autosomal dominant condition, has been generally accepted as a distinct type of chronic progressive ophthalmoplegia (CPEO) (Drachman, 1975). The nosological position of sporadic cases has been less certain, however, and investigation to exclude other causes of CPEO, particularly one of the mitochondrial myopathies, is necessary (Bastiaensen and Schulte, 1979). The recent description of different clinical, pathological and genetic forms of oculopharyngeal dystrophy (Bastiaensen and Schulte, 1979) has further confused the picture and the position of oculopharyngeal dystrophy as a separate entity has also been challenged (Roberts and Bamforth, 1968; Croft et al., 1977).

The purpose of this paper is to describe the clinical, pathological and genetic features of a South Australian family affected by oculopharyngeal dystrophy showing an autosomal dominant pattern of inheritance and a benign stereotyped clinical course.

Case Reports

The family comprised the following affected persons:

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Case 1

A 71-year-old man (III, 4 in fig. 3) was admitted to the Royal Adelaide Hospital in 1981 for the investigation of dysphagia. He had noted minor difficulty in swallowing for many years but this had progressed over the previous 2 years to the stage that he was unable to swallow foods such as custard, porridge or meat. He had first noted drooping of the eyelids at the age of 41 years and this had gradually progressed to the extent that vision was obscured until this disability was partially relieved by multiple surgical lid resections. He had also noticed mild proximal weakness of the upper limbs of 2 years' duration. Carcinoma of the prostate with bony metastases had been diagnosed in 1980.

Examination showed bilateral ptosis with weakness of lid closure, mild symmetrical lower facial weakness and mild symmetrical shoulder abduction weakness. The remainder of the neurological examination was normal and in particular the ocular movements, speech, palate and tongue movements, pupillary reflexes and fundi were normal. EMG, nerve conduction studies, serum creatine phosphokinase measurement and ECG were normal. Barium swallow examination showed that deglutition was very slow with difficulty in initiating the act and with pooling of the barium in the oropharynx consistent with neuromuscular dysfunction. A deltoid muscle biopsy showed the nonspecific myopathic features of random variation in muscle fibre size and atrophy of type 2A and 2B fibres. On electron microscopy the most striking abnormality was the presence of numerous vacuoles, predominantly sited in the intermyofibrillar spaces and showing granular impregnation with lanthanum tracer on their internal surfaces. There were no mitochondrial abnormalities.

Case 2

In 1976 a 75-year-old spinster (III, 9 in fig. 3) was admitted to the Royal Adelaide Hospital with ptosis and dysphagia. She had first noted drooping of both eyelids at the age of 65 years. This was followed 7 years later by progressive difficulty in swallowing solid foods and liquids. There was a past history of Ménières disease.

Examination showed bilateral ptosis, mild bilateral lower facial weakness, a nasal voice

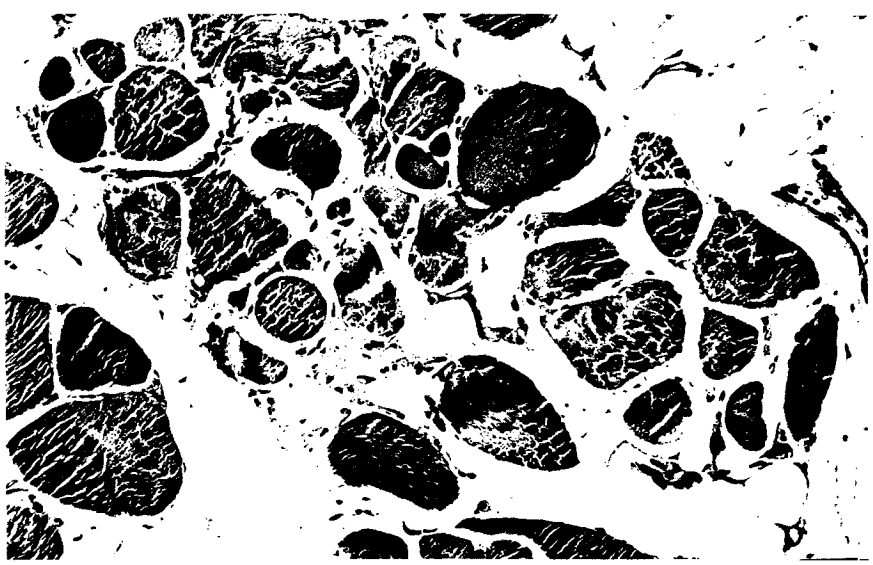

Fig. 1. Upper pharyngeal constrictor muscle showing variation in muscle fibre size, central nucleation and increased fibro-adipose connective tissue (H&E X 225).

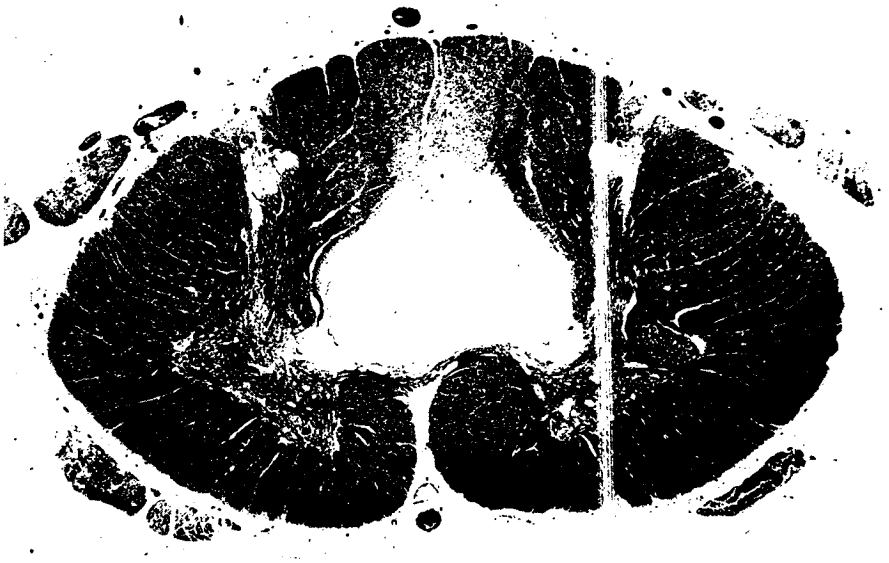

Fig. 2. Transverse section of C8 segment spinal cord showing hydromyelia (Weil X 12).

and nasal regurgitation on swallowing. There was mild bilateral hip flexion weakness. The ocular movements, pupillary reflexes and fundi were normal. The remainder of the neurological examination was normal except for bilateral neurosensory deafness consistent with Ménières disease, weak bilateral extensor plantar responses and absent ankle jerks.

Needle electromyography of the right biceps and brachioradialis showed mildly increased insertional activity, moderate reduction in interference patterns and frequent low amplitude polyphasic units consistent with myopathy. Nerve conduction in the right median and ulnar nerves was normal. Complete blood picture, ESR, skull and chest radiographs, CT head scan, serum creatine phosphokinase, ECG and blood VDRL were normal. Over the next 2 years the dysphagia progressed to the extent that it took her one hour to eat a meal. She finally died of bronchopneumonia.

At postmortem microscopy of the skeletal muscles (left deltoid, left abductor pollicis brevis, left sternomastoid and both quadriceps) showed myopathic changes with random variation in muscle fibre size with scattered small angular and rounded, 'giant' fibres (100μm), proliferation and central migration of sarcolemmal nuclei, loss of muscle fibres associated with increased fat and fibrous tissue and occasional fibres undergoing segmental degeneration.

The pharyngeal muscles (pharyngeal constrictors, upper oesophagus and stylohyoids) showed the most severe myopathic changes with marked disorganisation of muscle architecture, increased interstitial fibro-adipose connective tissue, loss of muscle fibres, central nucleation, variation in fibre size and segmental degeneration consistent with a very chronic muscular dystrophy (fig. 1).

The ocular muscles (superior, medial, inferior and lateral recti and superior and inferior obliques) showed marked variation in fibre diameter, many internal nuclei, sarcoplasmic masses and ringed fibres, and increased endomysial connective tissue similar to that seen in controls. The levator palpebrae muscles were not examined.

The brain stem was macroscopically normal and microscopic examination of the oculomotor, trochlear, abducens and medullary nuclei showed no evidence of neuronal loss or astrocytic reaction.

Section of the spinal cord at each segmental level showed an unusual hydromyelia with dilatation of the ependyma-lined central canal from C7 to T4 segments with maximal expansion (4mm) at C8 level (fig. 2). There was mild surrounding fibrogliosis and hyaline sclerosis of small blood vessels but the central grey matter and myelin were intact. The central canal above and below the hydromyelia was normal.

Case 3

A 69-year-old man (III, 3 in fig. 3) was admitted to the Royal Adelaide Hospital in 1972 for investigation of progressive bilateral ptosis of 6 years' duration. The ptosis had obscured his vision and he had been unsuccessfully treated with lid resections and ptosis props. For the past 5 years he had noted mild progressive difficulty with swallowing. There was a past history of partial gastrectomy and gastrojejunostomy for chronic prepyloric peptic ulcer.

On examination the only abnormality was bilateral ptosis. The ocular movements were normal. There was no evidence of fatiguability or myotonia. The remainder of the neurological examination was normal. Serum creatine phosphokinase was abnormal: 100/U/L (normal range 0-46). A barium swallow showed difficulty in initiating the act of swallowing, with retention of barium in the oropharynx and pooling in the pyriform recesses consistent with neuromuscular dysfunction. Electromyography of the right quadriceps, abductor pollicis brevis, deltoid and triceps was normal. Nerve conduction studies on the right median nerve were normal. Serum immunoglobulin showed elevation of the IgM to 340 mg/100mls (normal range 50-150) and normal IgA and IgG levels. The patient died of cardiorespiratory failure in 1975 following fracture of right neck of femur. A postmortem was not performed.

Case 4

An 80-year-old spinster (III, 8 in fig. 3) noted drooping of the eyelids at the age of 60 years and mild difficulty swallowing at the age of 65 years. On examination there was bilateral ptosis. Extra-ocular movements were normal. Mild bilateral hip flexion weakness was present. The remainder of the neurological examination was normal.

In 1976 the patient was investigated for transient ischaemic attacks producing dysphasia and right sided weakness which was attributed to an angiographically demonstrated left middle cerebral artery stenosis associated with essential hypertension and type IV hyperlipidaemia.

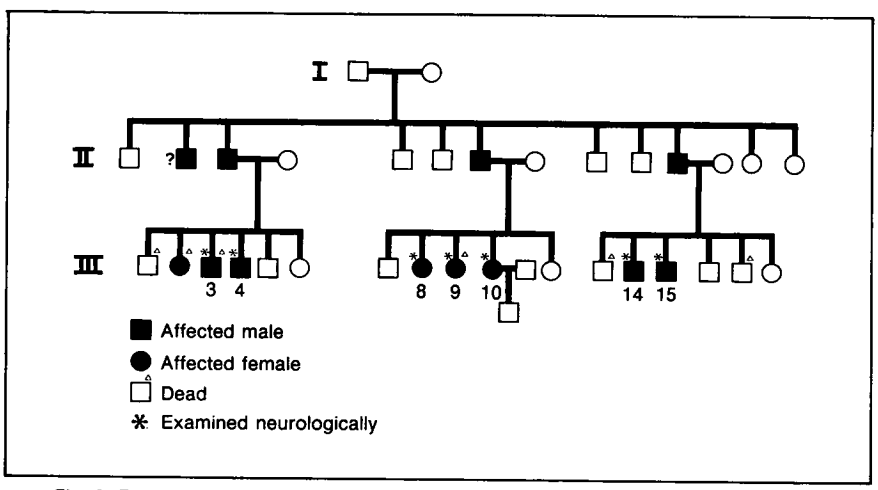

Fig. 3. Family tree showing members affected by oculopharyngeal dystrophy.

Case 5

A 70-year-old woman (III, 10 in fig. 3) had droopy eyelids for 10 years and dysphagia for 5 years. On examination she had bilateral ptosis and a nasal voice. Extra-ocular movements were normal. Minimal bilateral facial weakness was present. The remainder of the neurological examination was normal.

Case 6

A 70-year-old man (III, 14 in fig. 3) had noted progressive drooping of the eyelids for 10 years and difficulty swallowing solid foods for 5 years. He had lid resections performed at the age of 65 years. Difficulty in climbing stairs had been present for 5 years.

On examination he had bilateral ptosis and mild weakness of lower facial muscles. Extra-ocular movements were normal. Mild weakness of the proximal muscles of upper and lower limbs was noted.

Case 7

A 66-year-old man (III, 15 in fig. 3) had progressive drooping of the eyelids of 5 years' duration and difficulty in swallowing for 3 years. On examination there was bilateral ptosis, but normal eye movements. No facial, proximal or distal weakness was found.

Family Investigation

The family tree (fig. 3) shows that at least 12 members have been affected by oculopharyngeal dystrophy over 3 generations. The transmission in this family appears to be autosomal dominant with known involvement of 4 of 9 females and 8 of 18 males.

Discussion

The development of ptosis and dysphagia in late middle life was originally described in a French-Canadian family by Taylor (1915) who speculated that it was secondary to degeneration of the vagus and glossopharyngeal nuclei. Victor et al. (1962), however, showed by electromyographic examination and biopsy of affected muscles that the disease was a progressive myopathy of the dystrophic type. Most of the described cases have been of French-Canadian descent and Barbeau (1966, 1969) was able to establish an autosomal dominant pattern of inheritance and trace all the previously described cases (Taylor, 1915; Amyot, 1948; Hayes et al., 1963; Peterman et al., 1964 and Bray et al., 1965) through 11 generations, to a Frenchman who had migrated to Quebec in 1634.

The disease usually runs a benign stereotyped course, but death due to malnutrition and aspiration pneumonia, as in one of our cases, may occur (Taylor, 1915; Myrianthopoulus and Brown, 1954; Roberts and Bamforth, 1968; Weitzner, 1969). In the classical French-Canadian cases the other external ocular and skeletal muscles were little affected and this form of oculopharyngeal dystrophy has been termed palpebro-pharyngeal dystrophy. However, weakness of facial, extra-ocular and limb girdle muscles has been described in the French-Canadian cases (Murphy and Drachman, 1968) and our cases are very similar to this group. Similar pedigrees have also been described in Norwegians (Aarli, 1969), Eastern-European Jews (Victor et al., 1962) and Swedes (Lundberg, 1962).

The recent description of oculopharyngeal distal myopathy (Satoyoshi and Kinoshita, 1977), associated cardiomyopathy (Goto et al, 1977) and autosomal recessive patterns of inheritance (Matsunaga et al., 1973; Fried et al., 1975) has

made classification of this syndrome more complex. Indeed, it has been disputed that oculopharyngeal dystrophy merits separate classification and some authors (Roberts and Bamforth, 1968; Croft et al., 1977) claim that these cases are merely part of the spectrum of ocular myopathy in which dysphagia is particularly prominent.

The pathological studies of the skeletal muscles in oculopharyngeal dystrophy (Victor et al., 1962; Peterman et al., 1964; Rebeiz et al., 1969; Weitzner, 1969) have shown similar myopathic changes to those demonstrated in our family and have been interpreted as indicative of a chronic muscular dystrophy. The dystrophic nature of the process has been supported by the few available post-mortem studies (Rebeiz et al., 1969; Weitzner, 1969; Satoyoshi and Kinoshita, 1977) which have shown normal central and peripheral nervous systems.

Our cases did not show the 'rimmed vacuoles' described by Dubowitz and Brooke (1973) in a series of patients of Spanish-American descent, nor was there any inflammation as has been described in a single case (Bosch et al., 1979) in which it was suggested that some patients with oculopharyngeal dystrophy may pass through an initial phase of secondary muscle inflammation indistinguishable histologically from polymyositis and similar to some of the other heritable myopathies.

Many of the early descriptions of myopathic changes affecting the extra-ocular muscles need re-evaluation now that it has been recognised that marked variation in muscle fibre diameter, central nuclei, sarcoplasmic masses, ringed fibres and increased endomysial connective tissue are characteristic of normal eye muscles (Bethlem, 1980). The extra-ocular muscles in our Case 2, who had normal ocular movements during life, showed all these appearances but did not differ significantly from control muscles. Biopsies of the levator palpebrae muscle obtained at ptosis operations have usually only shown fibrosis (Bastiaensen and Schulte, 1979). Only a few ultrastructural examinations have been reported. Rebeiz et al. (1969) in a superior rectus muscle found only nonspecific degenerative changes which were more pronounced than those of control material. Johnson and Kuwabara (1974) found intermyofibrillar vacuolation continuous with the sarcoplasmic reticulum and T-tubule system in biopsies of levator palpebrae muscle removed at ptosis correction procedures. Abnormal mitochondria with paracrystalline inclusions and subsarcolemmal fingerprint bodies have only been described in a single report (Julien et al., 1974).

The dysphagia in oculopharyngeal dystrophy is secondary to degeneration of the pharyngeal muscles which show similar but more severe myopathic changes to those described in the skeletal muscles (Roberts and Bamforth, 1968; Rebeiz et al., 1969; Weitzner, 1969, 1971). The dystrophic muscles are unable to develop the necessary pressure in the hypopharynx to initiate the reflex relaxation of the oesophageal sphincter (Bastiaensen and Schulte, 1979). This can be demonstrated by manometric studies. The dysphagia may become severe with increasing age, as in our Case 1, and is reportedly alleviated by cricopharyngeal myotomy (Montgomery and Lynch, 1971).

Abnormalities in serum immunoglobulins, in particular elevation of IgG and IgA levels, have been described (Russe et al., 1969) but estimations in Case

estimations in Case 3 showed only a mild elevation of IgM.

We believe that the hydromyelia in Case 2 is a fortuitous association, though few spinal cords have been examined. Weitzner (1969) reported that the spinal cords in his 2 postmortem cases were normal and Satoyoshi and Kinoshita (1977) likewise found no spinal cord abnormality in their postmortem case of oculopharyngo-distal myopathy.

Summary

A family is presented in which 12 members over 3 generations have been affected by oculopharyngeal dystrophy. The clinical features of 7 affected members are described. All developed ptosis in middle age and dysphagia later in the clinical course. Four had mild bilateral facial weakness and mild proximal weakness. Extra-ocular movements were normal in all.

A deltoid muscle biopsy from a 71-year-old affected male showed nonspecific myopathic features (random variation in muscle fibre size and atrophy of type 2A and 2B fibres). The skeletal muscles and striated musculature of the pharynx and upper oesophagus of a 75-year-old affected female examined at postmortem showed histological myopathic changes (loss of muscle fibres, variation in size of fibres with scattered small angular and rounded 'giant' muscle fibres, proliferation and central migration of sarcolemmal nuclei, increase in fat and fibrous tissue and occasional fibres undergoing segmental degeneration). This appearance was consistent with a muscular dystrophy of chronic type. Detailed neuropathological examination of the brain stem nuclei was normal. The spinal cord showed an unusual hydromyelia affecting C7 to T4 segments.

References

Aarli, J.A.: Oculopharyngeal muscular dystrophy. Acta Neurologica Scandinavica 45: 484-492 (1969).

Amyot, R.: Hereditary, familial and acquired ptosis of late onset. Canadian Medical Association Journal 59: 434-438 (1948).

Barbeau, A.: The syndrome of hereditary late onset ptosis and dysphagia in French Canada; in Kuhn (Ed) Symposium über progressive Muskeldystrophie – Myotonie – Myasthenia pp.102-109 (Berlin, Springer-Verlag (1966).

Barbeau, A.: Oculopharyngeal muscular dystrophy in French Canada. Presidential address; in Brunette and Barbeau (Eds) Progress in Neuro-Ophthalmology. Vol. 2. Proceedings of the 2nd International Congress of Neuro-Genetics and Neuro-Ophthalmology, 1967. (Amsterdam, Excerpta Medica Foundation, International Congress Series 176: 3, 1969).

Bastiaensen, A.K. and Schulte E.P.M.: Oculopharyngeal dystrophy. Diagnostic problems and possibilities. Documenta Ophthalmologica 46, 2: 391-401 (1979).

Bethlem, J.: Myopathies, pp.65-75 (Elsevier/North Holland, 1980).

Bray, G.M.; Kaarsoo, M.M. and Ross, R.T.: Ocular myopathy with dysphasia. Neurology 15: 678-684 (1965).

Bosch, E.P.; Gowans, J.D.C.; and Munsat, T.: Inflammatory myopathy in oculopharyngeal dystrophy, Muscle Nerve 2: 73-77 (1979).

Croft, P.B.; Cutting, J.C.; Jewesbury, E.C.O.; Blackwood, W. and Mair, W.G.P.: Ocular myopathy (Progressive external ophthalmoplegia) with neuropathic complications. Acta Neurologica Scandinavica, 55: 169-197 (1977).

Drachman, D.A.: Ophthalmoplegia plus; a classification of the disorders associated with progressive external ophthalmoplegia; in Vinken and Bruyn (Eds) Handbook of Clinical Neurology. Vol. 22, part 2 pp.203-216 (Amsterdam, North Holland, 1975).

Dubowitz, V. and Brooke, M.H.: Ocular and oculopharyngeal dystrophies; in: Dubowitz and Brooke (Eds) Muscle Biopsy: A Modern Approach, Philadelphia pp.231-241 (W.B. Saunders Company, 1973).

Fried, K.; Arlozorov, A. and Spira, A.: Autosomal recessive oculopharyngeal muscular dystrophy. Journal of Medical Genetics 12: 416-418 (1975).

Goto, I.; Kanazawa; Y., Kobavashi, T.; Murai, Y. and Kuroiwa, Y.: Oculopharyngeal myopathy with distal and cardiomyopathy. Journal of Neurology, Neurosurgery and Psychiatry 40: 600-607 (1977).

Hayes, R.; London, W.; Seidman, J. and Embree, L.: Oculopharyngeal muscular dystrophy. New England Journal of Medicine 268: 163 (1963).

Johnson, C.C. and Kuwabara, T.: Oculopharyngeal muscular dystrophy. American Journal of Ophthalmology 77: 872-879 (1974).

Julien, J.; Vital, C.; Vallat, J.M.; Vallat, M. and Le Blanc, M.: Oculo-pharyngeal muscular dystrophy. A case with abnormal mitochondrial and 'fingerprint' inclusions. Journal of Neurological Sciences 21: 165-169 (1974).

Lundberg, P.O.: Ocular myopathy with hypogonadism. Acta Neurologica Scandinavica 38: 142-155 (1962).

Matsunaga, M.; Inokuchi, T.; Ohnishi, A. and Kuroiwa, Y.: Oculopharyngeal involvement in familial neurogenic muscular atrophy. Journal of Neurology, Neurosurgery and Psychiatry 36: 104-111 (1973).

Montgomery, W.W. and Lynch, J.P.: Oculopharyngeal muscular dystrophy, treated by inferior constrictor myotomy. Transactions of the American Academy of Ophthalmology and Otolaryngology 75: 986-993 (1971).

Murphy, S.F. and Drachman, D.B.: The oculopharyngeal syndrome. Journal of the American Medical Association 203: 1003-1008 (1968).

Myrianthopoulos, N.C. and Brown, I.A.: A genetic study of progressive spinal muscular atrophy. American Journal of Human Genetics 6: 387-411 (1954).

Peterman, A.F.; Lillington, G.A. and Jamplis, R.W.: Progressive muscular dystrophy with ptosis and dysphagia. Archives of Neurology 10: 38-41 (1964).

Rebeiz, J.J.; Caulfield, J.B. and Adams, R.D.: Oculopharyngeal dystrophy – a presenescent myopathy. A clinico-pathologic study; in Brunette and Barbeau (Eds) Progress in Neuro-Ophthalmology. Vol. 2, Proceedings of the 2nd International Congress of Neuro-Genetics and Neuro-Ophthalmology, 1967 pp.12-31 (Excerpta Medica Foundation, International Congress Series 176, Amsterdam 1969).

Roberts, A.H. and Bamforth, J.: The pharynx and oesophagus in ocular muscular dystrophy. Neurology (Minneapolis) 18: 645-652 (1968).

Russe, H.; Busey, H. and Barbeau, A.: Immunoglobulin changes in oculopharyngeal dystrophy; in Brunette and Barbeau (Eds) Progress in Neurogenetics. Vol. 1, Proceedings of the 2nd International Congress of Neuro-Genetics and Neuro-Ophthalmology, 1967 pp.62-65. (Excerpta Medica Foundation, International Congress Series 175, Amsterdam 1969).

Satoyoshi, E. and Kinoshita, M.: Oculopharyngodistal myopathy. Report of four families. Archives of Neurology 34: 89-92 (1977).

Taylor, E.W.: Progressive vagus-glossopharyngeal paralysis with ptosis: A contribution to the group of family diseases. Journal of Nervous and Mental Disorders 42: 129-139 (1915).

Victor, M.; Hayes, R. and Adams, R.D.: Oculopharyngeal muscular dystrophy. A familial disease of late life characterized by dysphagia and progressive ptosis of the eyelids. New England Journal of Medicine 267: 1267-1272 (1962).

Weitzner, S.: Changes in the pharyngeal and oesophageal musculature in oculopharyngeal muscular dystrophy. Report of two cases. American Journal of Digestive Diseases 14: 805-810 (1969).

Weitzner, S.: The histopathology of the pharynx and oesophagus in oculopharyngeal muscular dystrophy. Case report and literature review. American Journal of Gastroenterology 56: 378-382 (1971).

Hemimasticatory and Hemifacial Spasm: A Common Pathophysiology?

*P.D. Thompson and W.M. Carroll**

Hemimasticatory spasm is an uncommon involuntary facial movement, which has been described (Gowers, 1897; Kaufman, 1980) in association with facial hemiatrophy. One recent report of such a case (Kaufman, 1980) commented on the similarity of hemimasticatory spasm to hemifacial spasm. A case of hemimasticatory spasm without facial hemiatrophy is described and compared electrophysiologically with 6 cases of hemifacial spasm.

Case Report

A 60-year-old female presented with a 3-year history of painful spasm of the left temporalis and masseter muscles, causing tonic jaw closure. Spasms occurred several times daily, either spontaneously or during jaw movements and each episode would last for up to 1 minute. In addition she was troubled by short clonic spasms which would interrupt her speech and make her bite her tongue. These short spasms would either pass spontaneously or become repetitive in a crescendo fashion leading to a prolonged spasm. Four to 5 years prior to the onset of the masticatory spasm she developed an intermittent ache felt superficially in the left maxilla which she likened to a toothache. Its severity fluctuated and the pain resolved at the time the spasms commenced. Eighteen months later she experienced a further sensory disturbance, similar to a dental anaesthetic, in the maxillary and mandibular divisions of the trigeminal nerve. This resolved over several weeks. The jaw spasms have continued unabated.

Numerous medications, including phenytoin, carbamazepine, baclofen, valproate, clonazepam, haloperidol and amitriptyline, were tried without effect. A cryosurgical lesion of the motor root of the trigeminal nerve, subsequent to the investigations to be described, provided only temporary relief from the spasms. The general examination was normal. Neurological examination revealed marked hypertrophy of the left temporalis and masseter muscles. There was no weakness of the jaw musculature when spasm free, and the jaw jerk was present and normal. Facial sensation, in all divisions of the trigeminal nerve, was intact. The remainder of the neuro-

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logical evaluation was normal. Investigations, including complete blood examination, treponemal serology, antinuclear factor, cerebrospinal fluid, posterior fossa metrizamide myelography and carotid and vertebral angiography were all normal.

Electrophysiological Studies

Hemimasticatory Spasm

Blink reflex studies (Kimura, 1975) were normal for early (R_1) and late (R_2) components (fig. 1). The jaw jerk recorded when spasm free to mechanical stimulation showed an absent left masseter response (fig. 2). Needle electromyography of the left masseter showed no evidence of denervation and showed several patterns of activity at rest and during spasms, the common

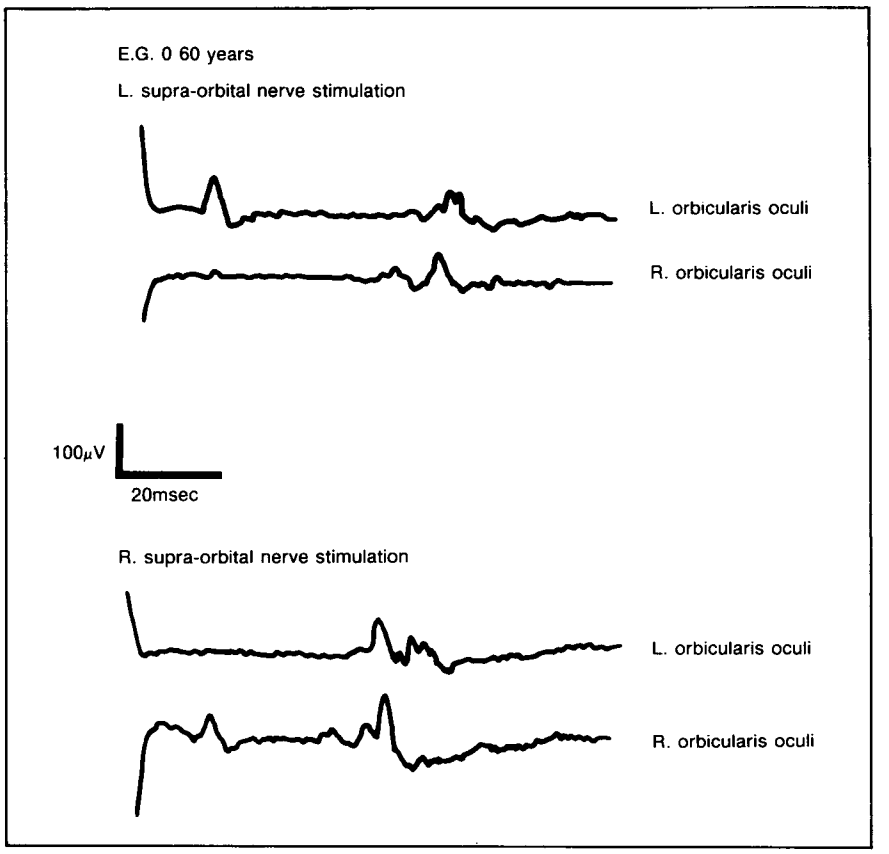

Fig. 1. Blink reflexes (electrical), recorded from right and left orbicularis oculi. Upper traces (left supra-orbital nerve stimulation) show ipsilateral R_1 (early response) and bilateral R_2 (late responses) at normal latencies (10 and 37 msec respectively). Lower traces following right supra-orbital nerve stimulation show R_1 and R_2 components at normal latencies (10 and 38 msec respectively).

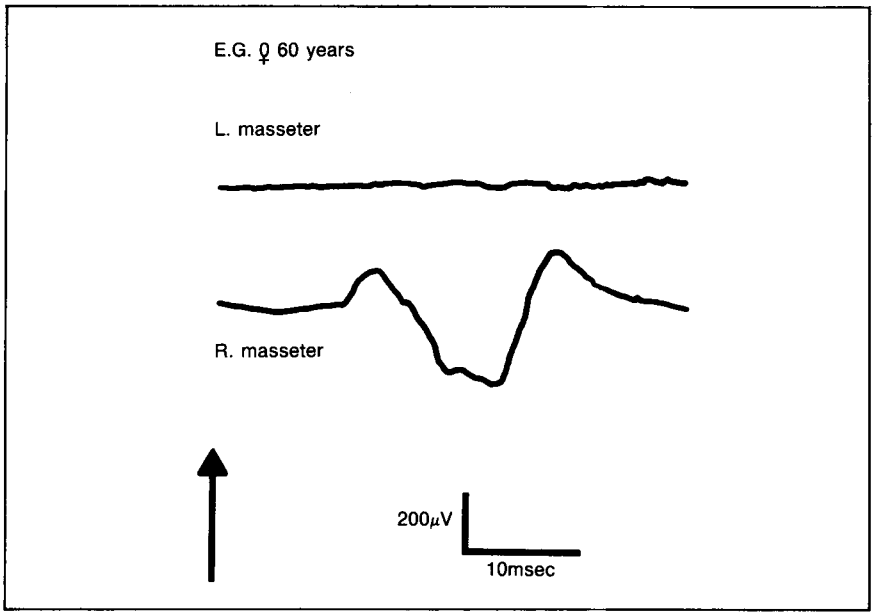

Fig. 2. Jaw jerk, mechanically elicited: Recording over the right and left masseter muscles. Note the absence of a response on the left.

features being the high discharge frequency of morphologically normal motor units and the tendency for these discharges to become repetitive. Single units discharged at rest, while during spasm multiple units were present, but their high discharge frequency did not allow close analysis of them (fig. 3). There was considerable variation in burst duration with short bursts of activity of between 20-100 msec duration and spasms of between 175 msec and 1 second duration, the latter activity being preceded by a crescendo of short bursts on some occasions (fig. 4) or occurring spontaneously in isolation (fig. 5). Right masseter activity was inhibited during spasm of the left masseter (fig. 4). The temporalis showed variable coactivation with the masseter throughout these spasms (fig. 6). Recordings from the lateral pterygoid were not made during spasm, but during voluntary jaw closure variable activity was recorded in this muscle without there being a definite relationship to masseter activity.

Hemifacial Spasm

By way of comparison, 6 patients with idiopathic hemifacial spasm were examined. The relevant clinical and electrophysiological features are summarised in table 1. Their ages ranged from 50 to 66 years and none were postparalytic. Facial weakness was not present in any and facial synkinesis was evident clinically in all. Blink reflex latencies, the presence of synkinesis and the discharge patterns of the motor units in the orbicularis oculi, nasalis and oris muscles were recorded. The findings were similar to those previously reported in this condition (Hjorth and Willison, 1973; Auger, 1979). The blink reflex latencies were normal in all cases and variable facial synkinesis was present spontaneously and after stimulation of the supra-orbital nerve in the ipsilateral, orbicularis oculi, oris and nasalis muscles. Needle electromyography revealed normal units in all muscles sampled in the absence of spasm. No fibrillation potentials were recorded and the motor unit firing pattern varied, with short bursts ranging from 15 to 100 msec

Table I. Summarised EMG findings in 6 patients with hemifacial spasm

Patient	Age	Sex	Short burst duration (msec)	Burst duration variability	Spasm duration (approx) (msec)	Motor discharge frequency	Involuntary coactivation (synkinesis)
BR	55	F	20-30	+	200	High	+
RA	66	F	15-75	+	200	High	+
CL	77	F	50-100	+	200	High	+
AO'D	61	M	20-50	+	400	High	+
BR	57	F	20-30	+	400	High	+
AB	50	F	20-40	+	200	High	+

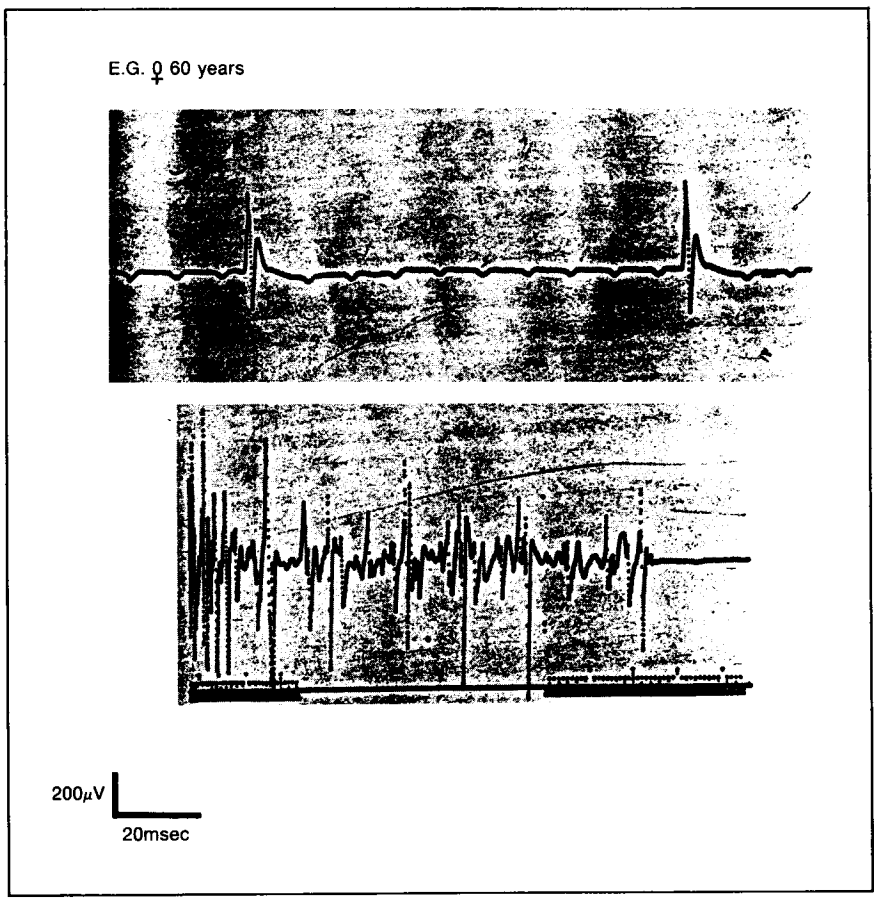

Fig. 3. Spontaneous left masseter EMG activity. Single random units of normal morphology (upper trace) and multiple units discharging at high frequencies during the latter part of a spasm (lower trace).

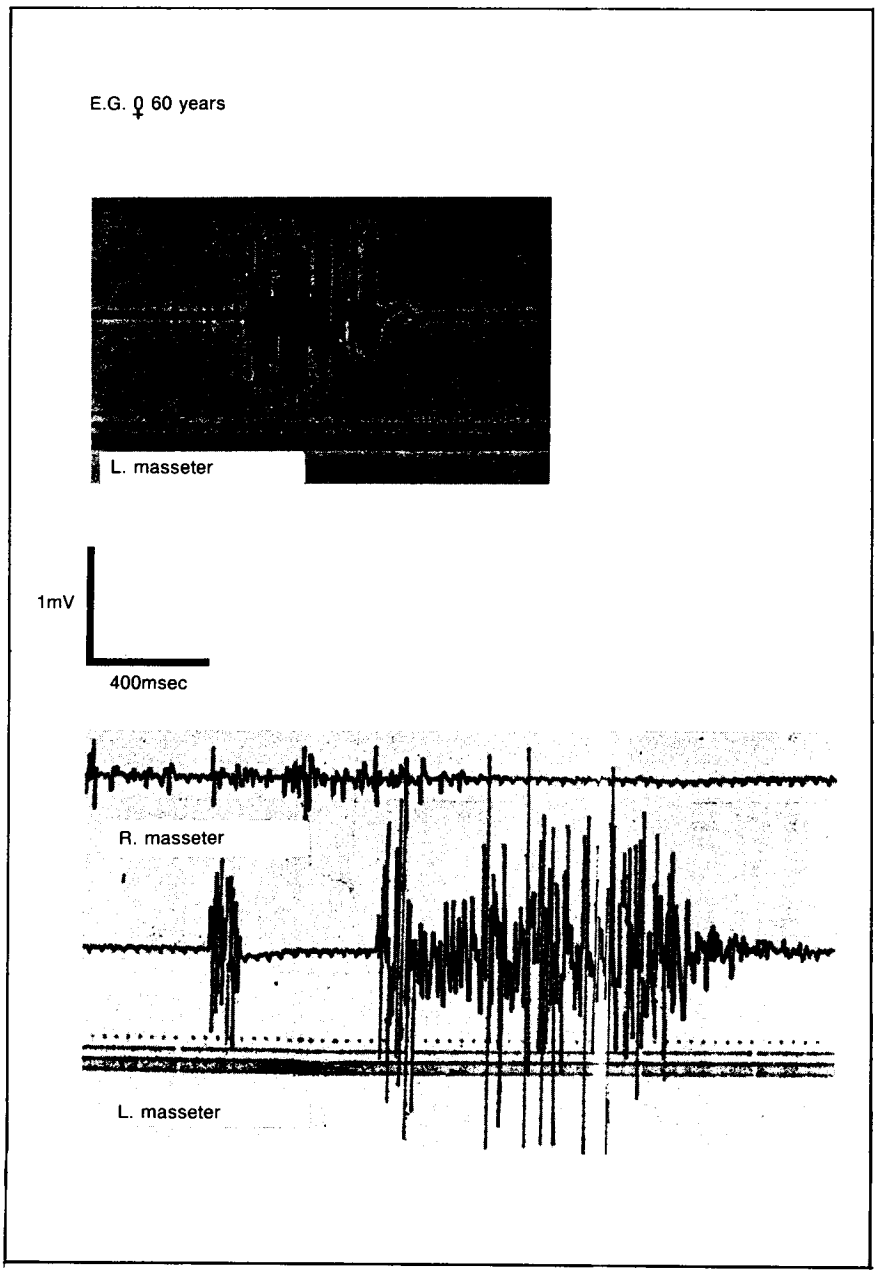

Fig. 4. Left masseter EMG (upper tracing) showing grouped bursts of up to 100 msec duration. Lower tracing shows a short burst of activity preceding masseter spasm (approximately 1 second). The activity in the right masseter muscle is inhibited.

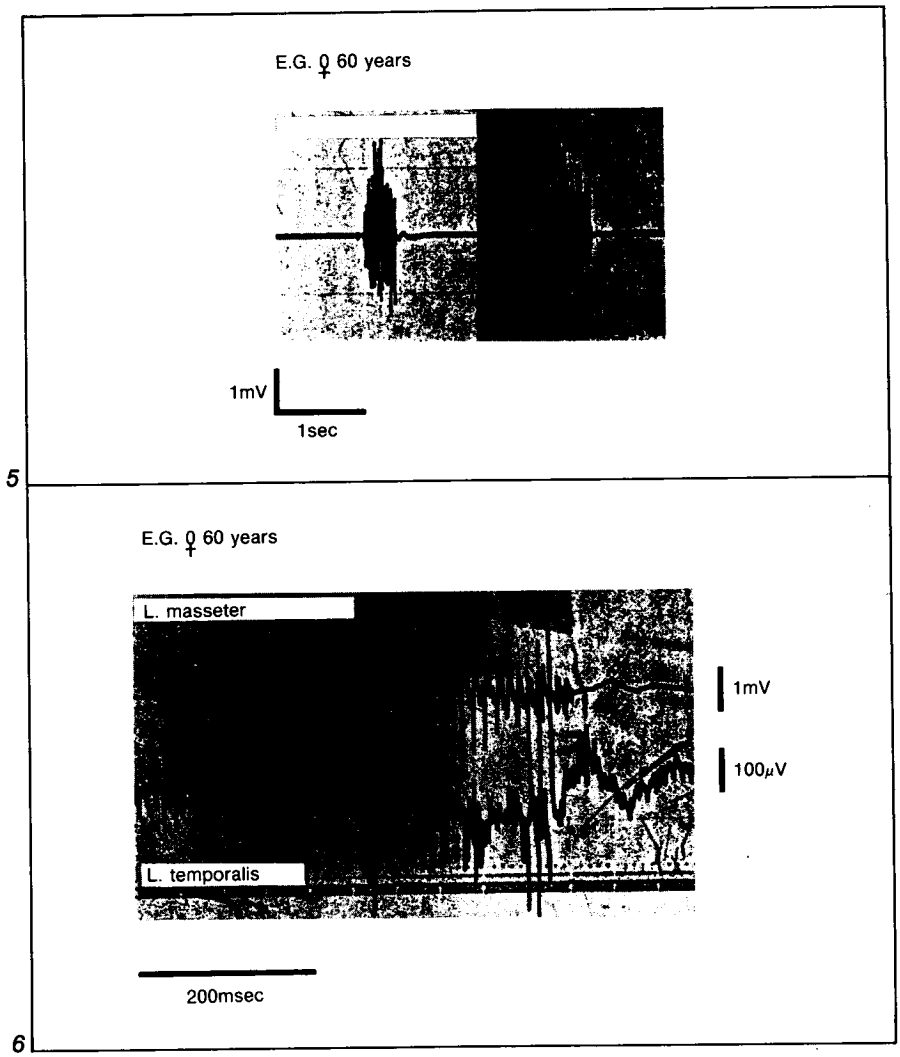

Fig. 5. Isolated spontaneous burst left masseter EMG activity.

Fig. 6. Spontaneous left masseter and left temporalis EMG activity with coactivation during spasm.

duration to prolonged spasms of up to 400 msec duration. The units comprising these spasms discharged at very high frequencies (fig. 7). Simultaneous recordings from the orbicularis oculi and oris showed irregular slowly discharging units which corresponded to the brief twiches seen in these muscles while synkinetic bursts of increasing duration often discharged in a crescendo fashion summating to a relatively prolonged contraction (fig. 8). This latter pattern of activity was similar to that seen in hemimasticatory spasm.

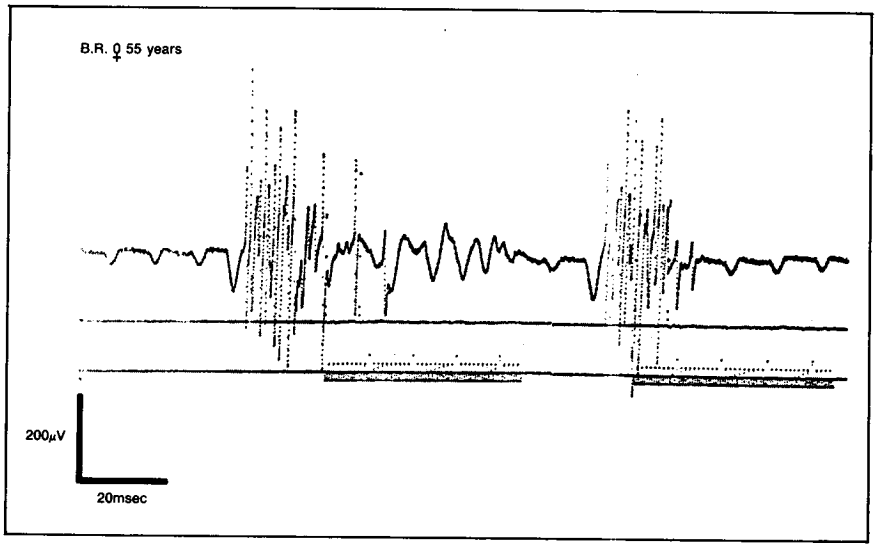

Fig. 7. Short bursts of rapidly discharging units recorded from orbicularis oculi in a patient with typical hemifacial spasm.

Discussion

Hemimasticatory spasm and hemifacial spasm are involuntary facial movements characterised by brief recurrent paroxysmal contractions of the masticatory and facial muscles. Their similarities are summarised in table II.

There were no definite precipitating factors, and weakness was not present in any of our cases although it has been reported in postparalytic hemifacial spasm (Wartenberg, 1952). Synkinesis, a prominent feature of hemifacial spasm (Auger, 1979), was difficult to demonstrate in hemimasticatory spasm. Variable coactivation of the masseter and temporalis was noted during spasm, however. It is not clear whether the activity recorded in the lateral pterygoid during jaw closure represented synkinesis or part of the normal sequence of muscle activation as described in limb movements (Hallett and Marsden, 1979). The variability of the relationship, however, favours a disturbance of the normal pattern. Overall, the patterns of motor unit activity comprising spontaneous high frequency discharges, their duration and their tendency to become repetitive in both conditions, appear comparable. On the basis of these similarities a peripheral lesion, as proposed in hemifacial spasm (Auger, 1979; Janetta et al., 1977), may also be responsible for hemimasticatory spasm.

Comparable patterns of activity have been recorded arising ectopically in peripheral nerves (Rasminsky, 1978; Lance et al., 1979; Ochoa and Torebjork, 1980) and are somewhat different from the discharges associated with known central nervous system lesions (for example facial myokymia and experimental dorsal column demyelination) which are characterised by couplets or short trains of impulses discharging regularly and relatively slowly (Hjorth and Willison, 1973;

Table II. Comparative EMG features of hemimasticatory and hemifacial spasm in 6 patients. Note that facial weakness was not seen in the present 6 cases, but can occur in postparalytic hemifacial spasm

Features	HMS (masseter)	HFS (orbicularis oculi)
Precipitating factors	–	–
Weakness	–	±
Synkinesis	+	+
Denervation	–	–
Single unit discharges	+	+
Burst occurrence	Irregular	Irregular
Short burst duration	20-100 msec	20-100 msec
Spasm duration	500 msec	400 msec
Motor unit discharge frequency	High	High

Smith and McDonald, 1980). Albers et al. (1981), however, have recorded both types of activity in patients with limb myokymia due to a variety of radiculopathies. In all these situations ectopically generated impulses have been thought to excite adjacent nerve fibres, by ephaptic cross-activation at the site of nerve injury. This mechanism has been invoked to explain synkinesis in hemifacial spasm (Auger, 1979). These several observations have contributed to the trend

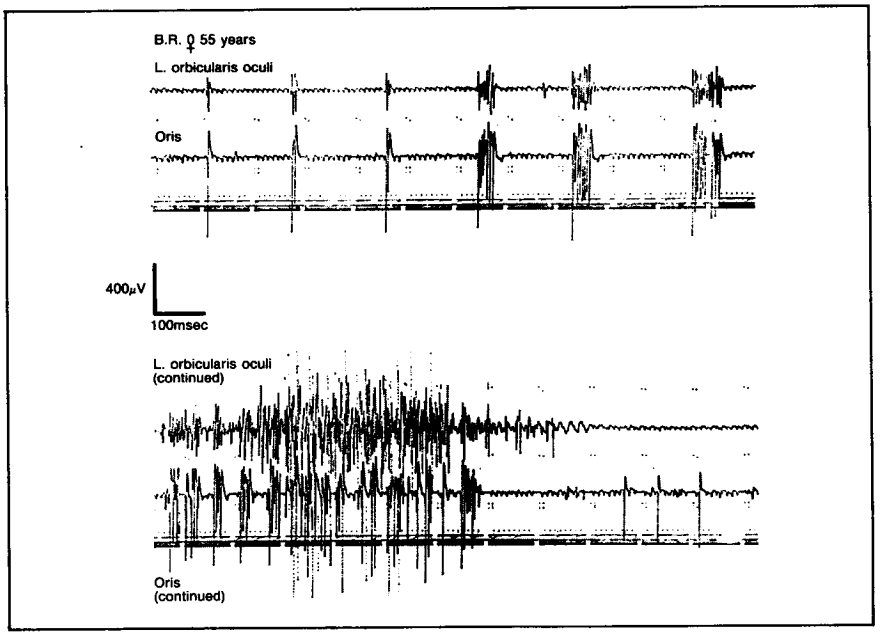

Fig. 8. Simultaneous EMG recording from left orbicularis oculi and oris muscles from the same patient with hemifacial spasm shown in fig. 7. Synkinetic bursts of increasing duration are seen in the lower traces leading to relatively prolonged spasm.

away from Wartenberg's (1952) theory of facial nucleus hyperexcitability, although a recent modification of this by Ferguson (1978) suggested that uninhibited nuclear discharge may result from nuclear deafferentation following nerve injury. Whether ectopic sensory afferent or antidromic motor impulses generated at the site of nerve injury alter nuclear firing or whether orthodromic activation of the motor axons at the site of the nerve injury occurs is not known.

The likelihood that a peripheral lesion is responsible for the masticatory spasm is further enhanced by the ipsilateral absence of the jaw jerk, implying involvement of Ia spindle afferents which traverse the motor root and mandibular division of the trigeminal nerve (McIntyre and Robinson, 1959), while the normal blink reflex latencies suggest that the central connections of the trigeminal nerve, at least with the facial nucleus, are intact. The antecedent sensory symptoms in this case are also consistent with a peripheral lesion. The nature of this lesion is, however, speculative. Inflammatory disorders, such as viral infections, have been invoked in cases of isolated trigeminal sensory neuropathies (Spillane and Wells, 1959) but a definite aetiology has not been established. Other possible mechanisms include vascular compression of the trigeminal nerve roots. The significance of the neurovascular relationships in the posterior fossa remains controversial. Improvement, however, both clinical and electrophysiological, has been recorded following vascular decompression of the facial nerve in hemifacial spasm (Janetta, 1977; Auger et al., 1981). Given the similarities between hemimasticatory spasm and hemifacial spasm, a strategically placed vascular loop cannot be dismissed as the offending lesion in the present case. The motor root of the trigeminal nerve lies rostral to the sensory root (Gudmunson et al., 1971) in a position susceptible to compression from above by the superior cerebellar artery, a finding observed by Sunderland (1948) in 3 of the 210 postmortems in which he studied the neurovascular anatomy at the base of the brain.

Finally, masticatory hypertrophy has not been a feature of previously reported cases of hemimasticatory spasm (which have all occurred in association with facial hemiatrophy) nor is facial muscle enlargement notable in hemifacial spasm. The significance of masticatory hypertrophy is not clear although it apparently results from sustained isometric contraction due to either deafferentation of the affected masticatory muscles, and /or an autonomous independently discharging focus.

In conclusion, the present case of hemimasticatory spasm shows many similarities to hemifacial spasm, both clinically and electrophysiologically. Although a definite aetiology has not been established in either syndrome, a peripheral cranial neuropathy is proposed, arising as a sequel to previous inflammation, or related to vascular compression. It appears that the generation of ectopic impulses at the site of nerve injury with ephaptic cross-activation of adjacent nerve fibres may well be the mechanism responsible for the characteristic patterns of muscle activity observed.

Summary

The case is described of a 60-year-old woman with a 4-year history of left

hemimasticatory spasm. Detailed electrophysiological studies are compared with those from 6 patients with typical idiopathic hemifacial spasm. On the basis of comparable patterns of EMG activity in the 2 conditions, it is concluded that they may have both a common pathophysiology and a peripheral site of involvement.

References

Albers, J.W.; Allen, A.A.II; Bastron, J.A. and Daube, J.R.: Limb myokymia. Muscle and Nerve 4: 494-504 (1981).

Auger, R.: Hemifacial spasm: Clinical and electrophysiological observations. Neurology 29: 1261-1272 (1979).

Auger, R.; Piepgras, D.; Laws, G. and Miller, R.: Microvascular decompression of the facial nerve for hemifacial spasm: Clinical and electrophysiological observations. Neurology 31: 346-350 (1981).

Ferguson, J.H.: Hemifacial spasm and the facial nucleus. Annals of Neurology 4: 97-103 (1978).

Gowers, W.R.: Manual of Diseases of the Nervous System, Vol. 2, pp.221-224 (Blakeston, Philadelphia 1897).

Gudmunson, K.; Rhoton, A.L. Jr and Rushton, J.G.: Detailed anatomy of the intracranial portion of the trigeminal nerve. Journal of Neurosurgery 35: 592-600 (1971).

Hallet, M. and Marsden, C.D.: Ballistic flexion movements of the human thumb. Journal of Physiology London, 294: 33-50 (1979).

Hjorth, R.J. and Willison, R.G.: The electromyogram in facial myokymia and hemifacial spasm. Journal of the Neurological Sciences 20: 117-126 (1973).

Janetta, P.J.; Abbasy, M.; Maroon, J.; Ramos, F.M. and Albin, M.S.: Aetiology and definitive microsurgical treatment of hemifacial spasm: Operative techniques and results in 47 patients. Journal of Neurosurgery 47: 321-328 (1977).

Kaufman, M.D.: Masticatory spasm in facial hemiatrophy. Annals of Neurology 7: 585-587 (1980).

Kimura, J.: Electrically elicited blink reflex in diagnosis of multiple sclerosis; Review of 260 patients over a 7-year period. Brain 98: 413-426 (1975).

Lance, J.W.; Burke, D. and Pollard, J.: Hyperexcitability of motor and sensory neurons in neuromyotonia. Annals of neurology 5: 523-532 (1979).

McIntyre, A. and Robinson, R.: Pathway for the jaw jerk in man. Brain 821: 468-473 (1959).

Ochoa, J.L. and Torebjork, H.E.: Parasthesia from ectopic impulse generation in human sensory nerves. Brain 103: 835-853 (1980).

Rasminsky, M.: Ectopic generation of impulses and crosstalk in spinal nerve roots of 'dystrophic' mice. Annals of Neurology 3: 351-357 (1978).

Smith, K. and McDonald, W.I.: Spontaneous and mechanically evoked activity due to central demyelinating lesion. Nature 266: 154-155 (1980).

Spillane, J.D. and Wells, C.E.C.: Isolated trigeminal neuropathy: A report of 11 cases. Brain 82: 391-416 (1959).

Sunderland, S.: Neurovascular relations and anomalies at the base of the brain. Journal of Neurology, Neurosurgery and Psychiatry 11: 243-257 (1948).

Wartenberg, R.: Hemifacial Spasm: A Clinical Pathophysiological Study. (Oxford University Press, New York 1952).

A Case of Lhermitte-Duclos Disease

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Lhermitte-Duclos disease (synonyms: dysplastic gangliocytoma of cerebellum, granule cell hypertrophy of cerebellum, diffuse cerebellar hypertrophy) is characterised by cerebellar enlargement, with abnormal granule cells and loss of normal cerebellar cortex. There may be associated developmental abnormalities. Patients usually present with a history of an expanding posterior cranial fossa lesion.

Case Report

The patient is now aged 34 years. She was born of a normal pregnancy and delivery, and her developmental milestones were normal. There is no family history of cerebellar disturbance, although there is a family history of large heads (head circumference of father = 65cm, head circumference of 10-year-old son = 55cm).

At the age of 18 years she became ataxic, and had small involuntary jerking movements of the face and shoulders. She had an intention tremor, and was hypotonic with pendular knee jerks. The antistreptolysin-0 titre was elevated (500u) and a diagnosis of Sydenham's chorea was made. She recovered completely within several months.

Five years later, at the age of 23, she developed severe headache, with vomiting, blurred vision. She had bilateral papilloedema, bilateral cerebellar signs, ataxia and occipital and lumbar bruits. A vertebral angiogram suggested a cerebellar tumour, and at operation there appeared to be a midline cerebellar lesion. The biopsy showed normal cerebellar cortex. Postoperatively she recovered completely.

At the age of 28 years her headache recurred. On examination she had papilloedema and cerebellar signs. A ventriculogram showed obstruction at the level of the fourth ventricle. At operation a tumour of the vermis was found, and the biopsy again showed normal cerebellar cortex, with an area of vascular malformation. A ventriculo-atrial shunt was inserted, and postoperatively she lost all her symptoms and signs.

By the age of 32 years she had deteriorated and had headache and ataxia. On examination she had a large head (63cm), proptosis, cerebellar signs, and occipital and spinal bruits.

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Plain X-rays of the thoracic spine showed marked erosion of ribs by angioma. Thoracolumbar angiograms showed an extensive angioma, extending from the spinal canal into the surrounding tissues. A myelogram showed extradural compression of the dye column by the angioma.

Vertebral angiograms again demonstrated a cerebellar tumour. Computerised axial tomography (CAT) scans showed the fourth ventricle was absent, but did not demonstrate a clear lesion within the posterior fossa.

The patient was so severely ataxic that further surgical decompression was performed. A midline cerebellar lesion was biopsied. The histology showed loss of normal cerebellar cortex, and the presence of hypertrophied granule cells. On this basis a diagnosis of Lhermitte-Duclos disease was made. Postoperatively she made some improvement, but still had ataxia and intention tremor.

Discussion

Lhermitte-Duclos disease was described in 1920 (Lhermitte and Duclos), and there are now 44 reported cases (Ambler, et al., 1969; Dastur et al., 1975; Leech et al., 1977; Pritchett and King, 1978; Banerjee and Gleadhill, 1979; Calvo et al., 1979; Ferrer et al., 1979; Rilliet and Mori, 1979; Brown et al., 1980). The sex distribution is: males = 28, females = 16. Sixteen of the 44 cases have come to postmortem, the remainder being diagnosed on surgical specimens. Information about other organ involvement must be incomplete, therefore.

Ambler et al. (1969) described the first familial cases. The index case was a young man who died of Lhermitte-Duclos disease. His mother had no neurological problems, but died of other causes, and was found at postmortem to have had Lhermitte-Duclos disease. Before her death she gave a history that large heads were common in her family. This led Ambler et al. to suggest that the disease is familial, with some members of the family being asymptomatic, and recognisable only by their large heads.

Some relatives of our patient have large heads and may belong in this group.

The majority of the 44 patients presented with a history of a posterior fossa expanding lesion, but some were asymptomatic, and diagnosed only at postmortem.

Various abnormalities have been described in association with Lhermitte-Duclos disease. These include megalencephaly (with brain weight up to 2150g), leontiasis ossea, heterotopia, polydactylia, mental retardation, and in one patient there was coexistant neurofibromatosis. Haemangioma also has been reported.

The pathology is of gross hypertrophy of cerebellar folia, with gradual transition from normal to abnormal areas. Histology shows loss of the normal cerebellar architecture, with hypertrophied granule cells and loss of normal cells. Myelinated fibres are also found in the cerebellar cortex on electron microscopy (Pritchett and King, 1978; Ferrer et al., 1979) and there are large granule cells, with prominent nuclei and nucleoli. Nuclear inclusions have been found, but these are not thought to be viral. In the cytoplasm there are plentiful mitochondria, and vesicles which look like catecholamine vesicles.

In other parts of the brain there is hypertrophy, but no abnormal cells or loss of architecture as found in the cerebellum. In other organs there may be

developmental anomalies. Many authors describe the cerebellar lesion as partly hamartoma and partly tumour, and Ambler et al. (1969) suggested that Lhermitte-Duclos disease could be best classified with the phacomatoses.

The prognosis for this condition is that the result would be relatively benign. There are 8 cases reported since 1975, of whom 6 had surgery with positive results. One of these patients had an earlier operation and has been followed up for 11 years with positive results. Our patient has been followed up to 16 years since her initial presentation, and for 7 years since her first surgery.

Summary

A 34-year-old patient has an 18-year history of cerebellar disturbance. She has histology typical of Lhermitte-Duclos disease. Her father and son have large heads, and it is possible that they may be asymptomatic cases of the disease, as first described by Ambler et al. (1969).

Acknowledgements

The authors would like to thank Prof. J.W. Lance and Dr B. Selecki for permission to report this history.

References

Ambler, M.; Pogacar, S. and Sidman, R.: Lhermitte-Duclos disease (granule cell hypertrophy of the cerebellum). Pathological analyses of the first familial cases. Journal of Neuropathology and Experimental Neurology 28: 622-647 (1969).

Banerjee, A.K. and Gleadhill, C.A.: Lhermitte-Duclos disease (diffuse cerebellar hypertrophy) – prolonged post-op survival. Irish Journal of Medical Science 148: 97-99 (1979).

Brown, W.R.; Angelo, J.N. and Kelly, D.L. Jr: Lhermitte-Duclos disease: case report with computerised tomographic scan. Neurosurgery 6: 189-191 (1980).

Calvo, A.; Chouza, C.; Parriel, J.A. and Aymone, F.: Gangliocitoma displasico de cerebelo o enfermedad de Lhermitte-Duclos. Acta Neurologica Latinoamericana 25: 97-106 (1979).

Dastur, H.M.; Pandya, S.K. and Deshpande, D.H.: Diffuse cerebellar hypertrophy. Lhermitte-Duclos disease. Neurology India 23: 53-56 (1975).

Ferrer, I.; Isamat, F. and Acelees, J.: A Golgi and electron microscopic study of a dysplastic gangliocytoma of the cerebellum. Acta Neuropathologica (Berlin) 47: 163-165 (1979).

.Leech, R.W.; Christoferson, L.A. and Gilbertson, R.L.: Dysplastic gangliocytoma (Lhermitte-Duclos disease) of the cerebellum. Journal of Neurosurgery 47: 609-612 (1977).

Lhermitte, J. and Duclos, P.: Sur un ganglioneurome diffus du cortex de cervelet. Bulletin de l'Association francaise pour l'étude du cancer 9: 99 (1920).

Prichett, P.S. and King, T.I.: Dysplastic gangliocytoma of the cerebellum – an ultrastructural study. Acta Neuropathologica (Berlin) 42: 1-5 (1978).

Rilliet, B. and Mori, Y.: Gangliocytome dysplasique de cervelet. Schweizer Archiv für Neurologie, Neurochirurgie and Psychiatrie (Zurich) 124: 13-27 (1979).

Developmental Anomalies Affecting the Fourth Ventricular Outflow Region: A Report of Four Cases

*G.L. Coffey, D.J. O'Sullivan and T.J. Connelley**

Developmental anomalies affecting the nervous system are especially frequent in the region of the lower brain stem, cerebellum and spinal cord, with associated involvement of the surrounding skeletal structures. (Salam and Adams, 1978; Spillane et al., 1957). In general terms and in varying degree these neurological malformations may consist of prolapse of the cerebellum or cerebellar tonsils into the cervical canal, obstruction of the fourth ventricular outflow region by arachnoid adhesions, dilatation with or without caudal displacement of the fourth ventricle, occasionally with cystic dilatation of the roof of the fourth ventricle and perhaps with hydromyelia or syringomyelia.

Arnold-Chiari Anomaly

The malformations described by Chiari in 1891 and 1896 and by Arnold in 1894 are certainly the most widely known and have been the subject of numerous reports (Saez et al., 1976; Rhoton 1976; Banerji and Millar 1974; Appleby et al., 1968; Peach 1965; Malis et al., 1951). The two major components of the Arnold-Chiari anomaly are, firstly, a prolongation of a tongue of cerebellar tissue from the inferior vermis region, either unilaterally or bilaterally, down into the cervical canal (an exaggeration of the normal 'cerebellar tonsils'). These tongue-like projections of cerebellar tissue are closely applied to the dorso-lateral surface of the lower medulla and upper cervical cord and are often bound down by firm adhesions. Secondly, a downward displacement of the medulla and at times of the lower pons as well may be evident, and this may be associated with attenuation

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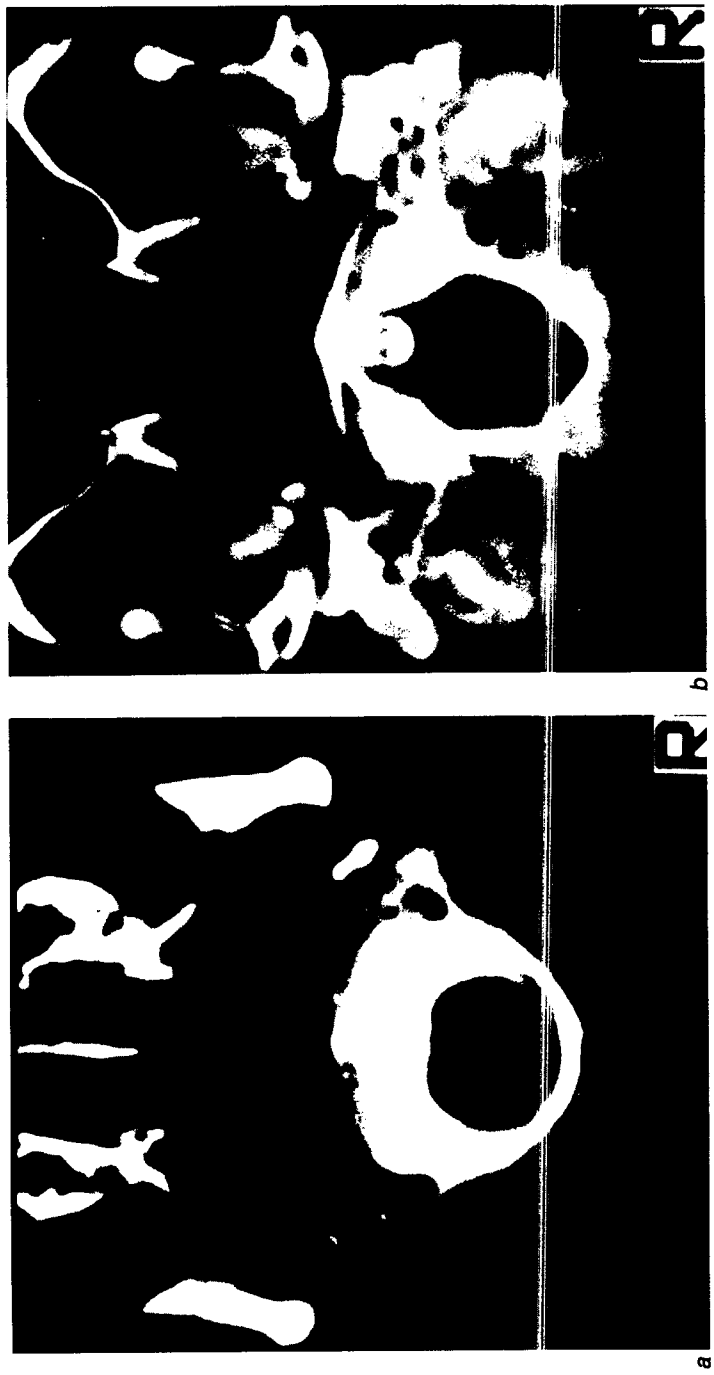

Fig. 1. Case 1: CT scans showing enlargement of upper cervical canal.

of the fourth ventricle which may extend into the upper cervical canal. When downward displacement of the medulla and lower pons is marked, there is often a buckling or kinking of the cervical cord at the cervico-medullary junction – 'the medullary nodule' – which presents as a bulbous expansion of the lower end of the fourth ventricle (Salam and Adams, 1978; Peach, 1965). Many associated anomalies both within the nervous system and in other tissues may also be seen and have been documented by Peach (1965).

Chiari in his original description divided the malformation into 4 categories:

Type 1. Showed a variable displacement of the cerebellar tonsils into the

Fig. 2. Case 1: Metrizamide myelogram showing prominent kink at cervico-medullary junction with prolapsed cerebellar tonsils posterior to this.

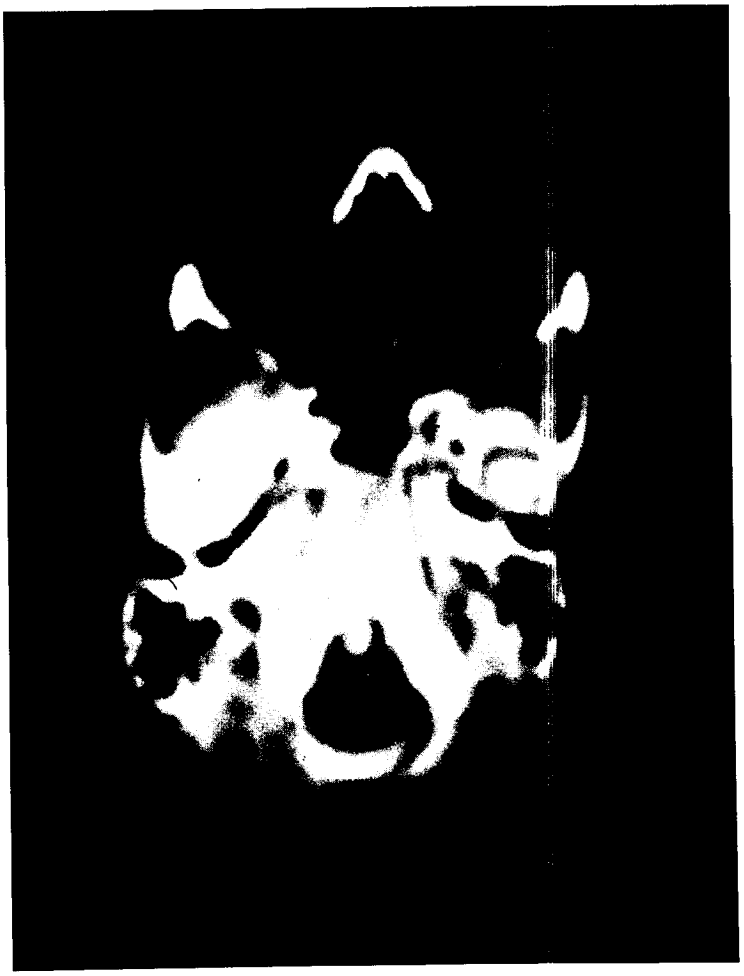

Fig. 3. Case 2: CT scan showing asymmetry of skull base and triangular shaped foramen magnum.

cervical canal with little downward displacement of the medulla.

Type 2. Showed, in addition to the prolapsed cerebellar tonsils, a significant caudal displacement of the lower pons and medulla together with that of an elongated fourth ventricle.

Type 3. Showed a downward displacement of the medulla with herniation of the cerebellum into an occipital meningocele.

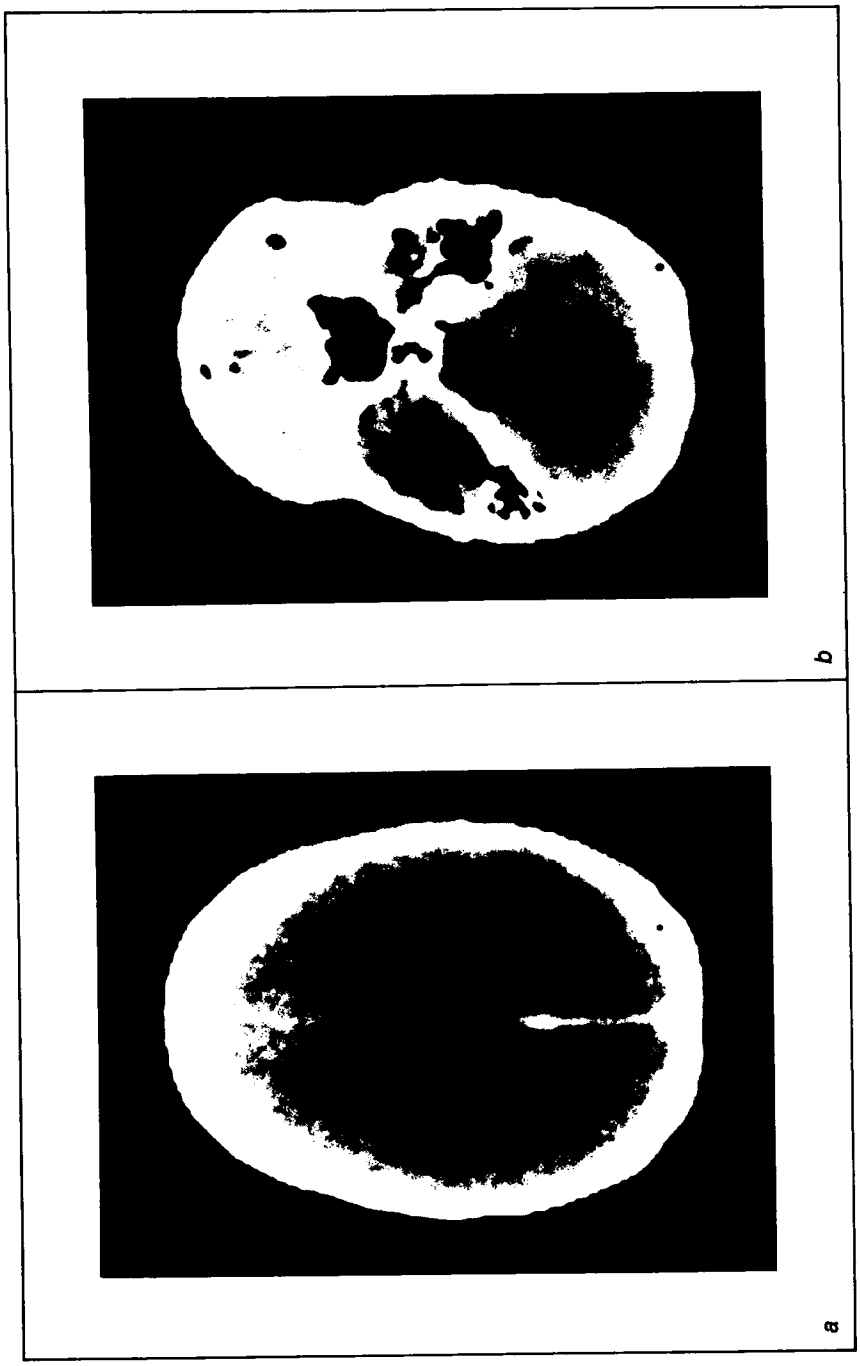

Fig. 4. Case 2: CT scans showing dilatation of ventricular system.

Type 4. Showed hypoplasia of the cerebellum as well as the features of Type 3.

In recent years the term 'Arnold-Chiari malformation' has been largely restricted to the Type 1 and Type 2 categories.

Dandy-Walker Syndrome

In the Dandy-Walker syndrome, atresia of the foramina of Luschka and Magendie has been advanced as the primary anomaly, with enlargement of the fourth ventricle, cystic dilatation of the fourth ventricular roof, and separation and hypoplasia of the cerebellar hemispheres being secondary phenomena (Dandy and Blackfan, 1914; Taggart and Walker, 1942; W.J. Gardner et al., 1957). This view, however, has been disputed by Benda (1954) and E. Gardner et al. (1975).

Spectrum of Developmental Anomalies

From the neurological point of view basilar impression, atlas assimilation and atlanto-axial dislocation are the most important of the bone malformations that are seen in association with these hind brain anomalies. However, as outlined by Heckl (1978) and Spillane et al. (1957), the pathological anatomical arrangements in these conditions may be exceedingly diverse with marked variability of the clinical syndromes so that patients with ostensibly similar lesions can have widely different neurological manifestations. Saez et al. (1976) in analysing their surgical experience with some 60 cases of the Arnold-Chiari malformation, noticed a considerable variability in the degree of tonsillar herniation and in the degree of buckling, rotation, displacement and deformity of the medulla and spinal cord, and concluded that the Arnold-Chiari malformation represented a pathological continuum secondary to a complex derangement of neural embryogenesis. These authors concluded that the classification into Type 1 and Type 2 should not be rigidly held to, but should be seen simply as part of the spectrum of this developmental anomaly.

This variability in anatomical structure and clinical expression is also seen among the various subtypes of hind brain anomaly, so that W.J. Gardner et al. (1957), in discussing embryonal atresia of the fourth ventricle in adults, concluded that the Arnold-Chiari malformation, congenital atresia of the foramen of Magendie with a diverticulum of the fourth ventricle (referred to as the Dandy-Walker syndrome), arachnoid cyst of the cerebellum, and syringomyelia, were merely varying expressions of the same disease process. These entities are thus believed to be produced by a common cause, namely a failure of the normal development of the outlets of the fourth ventricle in the rhombic roof of the embryo. In addition, Wickbom and Hanafee (1963) have stated that a considerable degree of overlap occurs between these entities so that a precise classification is not always possible. Other authors (Benda, 1954 and Gardner et al., 1975) however, preferred to take the view that the Arnold-Chiari and Dandy-Walker syndromes are separate developmental anomalies arising at different

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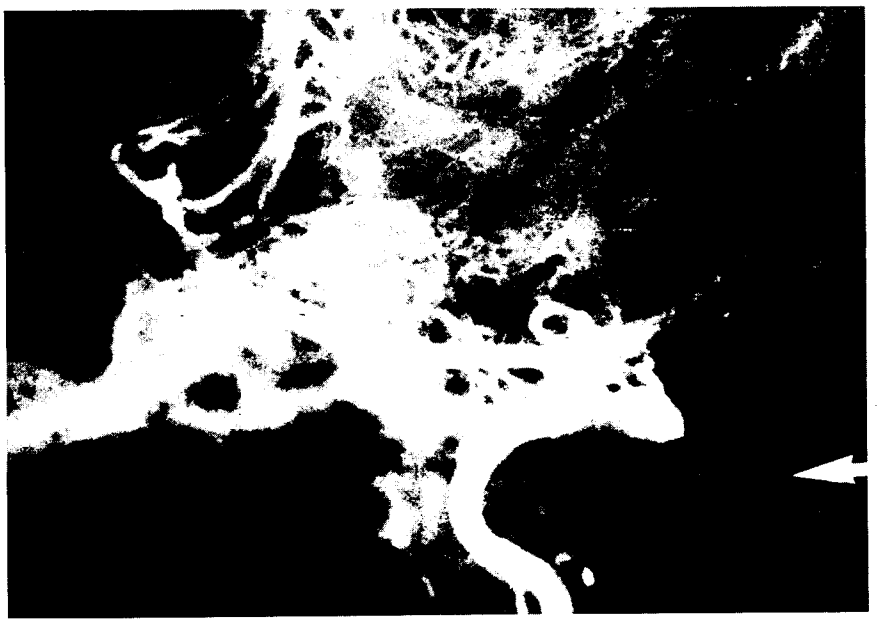

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Fig. 5. Case 2: Vertebral angiogram (AP view) showing caudal displacement of loop of posterior inferior cerebellar artery on the right associated with prolapse of the right cerebellar tonsil.

Fig. 6. Case 2: Vertebral angiogram (lateral view) showing caudal displacement of loop of posterior inferior cerebellar artery into upper cervical canal.

periods in embryogenesis and thus probably having different causes.

Irrespective of the above arguments the clinical syndromes seen in these hind brain anomalies do show a marked variability from case to case, with the degree of neurological disability often bearing little relation to the severity of the observed anatomical derangement. While the fully developed syndrome may be readily recognised clinically, it seems probable that milder examples of these anomalies may be overlooked and misdiagnosed as 'possible migraine' or 'possible multiple sclerosis', leading to delays in treatment. These syndromes do appear to be progressive at least in some instances (Saez et al., 1976; Rhoton 1976) especially as regards the development and progression of syringomyelic symptoms (Foster and Hudgson, 1973; Newman et al., 1981), and there is evidence that such symptoms, secondary to central cord cavitation, once established, respond less well to treatment (Saez et al., 1976).

The case reports of 4 patients with hind brain abnormalities affecting fourth ventricular outflow are detailed here, in order to show the diversity of clinical presentations which may occur and emphasise the fact that minimal or no objective neurological abnormality may be found in the presence of quite definite structural derangement. Saez et al. (1976) draw attention to this point, 13 of their patients having occipital headache as their only complaint. Six of these patients had no abnormal findings on neurological examination, their headaches

Fig. 7. Case 2: Air encephalogram showing anterior displacement of cervico-medullary region by posterior mass (prolapsed cerebellar tonsil) and failure of entry of air into fourth ventricle.

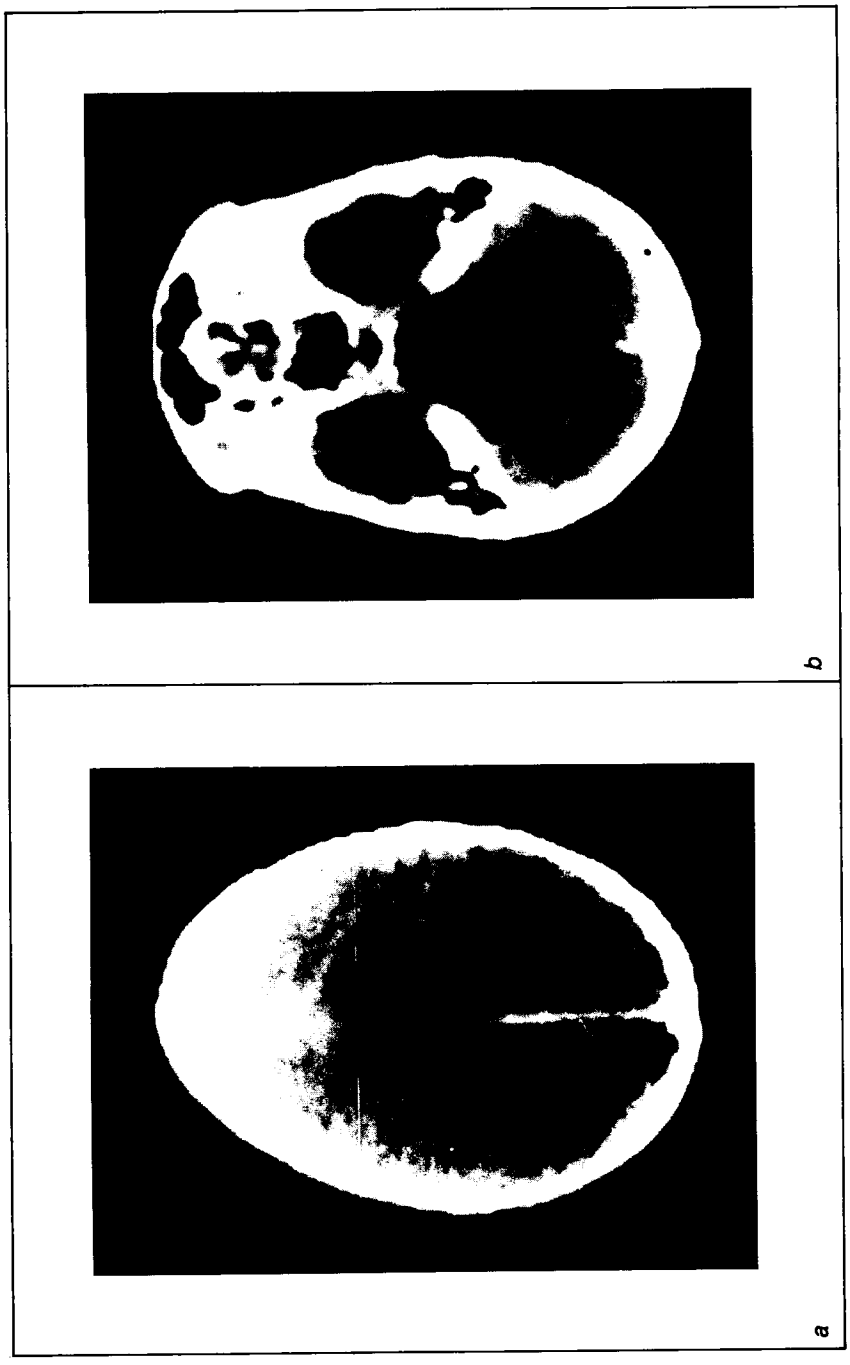

Fig. 8. Case 3: CT scans showing dilatation of ventricular system including that of fourth ventricle.

originally being considered functional in nature. In this respect CT scanning has an especially valuable role to play as an initial screening procedure and may provide the basis for more detailed neuro-radiological investigation. A normal or negative CT scan examination does not exclude the presence of a hind brain developmental anomaly, however, and it may be necessary to proceed to metrizamide myelography or pneumoencephalography in order to investigate fully certain patients in this group.

Suboccipital craniectomy and upper cervical laminectomy with adequate decompression of the foramen magnum region and upper cervical spine to establish a free outflow from the fourth ventricle, are the treatments of choice. However, additionally, in certain instances where the main pathology has been that of obstruction of the fourth ventricular outflow, ventricular shunting may be required for relief of continuing symptoms. It is postulated that such surgery, particularly in establishing a free outflow of CSF from the fourth ventricle, may also have a protective influence in the long term against the subsequent development of central cord damage due to hydromyelia or syringomyelia.

Case Reports

Case 1

Mrs J.M., aged 40 years, presented with a 10-month history of severe and persistent cervical-occipital headache, associated with neck stiffness. At times she experienced a burning pain in the neck which radiated down across both shoulders and into the upper arms. Neurological examination was normal.

Radiographs of the skull and cervical spine were normal. A CT brain scan showed that the cervical canal at the level of C_1 was rounder and larger than normal. Cisternal myelography demonstrated prolapsed cerebellar tonsils. The upper cervical cord was slightly expanded and kinked. No dye entered the fourth ventricle. Air encephalography confirmed the presence of prolapsed cerebellar tonsils. A small cisterna magna was present but air could be manoeuvred into the ventricular system.

A posterior fossa midline suboccipital craniectomy and excision of the arch of C_1 and C_2 was performed. A prominent kink at the cervico-medullary junction was seen, together with depressed cerebellar tonsils. The cerebellar tonsils were separated and the fourth ventricle was explored and the dilated origin of the cervical canal was seen.

The patient's postoperative progress was uneventful and she has remained free of headache over a 6-month follow-up.

Case 2

Miss S.L., aged 16 years, presented with a 2-year history of a nasal type of dysarthria which had become worse in the few months preceding admission so that it was difficult for her family to understand her. Difficulties in drinking fluids had been noted, with occasional regurgitation through the nose. For 12 months the patient complained of recurrent frontal headaches which were relieved by lying down.

On examination the left side of her face appeared smaller than the right. There was marked nasal dysarthria with absent palatal movement and no gag reflex. Her tongue was normal. There was wasting and weakness of the muscles of both shoulder girdles. The reflexes were symmetrical with no long tract signs.

Plain radiographs of the skull confirmed the cranial asymmetry. A CT scan showed generalised dilatation of the ventricular system with displacement of the fourth ventricle to the right. There was asymmetry of the skull base with a triangular shaped foramen magnum. Vertebral angiography showed downward displacement of the right posterior inferior cerebellar artery

loop, suggesting herniation of the right tonsil. On air encephalography the medulla was seen to be displaced anteriorly by a posterior mass bulging at the foramen magnum, but no air entered the fourth ventricle.

A posterior fossa craniectomy and high cervical laminectomy was performed. The right cerebellar tonsil was noted protruding down through the foramen magnum to the level of C_2. The left cerebellar tonsil was normal. CSF flowed freely from the fourth ventricle after it was decompressed and the central canal entering the floor of the fourth ventricle appeared to be normal.

The patient's postoperative progress was uneventful and there has been a steady improvement in symptoms and signs over a 12-month follow-up. Palatal movement returned to normal.

Case 3

Mrs L.B., aged 36 years, presented with a 12-month history of recurrent occipital headache which had been diagnosed as migraine. For 1 month before admission there were complaints

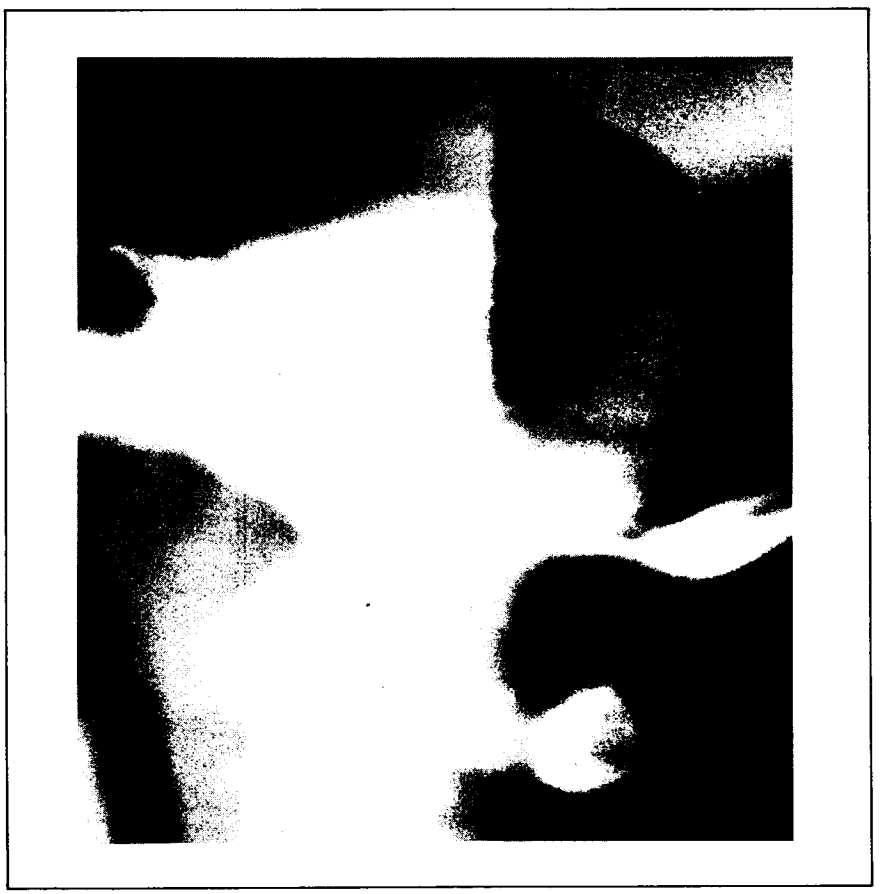

Fig. 9. Case 3: Air encephalogram showing considerable dilatation of fourth ventricle and lower aqueduct.

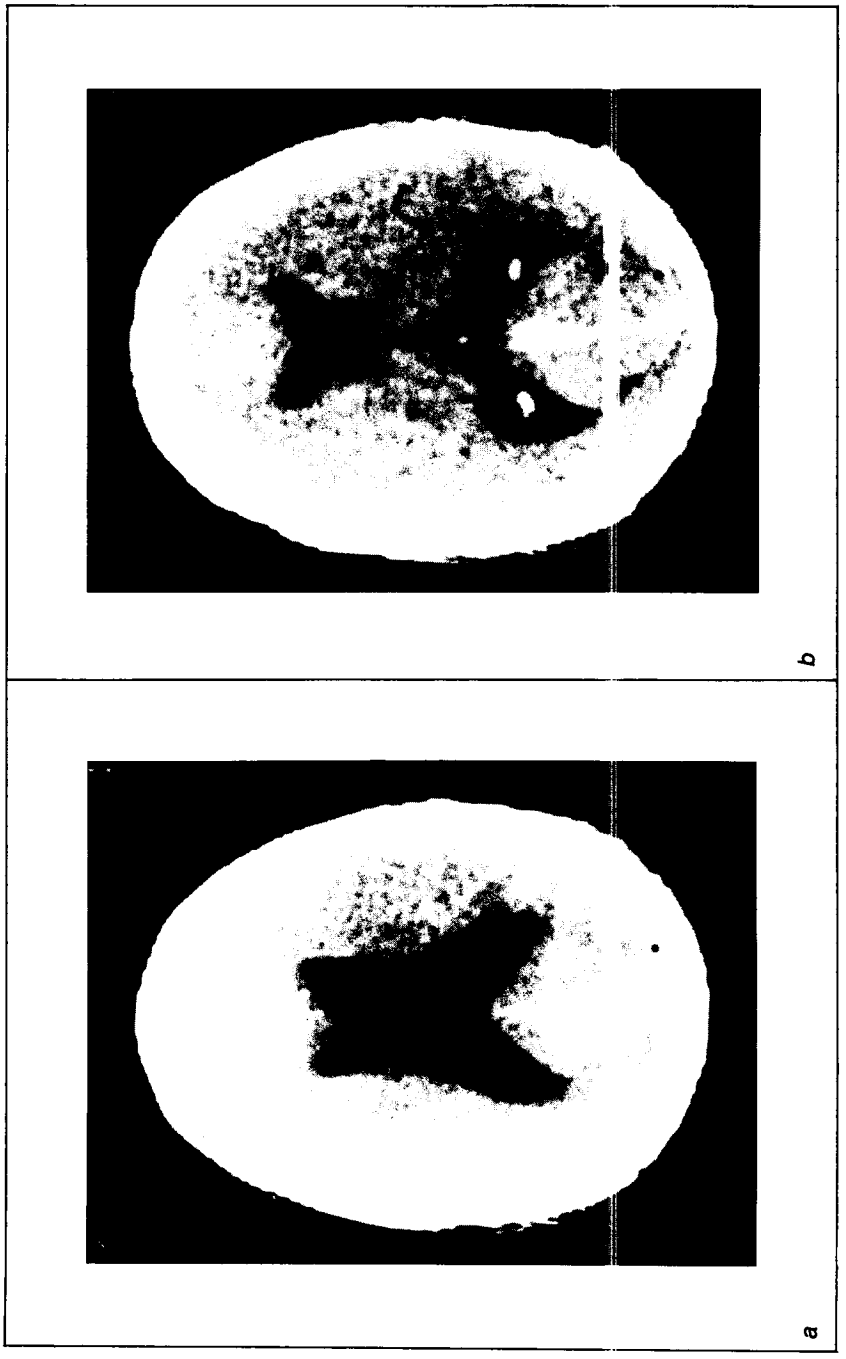

Fig. 10. Case 4: CT scans showing uniform dilatation of ventricular system.

of recurrent momentary giddy episodes brought on by any sudden change of position or by being driven in a car for more than a short time. Neurological examination was normal.

A CT scan showed considerable dilatation of the fourth ventricle with mild dilatation of the third and lateral ventricles. Vertebral angiography showed lateral displacement of the choroidal points of the posterior inferior cerebellar arteries on both sides suggesting lateral expansion of the fourth ventricle. The precentral cerebellar vein was also displaced, consistent with posterior enlargement of the fourth ventricle. On air encephalography air was held up for a considerable time in the cisterna magna and upper cervical canal before entry into the fourth ventricle was achieved. The fourth ventricle and aqueduct were shown to be considerably dilated. The findings were suggestive of partial, possibly intermittent, obstruction of the outlets of the fourth ventricle.

Posterior fossa suboccipital craniectomy was performed. The fourth ventricle was found to be considerably dilated and the roof of the fourth ventricle was covered by a thin layer of arachnoidal membrane with almost total obstruction of the foramen of Magendie. The central canal at the obex region was dilated in a funnel shape. The overlying membrane was cleared and a drainage tube inserted with the large central canal being plugged with muscle.

Postoperatively the patient developed meningitis which did not respond until the drainage tube was removed. Following this, however, persistent headaches once again developed and finally a ventriculo-peritoneal shunt was inserted. Steady improvement followed, and for the 6-month follow-up the patient remained well with no headache and only mild occasional dizziness.

Case 4

Mr D.R., aged 40 years, complained some 12 months prior to admission of occipital headache which radiated down into the neck. At that time he was noted to be slightly unsteady on

Fig. 11. Case 4: Ventriculogram showing caudal displacement of an enlarged fourth ventricle with outlet obstruction. The origin of the dilated central canal is also seen.

his feet. One month prior to admission he had a brief episode of loss of consciousness precipitated by sudden change of position but since then his gait and balance had been much worse and he had noted some clumsiness in his right hand.

On examination his gait was broad based and ataxic and he had mild finger/nose and heel/shin incoordination.

A CT scan showed considerable dilatation of the ventricular system with normal cortical markings. Carotid and vertebral angiography confirmed the presence of hydrocephalus. On air encephalography, air introduced by lumbar puncture failed to enter the ventricular system and was held up at the cranio-cervical junction. On air ventriculography air was manoeuvred from the third ventricle through the aqueduct into the fourth ventricle where it obstructed at the outlet of the fourth ventricle. The fourth ventricle was displaced inferiorly.

A posterior fossa craniectomy was carried out. At operation the arch of C_1 was noted to be incomplete. There was no recognisable development of the cerebellar tonsils. On separating the cerebellar hemispheres and inspecting the posterior aspect of the fourth ventricle, no recognisable exit foramen could be seen, the area being densely encased in fibrous tissue. Biopsies revealed fibrosis and gliosis. The dense adhesions were divided and the fourth ventricle opened to allow free drainage of CSF.

The patient's postoperative progress was uneventful. His gait and balance returned to normal, but 12 months later he again presented complaining of unsteadiness. A CT scan showed marked ventricular dilatation and ventriculo-peritoneal shunting has since been carried out.

Discussion

Certain developmental anomalies affecting the hind brain, cerebellum and spinal cord can be classified into well-recognised groups such as the Arnold-Chiari malformation and the Dandy-Walker syndrome, with each entity having specific distinguishing features. (Gilman et al., 1981; Benda 1954; Gardner et al., 1975).

Such anomalies may be associated with a variety of skeletal malformations affecting skull base and cervical spine (Heckl, 1978). These syndromes may occur without any associated skeletal anomaly, however, and identical clinical syndromes can have widely different structural bases (Spillane et al., 1957).

Although clear cut examples of the developmental anomalies exist, individual patients often show many features of overlap with a marked diversity and variability, both of structural features and of clinical presentation, so that precise classification becomes difficult or impossible (W.J. Gardner et al., 1957; Wickbom and Hanafee, 1963, Saez et al., 1976). The 4 cases here presented help to highlight this variability both in anatomical features and clinical expression, and tend to reinforce the conclusion of Gardner et al. (1975) that 'these pathological entities are merely varying expressions of the same disease process produced by a common cause'.

As stressed by Saez et al. (1976), patients with significant structural anomalies can present with symptoms which in the absence of neurological findings may be classified as being non-organic in nature. CT scanning may prove to have a valuable role in identifying these early cases by showing, for example, a dilatation or displacement of the fourth ventricle and thus providing an impetus for contrast radiological procedures to be undertaken. In this way, such patients may be offered surgical treatment at an earlier stage in the natural history of

their condition and before the appearance of changes due to progressive hydromyelia.

The aim of surgical treatment is to achieve free outflow of CSF from the fourth ventricle together with adequate decompression of the hind brain and upper cervical cord by posterior fossa craniectomy and upper cervical laminectomy (Saez et al., 1976; Rhoton, 1976).

Ventricular shunting may be necessary as an additional procedure but should not be regarded as sufficient treatment in its own right. There is evidence that hydromyelia can progress and syringomyelic symptoms develop when shunting alone has been used and the fourth ventricular outflow obstruction left uncorrected (Rhoton, 1976).

Summary

Developmental anomalies affecting the hind brain, cerebellum and spinal cord with associated malformations of the skull base and cervical spine, show a wide degree of variability and overlap so that cases are often difficult to classify into a fixed category such as the Arnold-Chiari malformation Type 1 or Type 2, or the Dandy-Walker syndrome.

The 4 cases presented here illustrate this problem and offer support for the hypothesis that these conditions may be merely the varying expression of a common pathological process.

The CT brain scan may prove to be a valuable means of allowing early recognition of these anomalies so that effective surgical treatment can be given at an early stage in their natural history, possibly thereby preventing the progression or development of central cord cavitation with its significant and permanent disabilities.

References

Appleby, A.; Foster, J.B.; Hankinson, J. and Hudgson, P.: The diagnosis and management of the Chiari anomalies in adult life. Brain 91: 131-140 (1968).

Arnold, J.: Myelocyste, transposition von Gewebskeimen und Sympodie. Beiträge zur pathologischen Anatomie und zur allgemeinen Pathologie 16: 1-28 (1894).

Banerji, N.K. and Millar, J.H.D.: Chiari malformation presenting in adult life. Its relationship to syringomyelia. Brain 97: 157-168 (1974).

Benda, C.E.: The Dandy-Walker syndrome or the so-called atresia of the foramen Magendie. Journal of Neuropathology and Experimental Neurology 13: 14-29 (1954).

Chiari, H.: Über Veränderungen des Kleinhirns in Folge von Hydrocephalie des Grosshirns. Deutsche Medizinische Wochenschrift 17: 1172-1175 (1891).

Chiari, H.: Über Veränderungen des Kleinhirns, des Pons und der Medulla oblongata in Folge von congenitaler Hydrocephalie des Grosshirns. Denkschr. K. Akad. Wissensch. Matnaturw. Kl. 63: 71-116 (1896).

Dandy, W.E. and Blackfan, K.D.: Internal hydrocephalus: An experimental, clinical and pathological study. American Journal of Diseases of Childhood 8: 406-482 (1914).

Foster, J.B. and Hudgson, P.: The surgical treatment of communicating syringomyelia; in Barnett, Foster, and Hudgson (Eds) Syringomyelia — Major Problems in Neurology pp.64-78 (W.B. Saunders, Philadelphia 1973).

Gardner, E.; O'Rahilly, R. and Prolo, D.: The Dandy-Walker and Arnold-Chiari malformations. Archives of Neurology 32: 393-407 (1975).

Gardner, W.J.; Abdullah, A.F. and McCormack, L.J.: The varying expressions of embryonal atresia of the fourth ventricle in adults. Arnold-Chiari malformation, Dandy-Walker syndrome, 'Arachnoid' cyst of the cerebellum and syringomyelia. Journal of Neurosurgery 14: 591-605 (1957).

Gilman, S.; Bloedel, J.R. and Lechtenberg, R.: Cerebellar anomalies in Disorders of the Cerebellum 13: pp.263-284 (F.A. Davis Company, Philadelphia 1981).

Heckl, R.W.: Bone malformations of the craniocervical region: Clinical aspects; in Vinken, P.J. and Bruyn, C.W. (Eds) Handbook of Clinical Neurology 32 (1): 66-98 (North Holland Biomedical Press, Elsevier 1978).

Malis, L.I.; Choen, I. and Bross, S.W.: Arnold-Chiari malformation. AMA Archives of Surgery 63: 783-798 (1951).

Newman, P.K.; Terenty, T.R. and Foster, J.B.: Some observations on the pathogenesis of syringomyelia. Journal of Neurology, Neurosurgery and Psychiatry 44: 964-969 (1981).

Peach, B.: Arnold-Chiari malformation – Anatomic features of 20 cases. Archives of Neurology (Chicago) 12: 613-621 (1965).

Rhoton, Jr A.L.: Microsurgery of Arnold-Chiari malformation in adults with and without hydromyelia. Journal of Neurosurgery 45: 473-483 (1976).

Saez, R.J.; Burton, M.O. and Takehiko Yanagihara.: Experience with Arnold-Chiari malformation, 1960 to 1970. Journal of Neurosurgery 45: 416-422 (1976).

Salam, M.Z. and Adams, R.D.: The Arnold-Chiari malformation; in Vinken and Bruyn (Eds) Handbook of Clinical Neurology 32 (2): pp.99-110 (North Holland Biomedical Press, Elsevier 1978).

Spillane, J.D.; Pallis, C. and Jones, A.M.: Developmental anomalies in the region of the foramen magnum. Brain 80: 11-48 (1957).

Taggart, J.K. and Walker, A.E.: Congenital atresia of the foramina of Luschka and Magendie. Archives of Neurology and Psychiatry 48: 583-612 (1942).

Wickbom, I. and Hanafee, W.: Soft tissue masses immediately below the foramen magnum. Acta Radiologica 84: 647-658 (1963).

Neurophysiological Evidence of Aging in Down's Syndrome

*R.A. Mackenzie, H. Creasey and C.Y. Huang**

Down's syndrome is a genetically determined disorder in which there appears to be an exaggeration and acceleration of the normal processes of aging. The aim of this study was to examine electrophysiological parameters of peripheral and central nervous system (CNS) function in Down's syndrome subjects and compare the findings with age-matched controls to determine whether there were changes related to aging.

Methods

Fifteen institutionalised persons with Down's syndrome were studied after informed consent was obtained from first degree relatives. There were 12 males and 3 females aged 25 to 59 years (mean 45.4 years). All had had trisomy 21 confirmed by appropriate chromosome studies, and all had some of the phenotypic defects appropriate to Down's syndrome. All were well cared for and had no external evidence of acquired peripheral or CNS damage.

Tests were carried out in a warm room and a skin temperature of 31°C was maintained at all times. Electrical stimuli were square wave pulses 0.2 msec in duration applied through a stimulus isolation unit and surface electrodes. Conventional techniques were used to measure sensory action potential (SAP) amplitude and latency (median, ulnar and sural nerves) and muscle action potential (MAP) amplitude and motor conduction velocity (median and common peroneal nerves). Somatosensory potentials were evoked by stimuli delivered to the left median nerve at the wrist (5/second) and to the left posterior tibial nerve at the ankle (3/second), sufficient to produce a visible twitch of the appropriate distal

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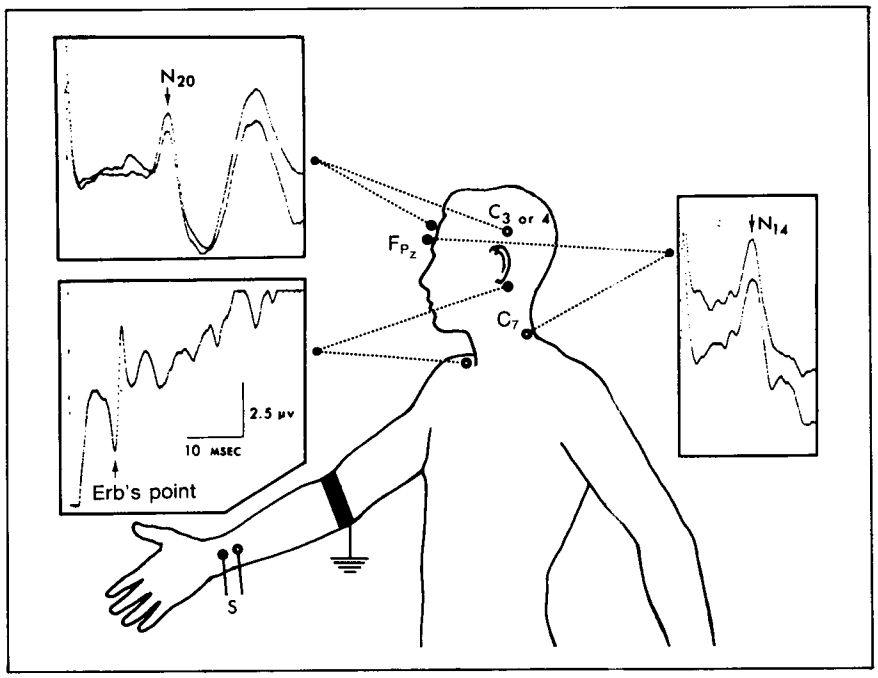

Fig. 1. Median nerve SEPs recorded over Erb's point, the seventh cervical spine (CV_7) and the contralateral scalp (C_4) with a central frontal electrode (F_z) as reference.

muscle. Recording electrodes were 5mm silver chloride discs secured to the skin by plastic tape and filled with an electrolytic salt gel to give inter-electrode impedence of less than 5 kOhm. Median nerve somatosensory evoked potentials (SEPs) were recorded over Erb's point (EP), the seventh cervical spine (CV_7) and the contralateral scalp (C_4); a central frontal electrode (F_z) was used for reference (fig. 1). Posterior tibial nerve SEPs were recorded over L1 spinous process with right iliac crest reference, and over the central scalp (C_z) with F_z reference (fig. 2). Signal averaging was performed with standard electromyographic equipment by a digital averager using 512 and 1024 addresses and superimposing photographically 2 separate runs for each recording. Results were compared with age-matched control subjects from previous studies (Mackenzie and Phillips, 1981; Huang, unpublished).

Results

Peripheral Nerve Function

Four Down's syndrome subjects had abnormalities of peripheral nerve function sufficient for the diagnosis of peripheral neuropathy. Three of these, aged

59, 55 and 53 years respectively, had absent median, ulnar and sural SAPs; the 2 older subjects also had mild slowing of conduction in one motor nerve while 2 of the 3 had reduced peroneal nerve MAP amplitude. The fourth patient, a female aged 35 years, had slowed motor conduction in both median and common peroneal nerves, but normal SAP and MAP amplitudes. A further 5 Down's syndrome subjects had non-diagnostic abnormalities; the oldest, aged 51 years, had borderline reduced sural SAP and mildly reduced median MAP amplitude but normal motor velocities; the other 4 subjects, aged 34 to 45 years, had either mildly reduced SAP amplitude or mildly reduced motor conduction velocity in one nerve. Yet another Down's subject had no recordable median nerve SAP and a prolonged distal MAP latency, but all other peripheral nerves tested were normal; these results were attributed to carpal tunnel syndrome. The other 5

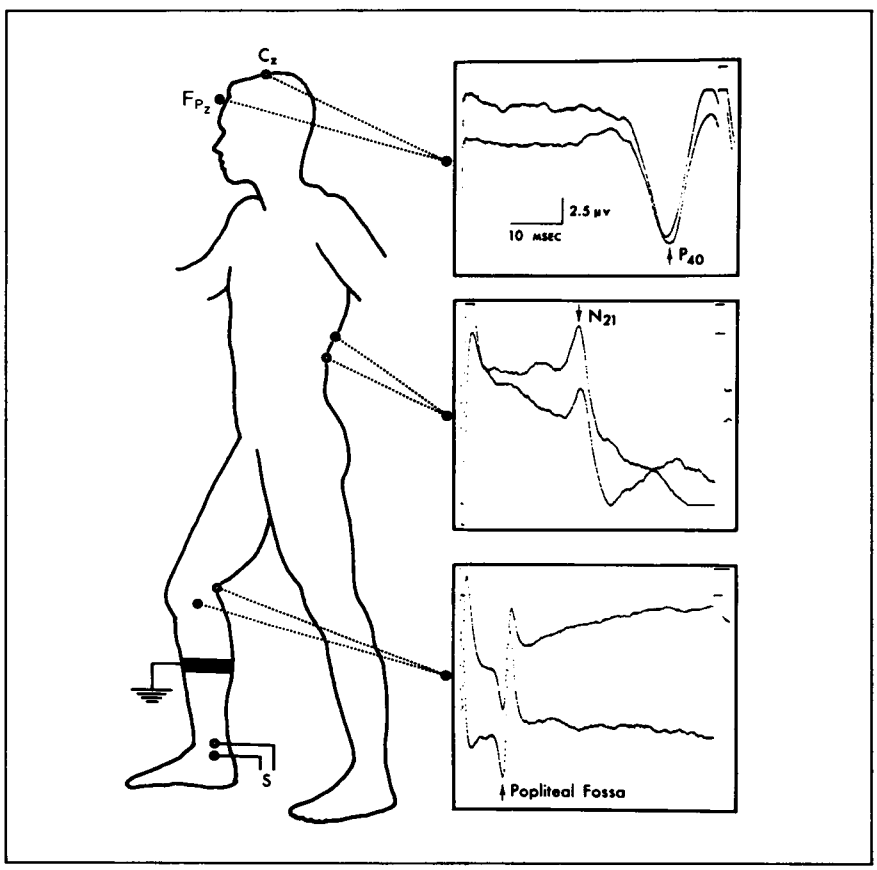

Fig. 2. Posterior tibial nerve SEPs recorded over L_2 spinous process with right iliac crest reference, and over the central scalp (C_z) with F_z as reference.

Table I. Electrophysiological parameters of peripheral nerve conduction: A comparison of Down's syndrome subjects with age-matched controls

	Down's syndrome	Controls	Significance
Age 25-45 years	(n = 7)	(n = 15)	
Median SAP (μV)	19.9 ± 9.5	21.0 ± 5.0	NSD
Sural SAP (μV)	10.5 ± 6.1	11.0 ± 2.5	NSD
Age 46-59 years	(n = 8)	(n = 15)	
Median SAP (μV)	9.8 ± 8.4	16.0 ± 5.0	$p < 0.05$
Sural SAP (μV)	6.5 ± 8.0	10.0 ± 2.5	NSD
Age 25-59 years	(n = 15)	(n = 30)	
Median SAP (μV)	14.5 ± 12	20.0 ± 5.0	NSD
Sural SAP (μV)	8.4 ± 7.2	12.0 ± 5.0	NSD
Median MAP (mV)	8.8 ± 3.6	10.7 ± 3.4	NSD
Median vel (m/sec)	53.1 ± 5.4	59.1 ± 5.0	$p < 0.05$
Peron. MAP (mV)	4.5 ± 1.6	7.3 ± 2.5	$p < 0.001$
Peron. vel (m/sec	47.9 ± 5.4	50.7 ± 3.3	NSD

All values are mean ± standard deviation
NSD = No significant difference

subjects, aged 59, 55, 46, 30 and 25 years respectively, had completely normal peripheral nerve conduction parameters.

Table I shows that median nerve SAP is significantly smaller in the older Down's subjects than age-matched controls; in fact, the decrease in mean SAP with age by 10μV is significantly greater than the 5μV decrease in controls ($p < 0.001$). Although mean sural SAP amplitude in the older Down's subjects is also less than controls, the large SD prevented statistical significance. Nevertheless, the mean decrease of 4μV compared with 1.0μV was significant ($p < 0.05$). Other parameters of peripheral nerve function were not significantly different when comparing the younger and older groups, but median nerve motor velocity and peroneal MAP were significantly reduced in the overall Down's group compared with age-matched controls.

Upper Limb SEPs

The absolute latency to peak of the potential recorded over Erb's point to median nerve stimulation was 8.5 ± 0.7 msec (arm length 49.3cm, extrapolated peripheral velocity 58 m/second) for Down's subjects, compared with 9.5 ± 0.5 msec (arm length 65cm, velocity 68.4 m/second). Upper limb 'central conduction time' was estimated by subtracting Ep latency from that of the potential at CV_7 (N_{14}) or at C_4 (N_{20}).

It may be seen from table II that both Ep − N_{14} and Ep − N_{20} are significantly prolonged in Down's compared with control subjects in all age groups. N_{14} to N_{20} age differences were not significant, however, even though the increase with age was 0.9 msec in Down's compared with 0.1 msec in control subjects.

Table II. Upper limb SEPs: Comparison of Down's syndrome subjects with age-matched controls

	Down's syndrome	Controls	Significance
Age 25-45 years	(n = 7)	(n = 15)	
EP-N_{14} lat	4.4 ± 0.6	3.3 ± 0.4	$p < 0.001$
EP-N_{20} lat	10.3 ± 1.1	9.3 ± 0.4	$p < 0.05$
N_{14}-N_{20} lat	5.9 ± 0.6	5.9 ± 0.4	NSD
Age 46-59 years	(n = 8)	(n = 15)	
EP-N_{14} lat	4.6 ± 1.0	3.5 ± 0.4	$p < 0.01$
EP-N_{20} lat	11.6 ± 2.2	9.5 ± 0.5	$p < 0.01$
N_{14}-N_{20} lat	6.8 ± 1.7	6.0 ± 0.4	NSD
Age 25-59 years	(n = 15)	(n = 30)	
EP-N_{14} lat	4.5 ± 0.8	3.4 ± 0.4	$p < 0.001$
EP-N_{20} lat	11.0 ± 1.8	9.4 ± 0.4	$p < 0.02$
N_{14}-N_{20} lat	6.4 ± 1.3	6.0 ± 0.4	NSD

All values are latencies in msec.
NSD = No significant difference

Lower Limb SEPs

The absolute latency to peak of the potential record over the thoracolumbar spine to posterior tibial nerve stimulation (N_{21}) was 21.1 ± 2.1 msec for Down's subjects and 21.4 ± 2.0 in controls. However, the mean height of the Down's group was 151.3cm compared with 169.1cm in controls and a previous study (Mackenzie and Phillips, 1981) has shown that there is a directly proportionate relationship between N_{21} latency and height. In table III a correction factor has been applied to N_{21} latencies of Down's subjects:

$$\text{Corrected latency} = \text{Absolute latency} \times \frac{\text{mean height of controls}}{\text{height of Down's subject}}$$

It can be seen from the table that the corrected N_{21} latency is significantly prolonged in Down's subjects aged 25 to 45 years, but the difference is not statistically significant in the older or the total group. N_{21} amplitude is significantly reduced in all groupings of Down's subjects. Lower limb 'central conduction time' has been estimated by subtracting (uncorrected) N_{21} latency from that of the initial scalp-recorded positive potential (P_{40}). It can be seen from the table that this parameter was significantly prolonged in all age groups of Down's syndrome. In fact this difference in central latencies was greater in the younger Down's group (17.9 msec) than in the older control group (16.7 msec) despite the difference in height in the 2 groups. This marked increase in central conduction time in both young and old groups may have been responsible for the failure of the figures to demonstrate a statistically significant increase in central conduction time with age in Down's syndrome, while the results in the control group did demonstrate such an increase (14.6 to 16.7 msec; $p < 0.01$).

Table III. Lower limb SEPs: Comparison of Down's syndrome subjects with age-matched controls

	Down's syndrome	Controls	Significance
Age 25-45 years	(n = 7)	(n = 15)	
N_{21} amp (μV)	0.5 ± 0.4	1.7 ± 0.8	$p < 0.01$
N_{21} lat[1] (msec)	23.5 ± 1.8	21.4 ± 2.0	$p < 0.001$
P_{40}-N_{21} (msec)	17.9 ± 2.3	14.6 ± 1.2	$p < 0.01$
Age 46-59 years	(n = 8)	(n = 15)	
N_{21} amp (μV)	0.5 ± 0.4	1.0 ± 0.4	$p < 0.05$
N_{21} lat[1] (msec)	23.5 ± 2.5	22.9 ± 1.9	NSD
P_{40}-N_{21} (msec)	18.7 ± 2.2	16.7 ± 1.4	$p < 0.01$
Age 25-59 years	(n = 15)	(n = 30)	
N_{21} amp (μV)	0.5 ± 0.4	1.3 ± 0.6	$p < 0.001$
N_{21} lat[1] (msec)	23.5 ± 2.0	22.1 ± 2.0	NSD
P_{40}-N_{21} (msec)	18.3 ± 2.2	15.7 ± 1.2	$p < 0.001$

1 Corrected latency = Absolute latency $\times \frac{\text{mean height of controls}}{\text{height of subject}}$

NSD = No significant difference

Discussion

Down's syndrome, unlike other disorders causing mental subnormality, is associated with a steeply rising mortality rate after the age of 40 years, to the extent that very few reach the age of 60 years (Richards, 1975). This phenomenon could be explained by assuming a more rapid rate of aging in this condition. The lifespans of most animal species, including man, have a genetically determined maximum. There are examples of human genetic mutations, such as progeria and Werner's syndrome, which produce a phenotype resembling premature aging and may involve genes related to the aging process. Down's syndrome also produces an appearance of premature aging and may be due to abnormal gene regulatory mechanisms (Brown, 1979). Changes in the immune competence of Down's syndrome subjects, such as disturbed mobility of cell membrane receptors of peripheral mononuclear cells (Naeim and Walford, 1980) and a deficiency of the T-dependent regulatory system (Francheschi et al., 1981) are consistent with precocious aging of the immune system. Neuropathologists recognise that Alzheimer type neurofibrillary tangles, cerebral atrophy and senile plaques occur in Down's syndrome, especially those surviving past the fortieth year (Schochet et al. 1973; Malamud, 1972).

Electrophysiological studies might be expected to assist in the understanding of any associated premature CNS disturbance. The EEG shows a progressive slowing of rhythms with increasing age in normal subjects, but a study of young and aged Down's subjects by Crapper at al. (1975) found no increase in EEG abnormalities with age; a single patient with mosaic Down's syndrome in ter-

minal stage showed progressive slowing of rhythms only in the last 3 months before death and postmortem showed Alzheimer degenerative change.

Event-related or brain evoked potentials have been shown to be sensitive to the effects of aging. Flash and pattern-reversal visual evoked potentials show increased latency in elderly subjects (Dustman and Beck, 1969; Celesia and Daly, 1977) and the onset latencies of scalp SEPs from median and posterior tibial nerve stimulation increase with age (Dorfman, 1977). These findings have been confirmed by others (Mackenzie and Phillips, 1981; Huang, unpublished), but Desmedt and Cheron (1980) found no increase in central conduction time in healthy octogenarians.

The results of the present study suggest increasing peripheral and central nervous system dysfunction with age in Down's syndrome. The changes in peripheral nerve function are similar to the well-known indications of axonal degeneration with increasing age in normal subjects (Behse and Buchthal, 1971; Nielsen, 1973). We have been unable to find a previous report of this finding in Down's syndrome. The upper limb SEP study showed prolonged Ep-N_{14} and Ep-N_{20} (but not N_{14}-N_{20}) latency in Down's compared with control subjects. These are the same latency measurements which were significantly prolonged in normal aging (Huang, unpublished). Direct age comparisons show that the conduction times in the younger Down's group were greater even than in controls aged over 66 years; the increase in conduction times with increasing age was not significant. The lower limb SEP study showed prolonged P_{40}-N_{21} latency in Down's compared with control subjects; again, similar (but lesser) changes have been described in aged controls (Mackenzie and Phillips, 1981).

The reason for these changes in conduction in Down's syndrome is not completely clear. Even the younger group of subjects differed from age-matched controls, so presumably at least some (central) pathology was present at this time. Changes in older subjects were similar in type but greater in degree, and followed a similar pattern known to occur with normal aging. It appears from this study that SEP measurement may provide a sensitive index of some types of neurological dysfunction, particularly those resulting from diffuse degenerative disease.

Summary

Fifteen subjects with Down's syndrome had measurements of peripheral and central nervous system conduction parameters. Conventional nerve conduction studies revealed evidence of peripheral nerve dysfunction consistent with an axonal degeneration. Upper limb somatosensory evoked potentials were delayed compared with age-matched controls in both young and older age groups of Down's subjects. Lower limb somatosensory evoked potentials were also delayed when correction for height was made; furthermore the 'central conduction time' was prolonged in young and older groups. These results suggest that both peripheral and central nervous system function is impaired in Down's syndrome and the pattern of change is similar to that found with aging in normal individuals.

References

Behse, F. and Buchthal, F.: Normal sensory conduction in the nerves of the leg in man. Journal of Neurology, Neurosurgery and Psychiatry 34: 404-414 (1971).

Brown, W.T.: Human mutations affecting aging – A review. Mechanics of Aging and Development 9: 325-336 (1979).

Celesia, G.G. and Daly, R.F.: Effects of aging on visual evoked responses. Archives of Neurology 34: 403-407 (1977).

Crapper, R.; Dalton, A.J.; Skopitz, M.; Scott, J.W. and Hachinski, V.C.: Alzheimer degeneration in Down's syndrome. Archives of Neurology 32: 618-623 (1975).

Desmedt, J.E. and Cheron, G.A.: Somatosensory pathway and evoked potentials in normal human aging; in Desmedt (Ed) Clinical Uses of Cerebral, Brainstem and Spinal Somatosensory Evoked Potentials, Progress in Clinical Neurophysiology. Vol. I, (Karger, Basel 1980).

Dorfman, L.J.: Indirect estimation of spinal cord conduction velocity in man. Electroencephalography and Clinical Neurophysiology 42: 26-34 (1977).

Dustman, R.E. and Beck, E.C.: The effects of aging and maturation on the waveform of visually evoked potentials. Electroencephalography and Clinical Neurophysiology 26: 2-11 (1969).

Franceschi, C.; Licastro, F.; Chiricolo, M.; Bonetti, F.; Zannotti, M.; Fabris, N.; Mocchegiani, E.; Fantini, M.P.; Paolucci, P. and Masi, M.: Deficiency of autologous mixed lymphocyte reactions and serum thymic factor level in Down's syndrome. Journal of Immunology 126: 2161-2164 (1981).

Mackenzie, R.A. and Phillips, L.H.: Changes in peripheral and central nerve conduction with aging. Journal of Clinical and Experimental Neurology (1981).

Malamud, N.: Neuropathology of organic brain syndromes associated with aging; in Gantz (Ed) Advances in Behavioral Biology, pp.63-87 Vol. 3 (Plenium Press, New York 1972).

Naeim, F. and Walford, R.L.: Disturbance of redistribution of surface membrane receptors on peripheral mononuclear cells of patients with Down's syndrome and of aged individuals. Journal of Gerontology 35: 650-655 (1980).

Nielsen, V.K.: Sensory and motor nerve conduction in the median nerve in normal subjects. Acta Medica Scandinavica 194: 435-443 (1973).

Richards, B.W.: Mental Retardation; in Howells (Ed) Modern Perspectives in the Psychiatry of Old Age, pp.336-368 (Churchill Livingstone, Edinburgh 1975).

Schochet, S.S.; Lampert, P.W. and McCormick, W.F.: Neurofibrillary tangles in patients with Down's syndrome: Light and electron microscopic study. Acta Neuropathologica 23: 342-346 (1973).

Parenchymal Brain Lesions in Spontaneously Hypertensive Stroke-prone Rats

*R.A. Rodda, T. Brain and S. Jones**

The spontaneously hypertensive stroke-prone (SHSP) rat developed by Okamoto et al. (1974) has been used as an experimental model for studying the brain lesions in spontaneous hypertension. Some of these lesions are obviously intracerebral haemorrhages but others have been variously described as cortical infarcts or necroses with cyst formation (Hazama et al., 1975a), combined infarct and haemorrhage (Hazama et al., 1976a), rarefaction (Hazama et al., 1975b), oedema (Yamori et al., 1975) and even arterio-necrotic-thrombogenic stroke (Yamori et al., 1976a; Yamori et al., 1977). In an attempt to clarify the nature of these lesions this paper describes the gross and histological features of the parenchymal lesions found on examination of the brain in some 60 SHSP rats.

Materials and methods

After weaning, the SHSP rats were segregated in pairs of the same sex and allowed food and water as desired. The animals were examined daily for any abnormal clinical and particularly neurological signs. Once a week they were weighed and the blood pressure was measured using a tail-cuff method without anaesthesia.

Animals which presented abnormal clinical features were anaesthetised with open ether, the thorax opened and a cannula inserted through the left ventricle into the ascending aorta. After dividing the vena cava the arterial system was washed out with 200ml of normal saline and perfused over 20 to 30 minutes with 500ml of 2% glutaraldehyde solution using a Watson-Marlow flow inducer

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Table I. Parenchymatous brain lesions recorded in spontaneously hypertensive stroke-prone (SHSP) rats

	Mean age of rats (weeks)			Number of rats with brain lesions			Number of discrete lesions	Mean number lesions per rat
	Male	Female	Both sexes	Male	Female	Both sexes		
Perfused (n = 46)	24(16-56)	41(26-50)	29(16-56)	30	13	43	143	3.3 (1-8)
Non-perfused (n = 14)	29(14-53)	53(37-68)	38(14-68)	8	6	14	46	3.3 (1-6)
Total (n = 60)				38	19	57	189	3.3 (1-8)

Table II. Details of the brain lesions found in SHSP rats

Lesions present	Number of rats	Number of lesions in perfused rats	Number of lesions in non-perfused rats	Total number of lesions	Micro-aneurysms	Lesions with cyst formation	Lesions with arteriolo-necrosis
Old haemorrhage	52	97	30	127	3	116	99
Recent haemorrhage	18	16	10	26	2	14	25
Focal necrosis and scarring (no haemorrhage)	13	15	6	21	–	10	10
Focal oedema with microcysts	12	15	–	15	–	15	–

maintaining a constant pressure corresponding to the last recorded systolic blood pressure of that animal. Immediately following perfusion fixation, 2 to 4ml of 12% warm gelatin solution dyed with 5% carmine was injected by syringe into the aortic cannula for the demonstration of brain artery dilatations which are not specifically considered in this report. When the gelatin had solidified the brain was carefully removed and further fixed in 2% glutaraldehyde for 1 hour before being transferred to 6% sucrose buffer for storage at 4°C.

The brains of animals which died before they could be perfused were removed and fixed in formalin. The thoracic and abdominal organs of all animals were examined grossly and by routine histological methods.

All the brains were examined with a stereomicroscope and any external abnormalities recorded photographically. Each brain was sliced transversely at 6 standard levels and the entire brain embedded in 6 paraffin blocks. Histological sections were cut from each of these blocks and in some animals interrupted serial sections at 50μm intervals were examined to delineate the extent of the parenchymal lesions. All sections were stained by HE; PTAH, MSB, myelin and iron stains were done on some sections. The location and nature of the brain lesions were charted on brain diagrams and recorded by photomicrographs.

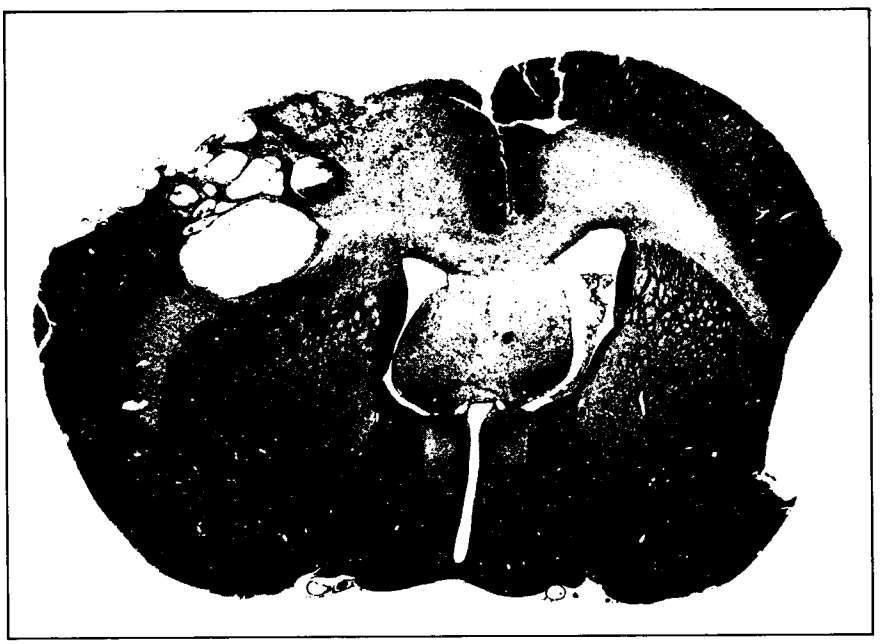


Fig. 1. Macrophotograph of transverse brain section showing large cystic pigmented scar in dorsal part of the left cerebral hemisphere of 24-week-old male SHSP rat. There is also recent haemorrhage into and around some of the cysts. Oedema and microcysts are seen medially in the corpus callosum and fornix. (HE X 12).

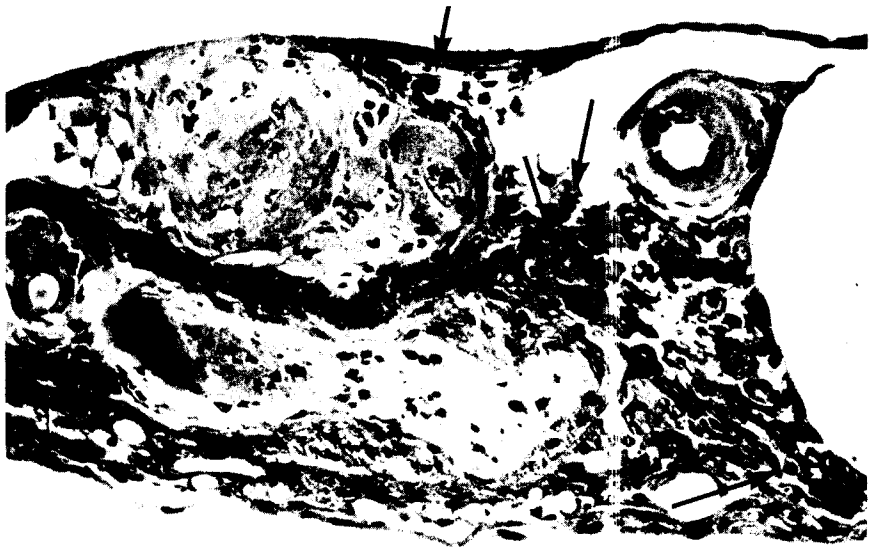


Fig. 2. Photomicrograph of thin outer wall of large cyst in left cerebral hemisphere of 18-week-old male SHSP rat showing arteriolonecrosis in leptomeninges and adherent outer cyst wall which also contains a few astrocytes and many macrophages some of which (arrows) include haemosiderin granules. There are a number of red blood cells leaking into the necrotic arteriole wall. (HE X 400).

Results

All the animals showed a rapid rise in blood pressure from about the age of 8 weeks to around the age of 12 weeks with the rise in males occurring almost 2 weeks before the rise in females. From the age of 12 weeks the rise was more gradual with mean pressures in millimetres of mercury of 260 systolic and 180 diastolic being recorded in the animals aged 20 weeks.

The abnormal clinical features observed were weight loss, lethargy, irritability, limb paralysis, convulsions, or coma. In these affected animals the blood pressure immediately before perfusion was frequently found to have fallen to a level considerably below the very high levels previously recorded in those same animals.

Table I shows the sex and ages of the rats examined and the numbers of parenchymatous lesions found in the brain in 57 (95%) of 60 rats. A further 20 rats which died were excluded, 16 because of death from extracerebral causes and 4 because the brain was too autolytic for adequate pathological study.

Old Brain Haemorrhage

The 127 lesions (table II), which showed evidence of old haemorrhage as demonstrated by the presence of iron containing haemosiderin laden macro-

phages, were variable in size. Some comprised large cysts replacing most of the cortex in a cerebral hemisphere and were clearly visible on the surface of the brain during removal. Some of the lesions comprised multiple smaller cysts (fig. 1). The cyst walls comprised astrocytes with scanty fibres and both pigmented and non-pigmented macrophages. Often fibrinoid arteriolonecrotic vessels were seen in relation to the pigment deposits (fig. 2). Some of these old haemorrhages were small focal non-cystic lesions. Seventy-one (56%) of the 127 lesions with evidence of old haemorrhage also showed recent haemorrhage in the same lesion. Most of the old haemorrhages were situated in the dorsolateral cerebral cortex, a number were in the inferolateral frontal cortex, some were in the brain stem and a very few were in the basal ganglia. Arteriolonecrosis was seen in 99 (78%) of the 127 old haemorrhagic lesions but microaneurysms were found in only 3 (2%) of the lesions (fig. 3).

Recent Brain Haemorrhage

The 26 isolated recent haemorrhages (table II) were generally less than 1mm in diameter. These lesions were found predominantly in the same parts of the cerebral cortex and brain stem as were the old haemorrhages and again were uncommon in the basal ganglia. Although nearly all the recent haemorrhages

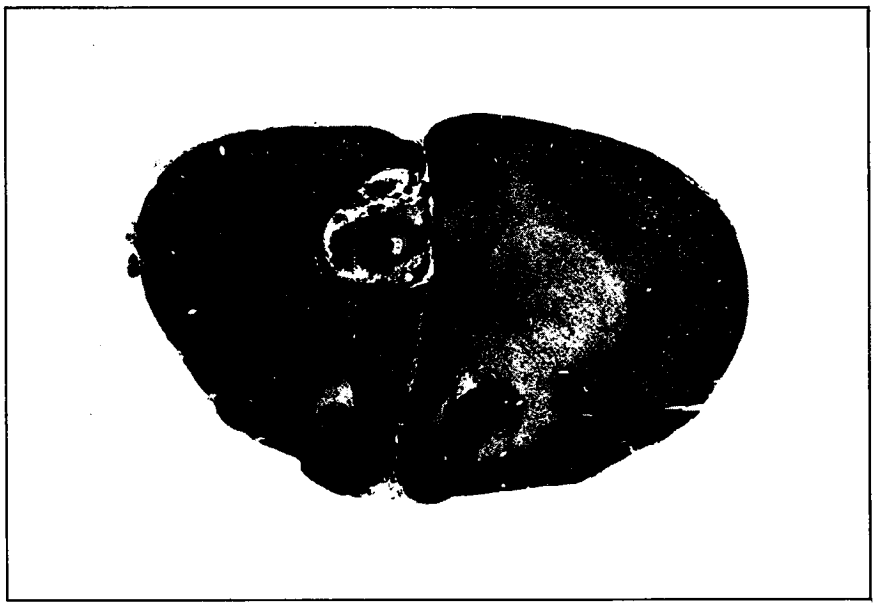


Fig. 3. Macrophotograph of transverse section through frontal lobes in 16-week-old male SHSP rat showing microaneurysms with old and recent haemorrhage and adjacent scarring in left dorsomedial cortex. (HE X 12).

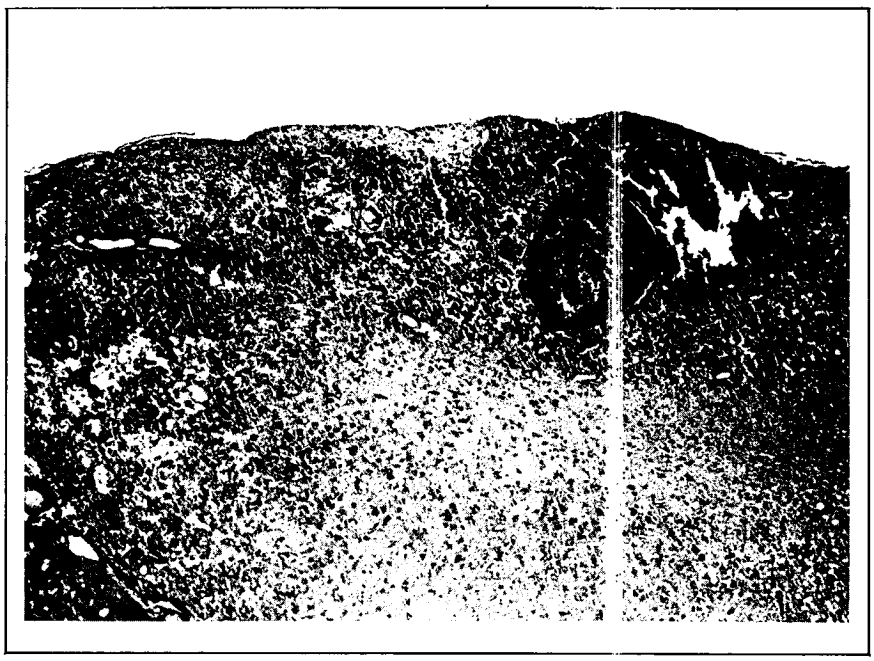


Fig. 4. Photomicrograph showing microaneurysm and recent haemorrhage in inferior right frontal cortex of 24-week-old male SHSP rat. There is adjacent oedema with microcysts. (HE X 100).

were associated with an arteriolonecrosis only 2 associated microaneurysms were recognised (figs 4 and 5). When the isolated recent haemorrhage lesions and the recent haemorrhages present in lesions with old haemorrhage are considered together, 97 (51%) of the total 189 lesions showed recent haemorrhage in 41 (72%) of the 57 rats.

Focal Necrosis and Scarring

There were 21 other small focal lesions with necrosis and scarring (table II) in which no evidence of recent or old haemorrhage was seen and in almost half of these lesions there was an associated arteriolonecrosis (fig. 6). No small focal or large areas of coagulative necrosis of brain parenchyma were found in any of the animals.

Focal Oedema with Microcysts

Many of the haemorrhagic and non-haemorrhagic lesions in both the perfused and non-perfused animals showed related areas of oedema with microcyst formation and this was evident too in areas with glia scarring (fig. 7). This

oedema was also prominent in the corpus callosum and fornix with a characteristic separation of the nerve fibres. In 12 rats (table II) there were 15 isolated and separate lesions with oedema and microcyst formation only (fig. 8). Some of these lesions were small but others were extensive and a few were bilateral.

Discussion

The rate of development and severity of the hypertension both in males and in females is similar to that in SHSP rats described by Okamoto et al. (1974)

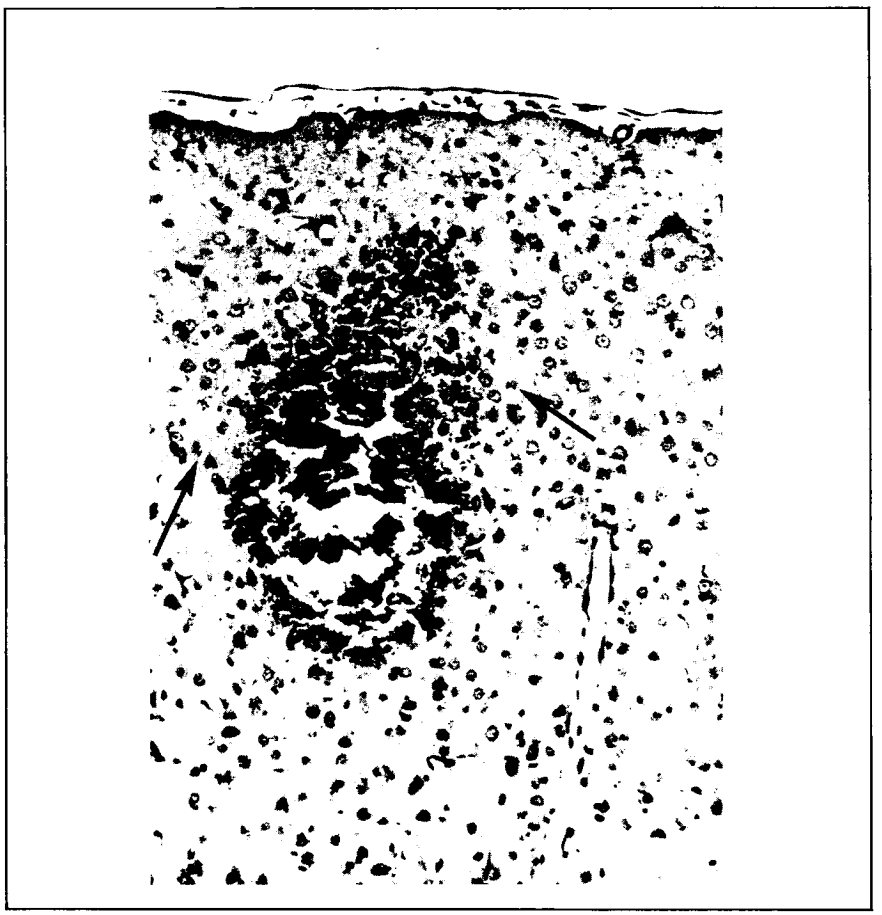


Fig. 5. Photomicrograph showing small recent haemorrhage from thin-walled microaneurysm in right dorsomedial parietal cortex of 30-week-old male SHSP rat. Among the neurones adjacent to the microaneurysm there are reactive astrocytes (arrows) and a few macrophages. (HE X 160).

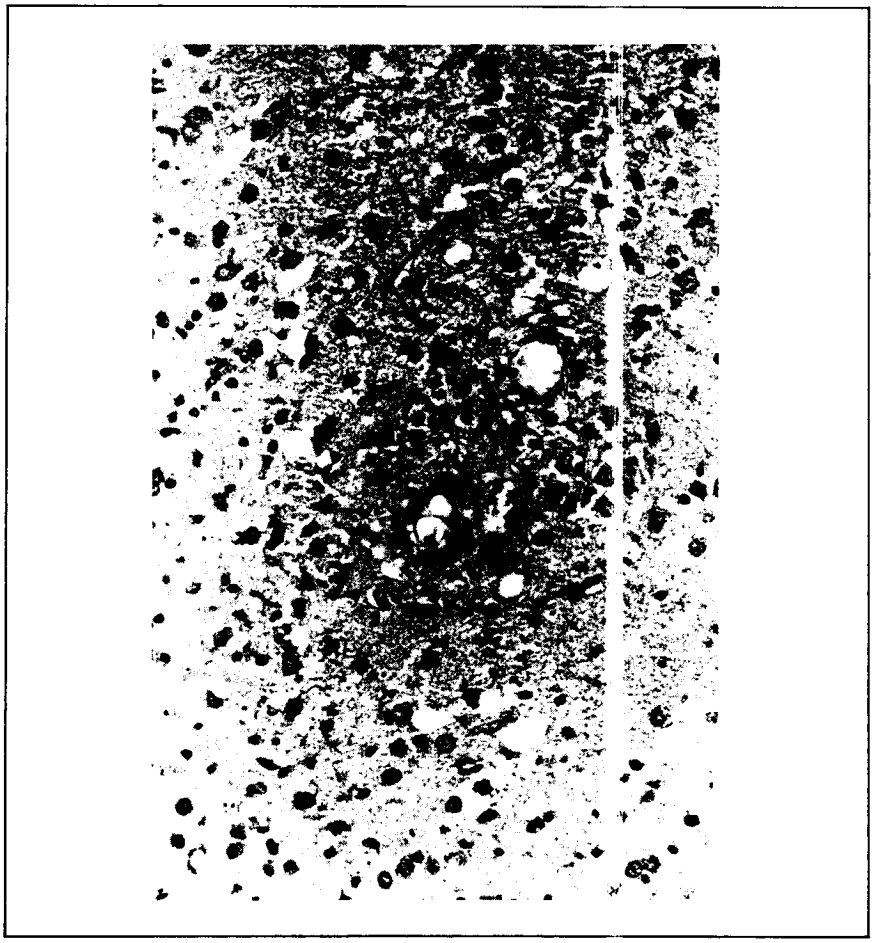
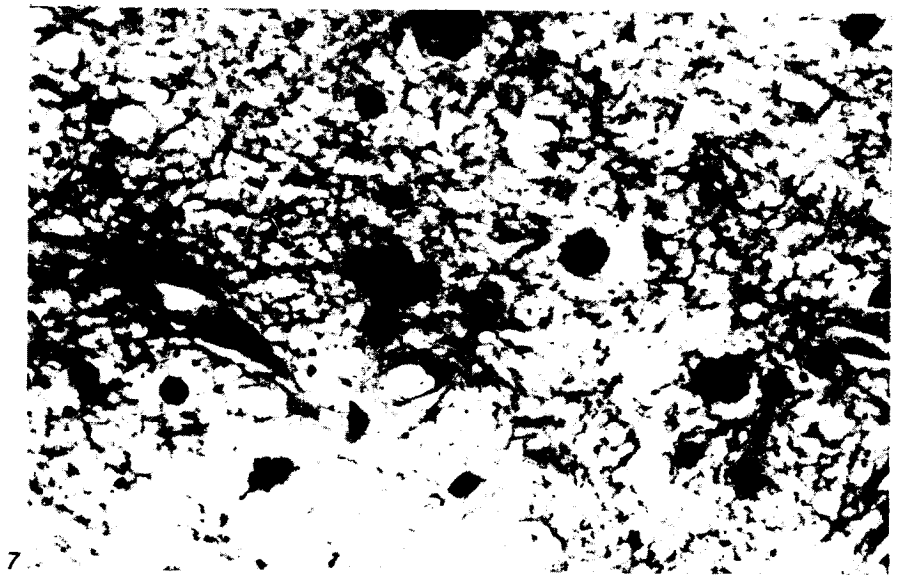


Fig. 6. Photomicrograph of focal right cortex lesion without evidence of haemorrhage in 40-week-old female SHSP rat. There is a central fibrinoid arteriolonecrotic vessel surrounded by necrotic cells with pyknosis, some phagocytes and occasional astrocytes (arrow). (HE X 260).

and others subsequently. The clinical features observed, too, are similar and confirm that the animals used in this study are characteristic of the SHSP strain. The distribution of the brain lesions in these SHSP rats follows that detailed by Yamori et al. (1976b) who demonstrated the common sites of the lesions to be in arterial boundary zones. They concluded that this was related to a pattern of recurrent arterial branching but the mechanisms by which this may influence microaneurysm formation and subsequent haemorrhage remains obscure.

When compared with massive intracerebral haemorrhage seen frequently in human hypertension, the recent intracerebral haemorrhages in the SHSP rat model



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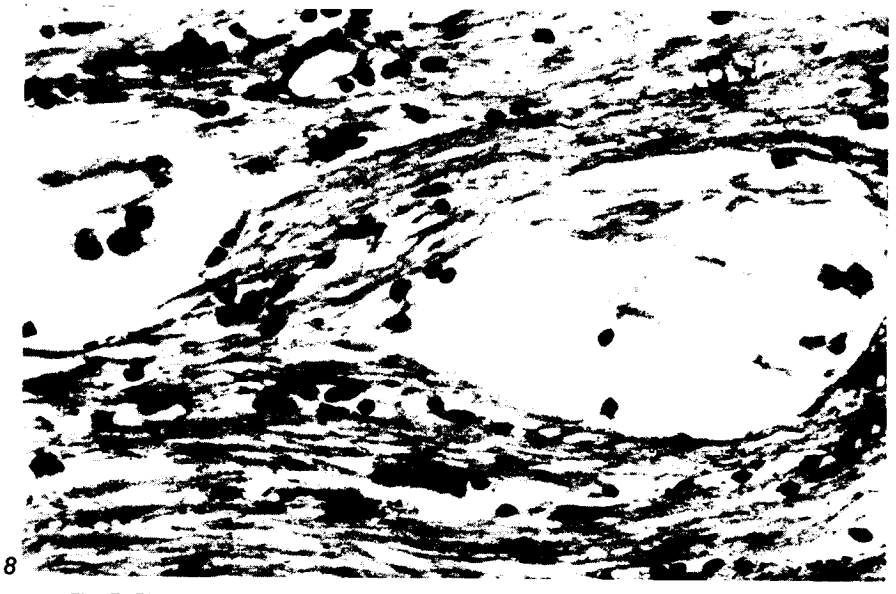

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Fig. 7. Photomicrograph of scarred wall of left frontal cortex cyst in 26-week-old male SHSP rat showing some surviving neurones, astrogliosis and appreciable oedema. (HE X 800).

Fig. 8. Photomicrograph of oedematous corpus callosum in 26-week-old male SHSP rat showing microcysts containing Gitterzellen type macrophages. (HE X 410).

are proportionately smaller and in our experience are similar to those seen in the rat with experimental renal hypertension (Byrom, 1969). It seems likely this difference between the human lesions and those in both animal models is a species difference due to the very different brain anatomy.

The brain lesions we have described in the present study have shown that 153 (81%) of the 189 separate lesions in 54 (95%) of the 57 rats are recent haemorrhages with erythrocytes, or old haemorrhages with iron containing haemosiderin pigment, or both old and recent haemorrhages. Although relatively few undoubted microaneurysms (5) were recognised in the histological material a significant sampling error is likely. Further, in 134 (71%) of the 189 lesions there was an obvious arteriolonecrosis and many of these vessels showed a leakage of erythrocytes (fig. 2).

Although the material from this study does not clearly demonstrate which blood vessels have leaked fluid, the presence of oedema and cysts in 155 (82%) of the 189 lesions emphasises that leakage of fluid from the vessels is also a major component of the parenchymatous lesions. Whereas the leakage of red cells appears to be from the necrotic arterioles, the leakage of fluid with oedema and microcyst formation is more widespread and the leakage may have occurred from damaged but not yet necrotic arterioles as well as from capillaries and venules as Nag et al. (1977) have demonstrated ultrastructurally in the rat with angiotensin-induced hypertension.

The lesions which we have described as focal necrosis and scarring without evidence of recent or old haemorrhage comprised only 21 (11%) of the 189 lesions. These focal lesions are similar to those in SHSP rats which Hazama et al. (1975c) described as infarcts and in human hypertensive encephalopathy which Chester et al. (1978) described as microinfarcts. Ogata et al. (1980), however, have stated that in their electronmicroscopic studies of SHSP rats, neurones showing shrinkage and condensation of the cytoplasm were never encountered. Almost half (10 of 21) of the focal necroses in our SHSP rats also showed microcyst formation and oedema and it seems likely these focal lesions are essentially the result of fluid leakage. Indeed Hazama et al. (1976b) have proposed that endothelial cell changes in SHSP rats play a significant role in the development of the parenchymal lesions.

Cole and Yates (1967) have concluded that small cystic cavities in the brain of human hypertensives are likely to be the result of old haemorrhages and our studies of the somewhat similar lesions in the SHSP rats suggest that these too are the result of previous haemorrhage.

In these SHSP rats we have not seen undoubted recent ischaemic necrosis and it seems the focal necroses are more likely the result of the insudation into the tissue of blood components from vessels damaged by the hypertension. We conclude that the parenchymatous brain lesions in SHSP rats are predominantly the result of vascular leakage.

Summary

The gross and histological features of 189 parenchymal brain lesions in 57

spontaneously hypertensive stroke prone rats are described. There were 127 lesions many of them cystic, showing evidence of old haemorrhage. Of these, 71 also showed recent haemorrhage and there were 26 lesions showing recent haemorrhage only. There were 21 small focal lesions with necrosis and scarring but without any old or recent haemorrhage and 15 other lesions showing focal oedema with microcysts. Undoubted histological evidence of recent ischaemic necrosis was not seen.

In this animal model which spontaneously develops severe hypertension, the brain lesions are predominantly the result of leakage of blood components from small vessels.

Acknowledgements

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References

Byrom, F.B.: The Hypertensive Vascular Crisis: An Experimental Study, pp.22-23 (Heinemann, London 1969).

Chester, E.M.; Agamanolis, D.P.; Banker, B.Q. and Victor, M.: Hypertensive encephalopathy: A clinicopathologic study of 20 cases. Neurology 28: 928-939 (1978).

Cole, F.M. and Yates, P.: Intracerebral microaneurysms and small cerebrovascular lesions. Brain 90: 759-768 (1967).

Hazama, F.; Amano, S.; Haebara, H. and Okamoto, K.: Changes in vascular permeability in the brain of stroke-prone spontaneously hypertensive rats studied with peroxidase as a tracer. Acta Pathologica Japonica 25: 565-574 (1975a).

Hazama, F.; Haebara, H.; Amano, S. and Okamoto, K.: Pathology of cerebrovascular disease in spontaneously hypertensive rats; in Seventh International Congress of Neuropathology, Budapest, pp.517-520 (Excerpta Medica, Amsterdam 1975b).

Hazama, F.; Ooshima, A.; Tanaka, T.; Tomimoto, K. and Okamoto, K.: Vascular lesions in the various substrains of spontaneously hypertensive rats and the effects of chronic salt ingestion. Japanese Circulation Journal 39: 7-22 (1975c).

Hazama, F.; Amano, S.; Haebara, H.; Yamori, Y. and Okamoto, K.: Pathology and pathogenesis of cerebrovascular lesions in spontaneously hypertensive rats; in Cervós-Navarro et al. (Eds) The Cerebral Vessel Wall, pp.245-252 (Raven Press, New York 1976a).

Hazama, F.; Amano, S.; Ozaki, T. and Okamoto, K.: Pathology and morphogenesis of cerebrovascular changes in SHR; in Spontaneous Hypertension: Its Pathogenesis and Complications. Proceedings Second International Symposium on the Spontaneously Hypertensive Rat, pp.247-253 (U.S. Department of Health, Education and Welfare, Washington D.C. 1976b).

Nag, S.; Robertson, D.M. and Dinsdale, H.B.: Cerebral cortical changes in acute experimental hypertension: An ultrastructural study. Laboratory Investigation 36: 150-161 (1977).

Ogata, J.; Fujishima, M.; Tamaki, K.; Nakatomi, Y.; Ishitsuka, T. and Omae, T.: Stroke-prone spontaneously hypertensive rats as an experimental model of malignant hypertension. Acta Neuropathologica (Berlin) 51: 179-184 (1980).

Okamoto, K.; Yamori, Y. and Nagaoka, A.: Establishment of the stroke-prone spontaneously hypertensive rat (SHR). Circulation Research 34 and 35 (Suppl. I): 143-153 (1974).

Yamori, Y.; Horie, R.; Akiguchi, I.; Nara, Y.; Ohtaka, M. and Fukase, M.: Pathogenic mechanisms and prevention of stroke in stroke-prone spontaneously hypertensive rats; in De Jong, Provoost and Shapiro (Eds) Hypertension and Brain Mechanisms, Vol. 47, Progress in brain research, pp.219-234 (Elsevier, Amsterdam 1977).

Yamori, Y.; Horie, R.; Akiguchi, I.; Ohtaka, M.; Nara, Y. and Fukase, M.: New models of spontaneously hypertensive rat (SHR) for studies on stroke and atherogenesis. Clinical and Experimental Pharmacology and Physiology (Suppl. 3): 199-203 (1976a).

Yamori, Y.; Horie, R.; Handa, H.; Sato, M. and Fukase, M.: Pathogenic similarity of strokes in stroke-prone spontaneously hypertensive rats and humans. Stroke 7: 46-53 (1976b).

Yamori, Y.; Horie, R.; Sato, M.; Sasagawa, S. and Okamoto, K.: Experimental studies on the pathogenesis and prophylaxis of stroke in stroke-prone spontaneously hypertensive rats (SHR). (1) Quantitative estimation of cerebrovascular permeability. Japanese Circulation Journal 39: 611-615 (1975).

Embolisation of Cerebral Arteriovenous Malformations

*P.G. McManis, G.M. Selby and W.A. Sorby**

The use of embolisation techniques in the management of cerebral arteriovenous malformations was originally described by Luessenhop and Spence in 1960. Embolisation is not widely practised in Australia, however, possibly because the results have been felt to be unpredictable and the risks of causing permanent neurological damage too high.

We have recently treated 7 patients with inoperable malformations by embolising them with silicone rubber (Silastic) spheres, and in 4 of these patients lasting symptomatic relief was obtained. The degree of improvement appeared related to the reduction in size of the malformation. Embolisation was carried out in several stages, each stage followed by clinical and radiographic evaluation and reappraisal of risks and possible benefits. This was done to minimise the risk of aberrant emboli, a risk which is known to increase as blood flow through the malformation decreases.

We have attempted to determine criteria for selecting patients for embolisation and to evaluate the effect of the procedure on symptoms attributed to the malformations.

Materials and Methods

Investigations

All patients with malformations underwent 4-vessel cerebral arteriography (including the external carotid circulation where appropriate) to identify the size

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and number of feeding vessels. Angiography was repeated after the embolisation to determine the degree of flow reduction achieved. Computerised tomographic (CT) scanning was also performed before and after the procedure to document reduction in size of the malformation and to identify areas of cerebral ischaemia resulting from aberrant emboli or occlusion of major vessels.

Equipment and Procedure

In all cases embolisation was performed by means of a flexible catheter introduced into the femoral artery by the Seldinger technique. The catheter tip was positioned in the internal carotid artery when embolising malformations fed by anterior or middle cerebral arteries, and in one vertebral artery for malformations involving the posterior circulation. In 2 patients with massive anastomotic supply through branches of the external carotid system the middle meningeal and occipital arteries were selectively catheterised.

Barium-impregnated Silastic spheres (American Hospital Supplies, North Ryde, NSW) varying in diameter from 0.5mm to 2.0mm and in 2 instances larger plugs cut from ophthalmic Silastic sponge were used as emboli (fig. 1). Spheres of 0.5mm or 1.0mm diameter were introduced first, and if these passed directly through the malformation, progressively larger spheres were employed until the

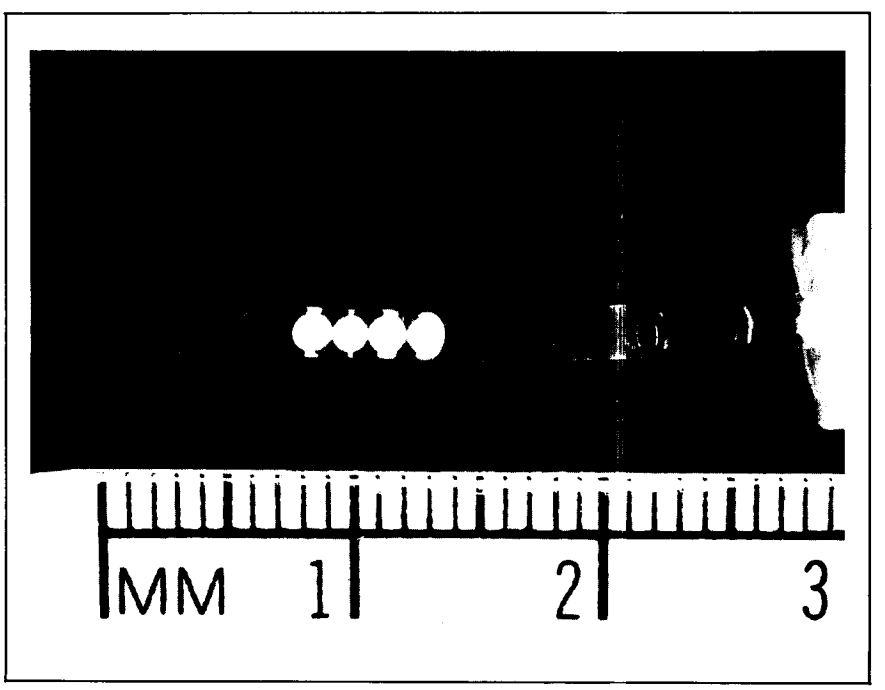

Fig. 1. Plastic tube containing Silastic emboli ready for injection.

Table I. Summary of clinical details of 7 patients with cerebral arteriovenous malformations

Sex, age	Presenting symptom	Other symptoms	No. of embolisations	Outcome	Duration of follow-up (months)
F, 37	Headaches	TIA (hemianopia)	3	Headaches relieved TIA persist	9
M, 49	Epilepsy	Progressive dementia Headaches Mild hemiparesis	3	Dementia improved Seizures less frequent Headaches improved Temporary hemiparesis and dysphasia	16
M, 41	Epilepsy (well controlled)	Headaches Ataxia Mild hemiparesis TIA (vertigo)	2	Ataxia, headaches improved Hemiparesis unchanged AVM resected	12
M, 47	Epilepsy (poorly controlled)	Episodic cerebral hypoperfusion	1	Middle cerebral artery occlusion TIA ceased Epilepsy unchanged	16
F, 46	Epilepsy (poorly controlled)	Progressive dementia Mild hemiparesis Headaches	1	Dementia improved Hemiparesis, headaches and epilepsy unchanged	17
M, 18	Epilepsy (poorly controlled)	Mild hemiparesis Subarachnoid haemorrhage	2	Seizures improved Hemiparesis unchanged	6
M, 63	Subarachnoid haemorrhage	Epilepsy (well controlled) Hemianopia TIA (hemiparesis) Subarachnoid haemorrhage	1	3rd subarachnoid haemorrhage Hemianopia, TIA unchanged	14

smallest size that would lodge within the malformation was found. Emboli were then injected in lots of 5 to 10 into one or more feeding vessels while the effect was monitored with angiography. The procedure was terminated at the discretion of the operator, after considering the time taken, the volume of contrast material used, and the results.

After each embolisation the patients were reassessed to determine the degree of reduction in blood flow and size of the malformation, and this was correlated with changes in the patients' symptoms. In most cases the initial procedure resulted in only small changes in the malformation and little symptom relief. Four of the 7 underwent embolisation on more than one occasion, 2 gaining adequate symptom relief from the second procedure while 2 others required a third embolisation.

Three patients have had only a single embolisation. An asymptomatic

middle cerebral artery occlusion occurred in one of these cases and further treatment was considered unwise. A second patient declined further treatment. A subarachnoid haemorrhage took place in the third patient after embolisation and further treatment is still under consideration.

It should be noted that the technique depends entirely on the massive flow of blood through the malformation and the dilatation of the feeding vessels to determine the accuracy of embolus placement. It has been shown (Luessenhop et al., 1965; Wolpert and Stein, 1979) that where the feeding vessel is more than twice the size of the normal arteries branching from it, 90% or more of emboli will remain in the larger vessel independent of embolus size. This effect is enhanced by the high flow of blood through the abnormal vessels. For these same reasons, however, the risk of emboli entering normal vessels increases with progressive occlusion of the malformation.

Patient Selection

Patients were considered for embolisation if the malformation could not be removed surgically because of its site or size, and if the symptoms could not be relieved adequately by drug therapy. Each patient who underwent embolisation had a single very large supratentorial malformation. No aneurysms were seen in association with these.

All 7 of the patients chosen for embolisation had symptoms caused by a redistribution of cerebral blood flow. In 5 cases this produced transient or fixed hemiparesis and 2 patients complained of progressively deteriorating intellectual function. The mass effect of the malformation may have contributed to the fixed deficits. Other 'steal' symptoms included transient visual field defects, ataxia of gait, and symptoms of cerebral hypoperfusion (dimness of vision, lightheadedness and vertigo). Several patients complained of more than one of these. Six patients also experienced partial or generalised seizures and 4 had severe and frequent headaches. Two patients had suffered a subarachnoid haemorrhage but there were no instances of intracerebral haemorrhage. All of these patients had been treated medically for between 5 and 25 years prior to embolisation and had either no improvement or at best only partial control of their symptoms.

At the time of diagnosis of a malformation the patients ranged in age from 13 to 43 years (mean, 31 years). When embolisation was performed the patients were aged between 18 and 63 years (mean, 43 years). There were 5 males and 2 females in the series. Individual patient details are provided in table I.

Results

Benefits of Embolisation

Embolisation was performed on 1, 2 or 3 occasions at intervals varying from 8 days to 6 months. Four patients, all of whom underwent multiple embolisations and had major reductions in malformation size (fig. 2), obtained significant

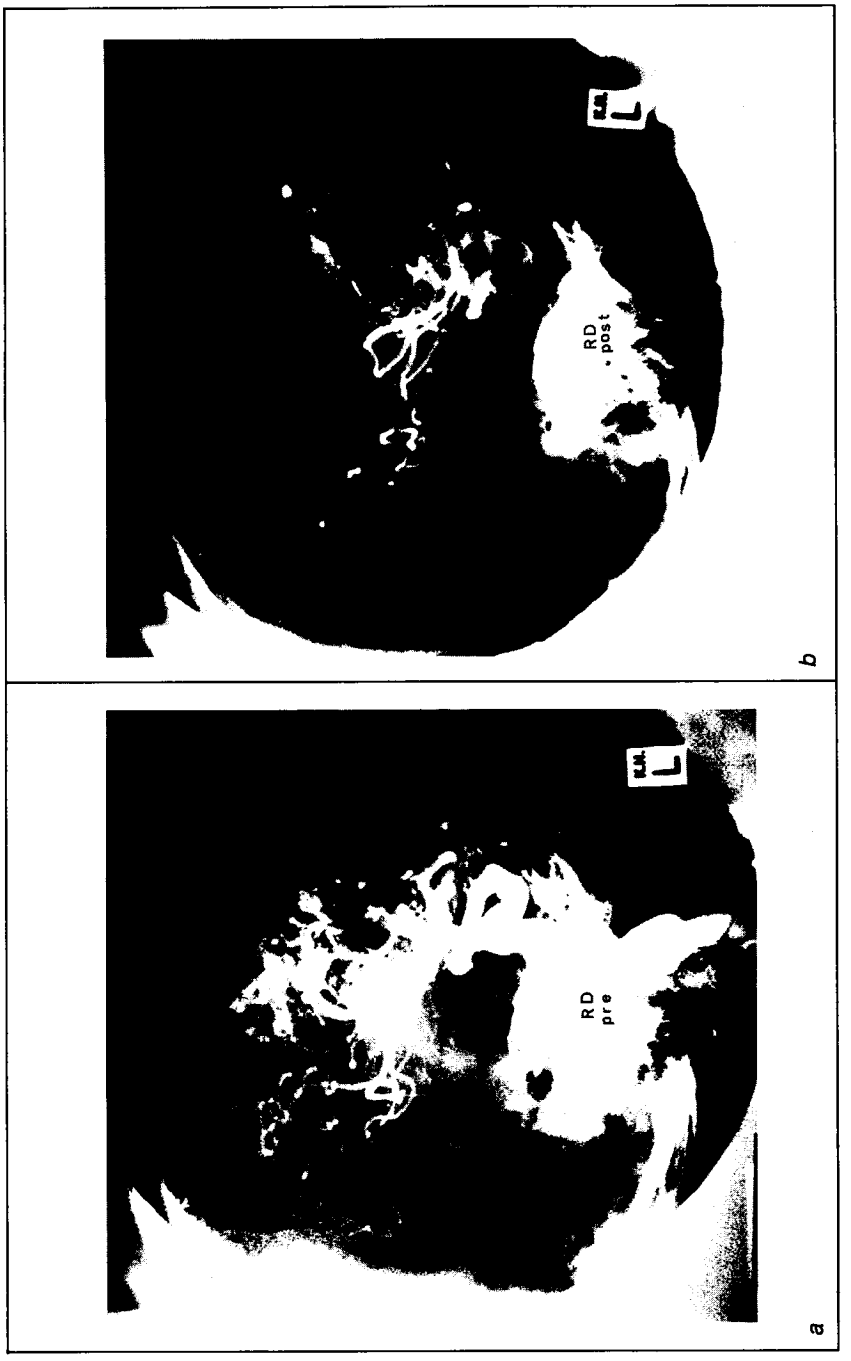

Fig. 2. Massive malformation in left cerebral hemisphere before (a) and after (b) embolisation.

relief of their symptoms from the procedure. A fifth patient noted a partial response and 2 patients had little or no response from single procedures. The degree of symptom relief appeared to be related to the reduction in flow through the malformation. When initial embolisation produced only minor changes in flow there was little change in symptoms, but when substantial reductions in flow were obtained with successive procedures, each occasion resulted in greater symptom relief.

Headache

Three of 4 patients with intractable headaches were greatly improved by embolisation. The best results were obtained in 2 patients with extensive extracranial anastomoses which could all be safely occluded with emboli (fig. 3).

Steal/mass Effect

The 2 patients who complained of progressive intellectual deterioration said that this had ceased after embolisation. Of the 5 patients with fixed neurological deficits, only one was improved by embolisation while 2 of 4 patients with transient focal or generalised cerebral ischaemia were better. It is of interest that one patient with visual field deficits accompanying severe migraine was relieved of her headaches, but not the visual disturbances, by obliteration of all extracerebral feeding vessels. At the same time there was only a small reduction in the size of the occipital malformation.

Seizures

Six patients had epilepsy, but in 2 of these cases the seizures were well controlled by anticonvulsants prior to embolisation. Of the remaining 4, 2 appear to have benefited from the procedure. One patient with poorly controlled seizures has had only infrequent seizures since embolisation, and the other has had no further seizures apart from a transient increase in seizure frequency immediately after embolisation.

Haemorrhage

Two patients had histories of subarachnoid haemorrhage, and 1 of these has had a further episode since embolisation. However, only a minor reduction in malformation size had been achieved during that procedure.

Complications

Two of the 7 patients had areas of cerebral infarction demonstrated on CT scans (fig. 4) but only 1 of these patients developed symptoms. In this case the infarct in the dominant cerebral hemisphere caused hemiparesis and dysphasia, but the weakness resolved and dysphasia improved within one week. A mild

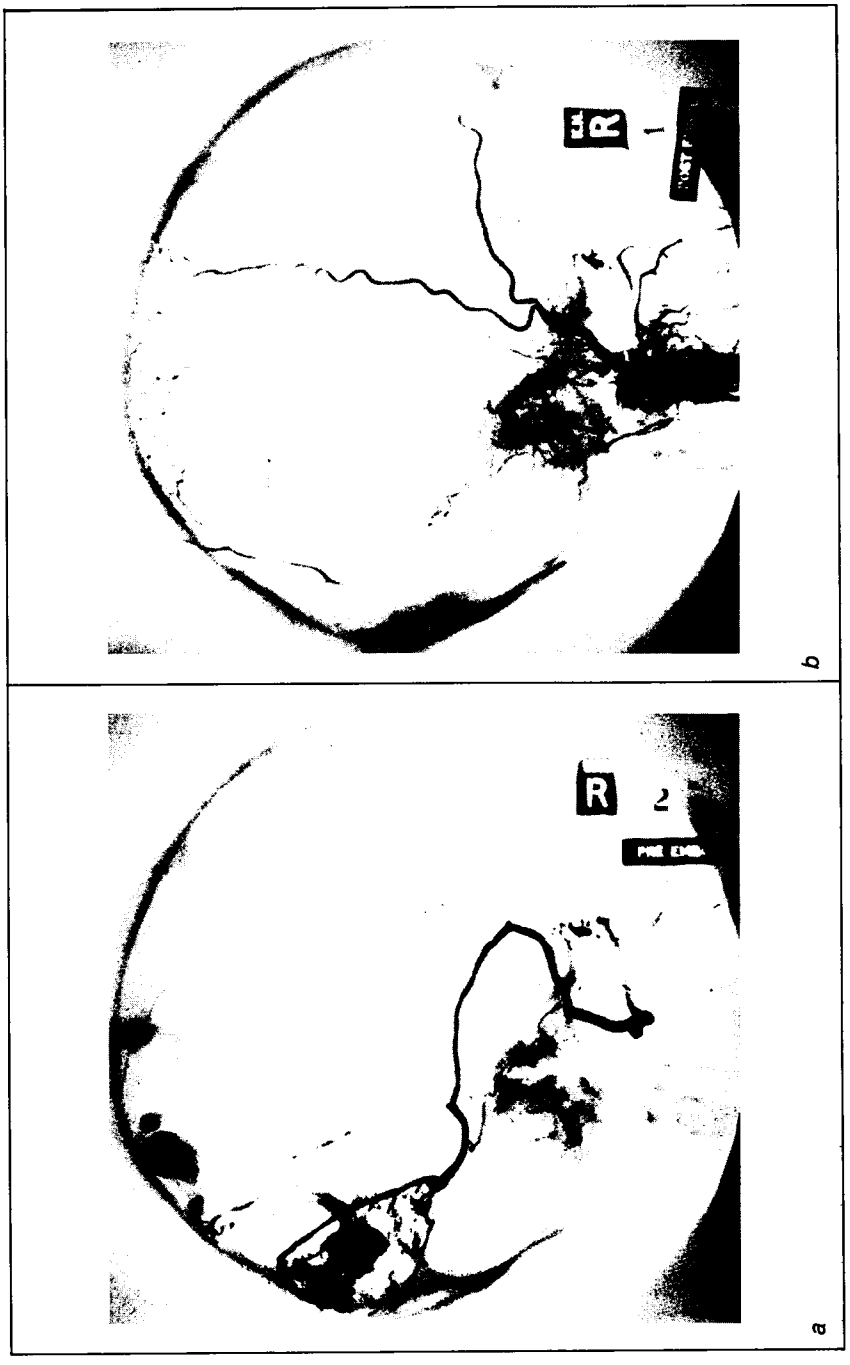

Fig. 3. Extensive extracranial anastomoses before (a) and after (b) embolisation.

hesitancy of speech remains, however. One patient had persistent headache and vomiting after the procedure, but these symptoms resolved after 4 days when oral corticosteroids were given. The symptoms were thought to be either the result of venous stasis and congestion related to extensive thrombosis in the vessels of the external carotid artery, or the result of meningeal irritation caused by occlusion of the middle meningeal artery. Another patient experienced a transient increase in focal seizure activity on each occasion embolisation was performed, but has had no other seizures since the first procedure.

No patient developed thrombosis related to the catheter tip, or spasm of the internal carotid or vertebral arteries, nor were there any instances of emboli arresting in arteries proximal to the malformation once embolisation had begun.

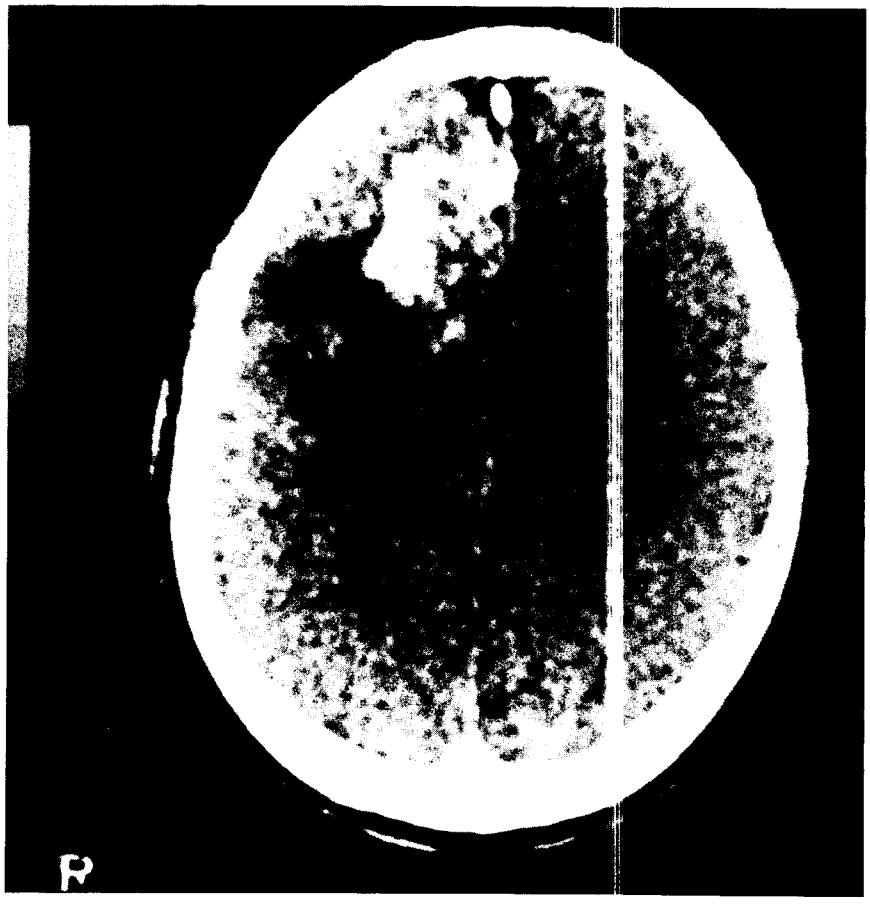

Fig. 4. CT scan showing large area of infarction resulting from middle cerebral artery occlusion.

Follow up

The patients have been followed for between 6 and 17 months (average 13 months) since the final procedure or from the start of symptom relief. One patient with severe ataxia experienced a relapse 3 weeks after initial improvement but recovered with further embolisation. This patient has subsequently undergone resection of the malformation. No other patients have noted recurrence of symptoms during the period of observation.

Discussion

There is universal agreement that the optimal management of cerebral arteriovenous malformations is complete surgical excision where this is feasible. However, even with recent advances in neurosurgical technique such as the operating microscope, there remains a proportion of malformations which cannot be excised because of their size or location. Malformations situated deeply in either cerebral hemisphere, or in eloquent areas, particularly in the dominant hemisphere, remain largely inoperable. Deep x-ray therapy, focused proton beams, stereotactic electrothrombosis and cryocoagulation have been employed in attempts to palliate the symptoms and to reduce the risk of haemorrhage and death in such cases, but these measures have proved either ineffective or damaging to surrounding normal brain.

Embolisation is theoretically attractive as it promises to eradicate the malformation without the need for neurosurgery. The aim of treatment is to cause thrombosis within the malformation itself. There is little to be gained by occluding the proximal feeding vessels of the malformation because previously unsuspected minor tributaries will enlarge rapidly until the malformation returns to its former size. This effect has been noted after neurosurgery in which all known feeding vessels were tied, yet the symptoms from the malformation soon returned. The effect occurs because the low resistance of the arteriovenous shunt encourages increasing flow through small vessels supplying the malformation after the major arteries are removed. For this reason thrombosis of the shunt vessels themselves or the immediately adjacent arterioles will be far more effective in preventing recurrence. To achieve this, the smallest emboli that will lodge within the malformation must be determined so that the emboli are not trapped within proximal vessels and the low resistance shunt itself can be blocked.

The patients selected for embolisation all had very large malformations and it was impossible to thrombose the malformation completely because of the risk of permanent neurological damage from aberrant emboli. Therefore, the object was to achieve the maximum reduction in flow consistent with an acceptably low risk of side effects. We found that this was best done by performing embolisation in several stages with careful reappraisal between procedures. When the main indication was headache, the degree of response to each embolisation could be judged rapidly, but symptoms such as epilepsy and intellectual deterioration required long term assessment. This accounts for the differing time intervals between embolisation procedures.

Four of our 7 patients obtained significant improvement in their symptoms. The patients deriving the most benefit were those suffering from severe headaches which probably arose from extracerebral blood vessels. These vessels can be completely embolised in relative safety by selective external carotid catheterisation. In addition, some patients may have raised intracranial pressure from the mass effect of the malformation, and this can be reduced by embolisation.

We were less successful in treating fixed focal neurological deficits. If these are due either to a local mass effect with pressure on normal surrounding brain, or to long term ischaemia resulting from 'steal', it is likely that permanent damage has taken place which cannot be reversed by removal of the malformation. On the other hand, episodes of transient cerebral ischaemia should become less frequent with adequate reduction in 'steal'. Of our 4 patients with transient cerebral ischaemia, 2 were relieved of this symptom while the other 2 continue to have episodes.

The place of embolisation in the management of symptomatic epilepsy is disputed, some authors claiming dramatic improvements in seizure control (Kunc, 1974; Kusske and Kelly, 1974) while others attribute the noted decrease in seizure frequency to other factors such as changes in anticonvulsant therapy. Two of our 6 patients with epilepsy were well controlled prior to embolisation, but 2 of the remaining 4 had a marked reduction in seizures afterwards without a change in anticonvulsant dosage. This proportion is similar to the large series reported by Luessenhop and Presper (1975) who describe a major improvement in seizures in 8 of 19 patients, 3 of whom became completely seizure-free. In the light of our own experience and the reports of others, we feel that at least part of this improvement can be attributed to embolisation.

The reason for advocating total excision of malformations is that no other method of treatment is effective in reducing the risk of recurrent intracranial haemorrhages. This can only be assessed in a long term study, and the series published by Luessenhop and Presper is the only such report of the effectiveness of embolisation used alone. These authors found that the risk of haemorrhage from malformations that had not previously bled was small (1 of 24 patients) but that embolisation had no protective effect in patients with a history of rupture, 11 of 21 patients in this category having subarachnoid or intracerebral haemorrhage in an average follow-up of 4.5 years. It is too early to comment on our own experiences, but one of the 2 patients with previous subarachnoid haemorrhages has had a recurrence after initial embolisation. It is likely that the prevention of recurrent bleeding will depend on the completeness of embolisation and on the presence or absence of associated arterial aneurysms, a frequent cause of haemorrhage in patients with malformations (Drake, 1979; Luessenhop and Presper, 1975).

The attempted obliteration of malformations with flow-directed emboli is not without risk. Occlusion of normal vessels occurred in 2 patients, fortunately not resulting in major permanent sequelae. The risk of aberrant emboli may decrease with further experience in the technique but can only be eliminated by selective catheterisation of malformation vessels. This cannot be done with the catheters currently available in Australia using Silastic emboli, but overseas ex-

perience with microcatheters employing tissue adhesives in place of emboli indicates that this will be the method of choice in the future.

During attempts to determine the smallest embolus size to block the shunt vessels it is inevitable that some Silastic balls will travel to and lodge in the lungs. This has not caused any clinical problems in our own patients or in other studies, probably because the number of emboli involved is small and the Silastic is relatively inert. Problems could ensue if large numbers of emboli passed through the malformation to the lungs.

Conclusions

Embolisation should be considered in the management of patients with malformations that cannot be removed surgically. The procedure should be reserved for those patients whose symptoms are disabling and cannot be adequately relieved with drug therapy. It can be anticipated that headaches will respond well to the procedure, especially when they are caused by dilated dural and extracranial vessels. The response of seizures and neurological deficits is less predictable, but in some cases these symptoms also improve after embolisation. Embolisation would appear to have little protective effect in patients with recurrent intracranial haemorrhages.

Summary

Seven patients with inoperable cerebral arteriovenous malformations have been treated with embolisation using Silastic spheres and plugs. Indications for using this technique were (i) intractable migraine, (ii) episodes of cerebral ischaemia ('steal' syndromes), (iii) intracranial haemorrhage, and (iv) partial or generalised epilepsy. All 7 patients had been treated medically for between 5 and 25 years with unsatisfactory control of symptoms.

Four of the 7 patients obtained some improvement which appeared related to the reduction in flow through the malformation. Although there are risks associated with embolisation, it would seem to be a worthwhile procedure in selected cases.

Acknowledgements

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References

Bank, W.O.; Kerber, C.W. and Cromwell, L.D.: Treatment of intracerebral arteriovenous malformations with isobutyl 2-cyanoacrylate: Initial clinical experience. Radiology 139: 609-616 (1981).

Debrun, G.; Lacour, P.; Caron, J-P.; Hurth, M.; Comoy, J. and Keravel, Y.: Detachable balloon and calibrated-leak balloon techniques in the treatment of cerebrovascular lesions. Journal of Neurosurgery 49: 635-649 (1978).

Drake, C.G.: Cerebral arteriovenous malformations: Considerations for and experience with surgical treatment in 166 cases. Clinical Neurosurgery 26: 145-208 (1979).

Henderson, W.R. and Gomez, R. de R.L.: Natural history of cerebral angiomas. British Medical Journal 4: 571-574 (1967).

Johnson, J.R.T.: Radiotherapy of cerebral angiomas with a note on some problems in diagnosis; in Cerebral Angiomas: Advances in Diagnosis and Treatment (Springer-Verlag, Berlin 1975). (Drake, C.G., 1979 loc. cit.).

Kunc, Z.: Surgery of arteriovenous malformations in the speech and motor-sensory regions. Journal of Neurosurgery 40: 293-303 (1974).

Kusske, J.A. and Kelly, W.A.: Embolisation and reduction of the 'steal' syndrome in cerebral arteriovenous malformations. Journal of Neurosurgery 40: 313-321 (1974).

Luessenhop, A.J.; Kochmann, R.; Shevlin, W. and Ferrero, A.A.: Clinical evaluation of artificial embolisation in the management of large cerebral arteriovenous malformations. Journal of Neurosurgery 23: 400-417 (1965).

Luessenhop, A.J. and Presper, J.H.: Surgical embolisation of cerebral arteriovenous malformations through internal carotid and vertebral arteries. Long term results. Journal of Neurosurgery 42: 443-451(1975).

Luessenhop, A.J. and Spence, W.T.: Artificial embolisation of cerebral arteries. Journal of the American Medical Association 172: 1153-1155 (1960).

Stein, B.M. and Wolpert, S.M.: Arteriovenous malformations of the brain. II: Current concepts and treatment. Archives of Neurology 37: 69-75 (1980).

Wolpert, S.M.; Barnett, F.J. and Prager, R.J.: Benefits of embolisation without surgery for cerebral arteriovenous malformations. American Journal of Neuroradiology 2: 535-538 (1981).

Wolpert, S.M. and Stein, B.M.: Factors governing the course of emboli in the therapeutic embolisation of cerebral arteriovenous malformations. Radiology 131: 125-131 (1979).

Senile Dementia and Hydrocephalus due to Carotid Dolichoectasia

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Dolichoectasia of cerebral arteries is an uncommon condition which has been reported mostly in the basilar arteries and, in a few instances, in the carotid arteries (Little et al., 1981, Thompson et al., 1976). The majority of these cases presented with symptoms suggestive of intracranial tumour. Dementia has been reported in a few instances, mostly in dolichoectasia of the basilar arteries and in 2 cases of carotid dolichoectasia (Little et al., 1981). We wish to add a further case of dementia associated with carotid dolichoectasia.

Case Report

In 1977 a 65-year-old retired clerk was found to have hypertension but he did not seek regular treatment. Three years later he had an episode of sudden right lower limb weakness on waking up in the morning. Subsequently, he gradually developed bilateral lower limb weakness and became wheel-chair bound 1 year later. Two months before admission he started to have incontinence of urine, confusion and at times, fluctuation in orientation. There were no significant past health problems. He neither smoked nor drank alcohol.

There was no significant family history.

Physicial examination on admission showed the patient to be demented, incontinent, and unable to give a history. He could not stand without support. Power was grade 3 in the lower limbs and grade 4 in the upper limbs. Tendon reflexes were brisk but the plantar reflexes were flexor bilaterally. There were grade II changes in the fundi. Sensory testing was unreliable. Neurological examination otherwise was normal. Other systems were essentially normal. Blood pressure was 200/110. Investigations showed a normal complete blood count, normal serum electrolytes, normal serum calcium, blood sugar, liver and renal function. The VDRL was negative. Radiographs of the chest showed cardiomegaly but normal lung fields. A lumbar puncture showed a pressure of 70 to 80mm H_20, clear CSF with no cells. CSF protein was elevated to 1.0 g/L

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with normal glucose level. CSF culture yielded no growth (including culture for cryptococcus) and the VDRL was non-reactive in the CSF.

An EEG showed excessive diffuse non-rhythmic delta activity

A CT scan showed peculiar features of a calcified tubular mass in the parasellar and temporal regions and, after contrast infusion, aneurysmal dilatation of the middle cerebral arteries which was more marked on the right side (figs 1, 2). The lateral ventricles were dilated, but not the others. Bilateral carotid angiograms showed a slow cerebral circulation, with marked tortuosities, atherosclerotic changes and fusiform aneurysmal dilatation of the intracranial internal carotid and middle cerebral arteries on both sides (figs 3, 4).

The patient's mental state deteriorated for a few days after the angiograms. His family refused shunting procedure for the hydrocephalus and he died 5 months later. Postmortem examination was refused.

Discussion

Dolichoectasia occurs more frequently in males and over the age of 50 years. Dolichoectasia of the basilar arteries has been reported to cause cranial nerve palsy, facial spasm, trigeminal neuralgia, vertigo (Peterson et al., 1977; Deek et al., 1979; Moseley and Holland, 1979), dementia (Breig et al., 1967; Ekbom et al., 1969b; Rozario et al., 1978; Scotti et al., 1978; Deek et al., 1979; Moseley and Holland, 1979), and posterior fossa compressive symptoms (Bladin and Donnan, 1963). Carotid territory dolichoectasia has been reported to cause seizures (Thompson et al., 1976) and headache, visual impairment, cranial nerve palsy, dementia and hydrocephalus (Little et al., 1981). Apart from dementia and hydrocephalus which have been reported with both carotid and basilar artery dolichoectasia, basilar artery dolichoectasia may present with features of a cerebellopontine angle mass lesion, with compression of neighbouring cranial nerve structures. Carotid artery dolichoectasia on the other hand may cause optic atrophy, and ophthalmoplegia, and therefore may act as a parasellar mass lesion. Seizure, and hemiplegic migraine have been reported in one case. Features suggestive of an ischaemic episode have been reported both in basilar dolichoectasia (Bladin and Donnan, 1963) and carotid dolichoectasia (Case 7, of Little et al., 1981, and our case).

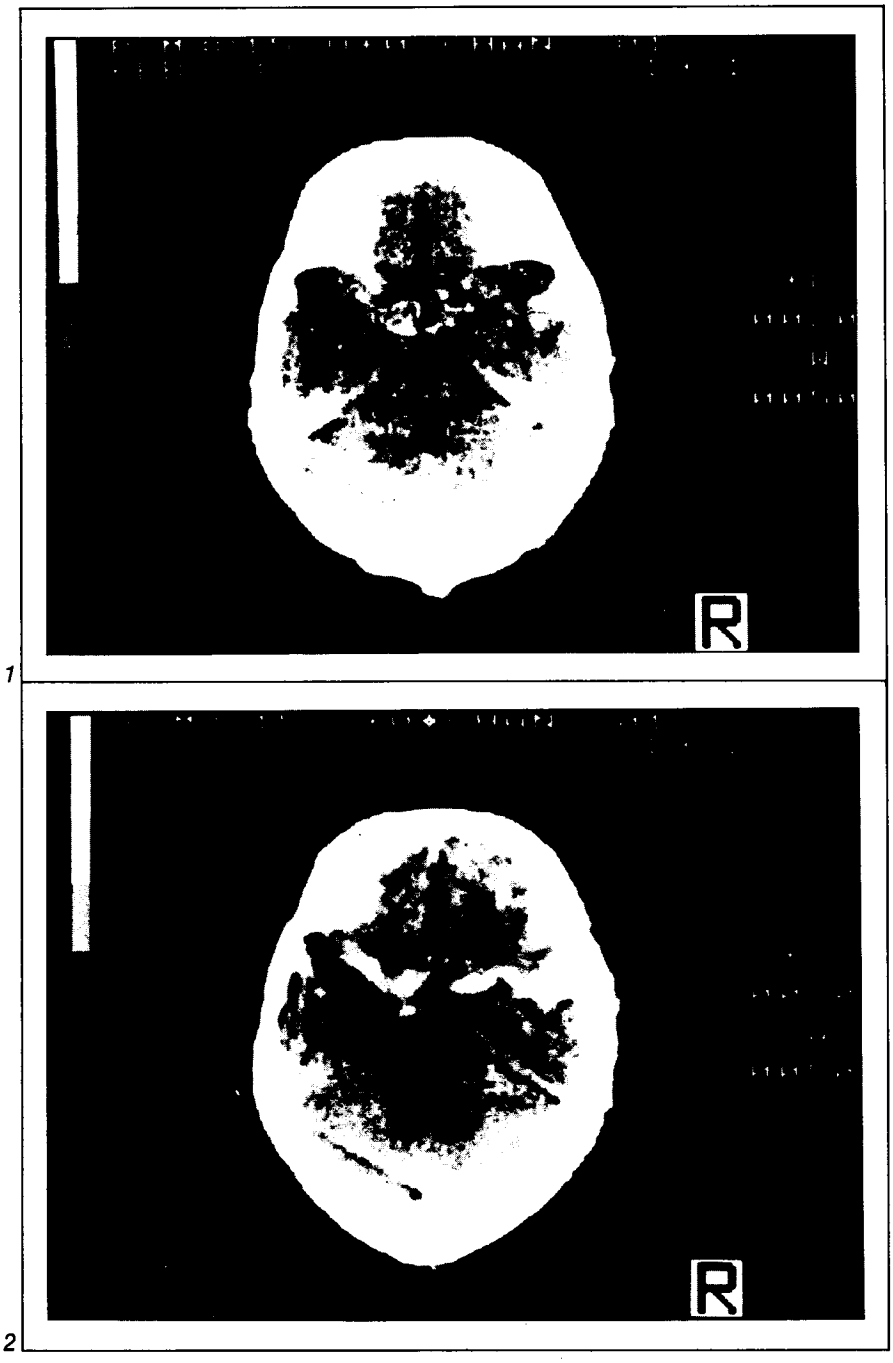
The dementia appears always to be associated with gait disorder and hydrocephalus. The 2 cases of carotid dolichoectasia described by Little et al. (1981) causing dementia, and our case, also had gait disturbance. Gait disorder was also associated with dementia in basilar dolichoectasia (Ekbom et al., 1969b; Moseley and Holland, 1979; Rozario et al., 1978).

The cause of the hydrocephalus is presumed to be secondary to pressure effect from the dolichoectasia. Rozario et al. (1978) demonstrated an ectatic basilar artery obliterating the posterior third ventricle and obstructing CSF flow.

The arterial pulsation from an ectatic artery has also been postulated to exert

Fig. 1. Unenhanced CT scan shows tubular calcified carotid arteries.

Fig. 2. CT scan after contrast infusion shows dolichoectasia of the carotid arteries.



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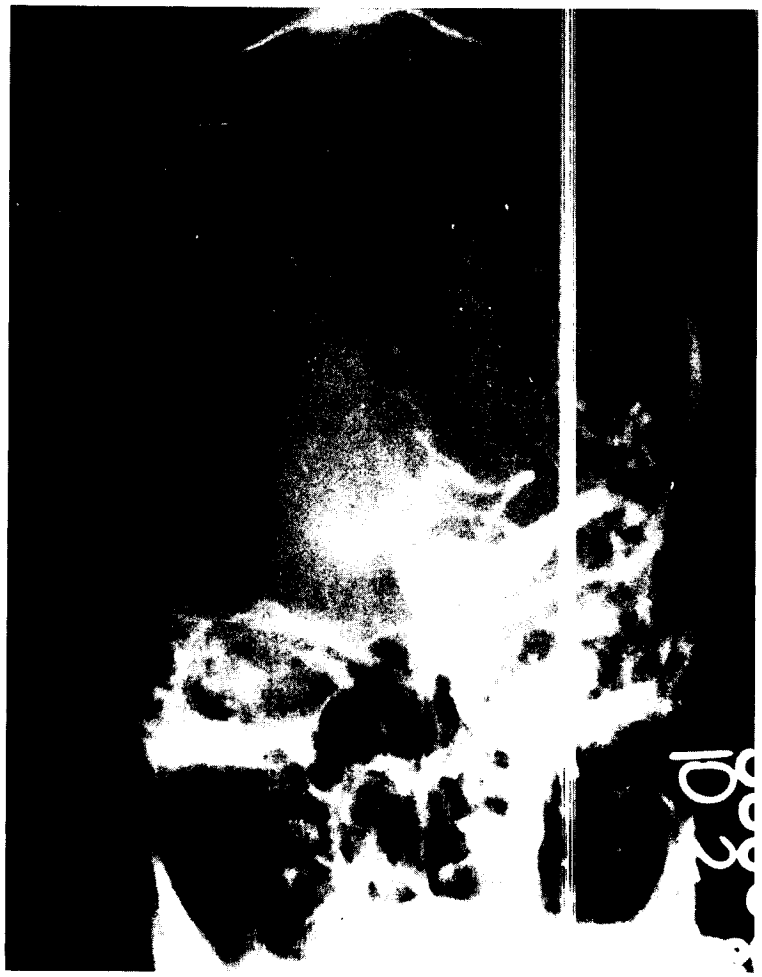

Fig. 3. Angiogram showing elongated dilatation of the left carotid artery.

a water hammer effect which impedes CSF outflow from the lateral ventricles. Ekbom et al. (1969a) subsequently demonstrated increased intraventricular pulse amplitude in basilar artery ectasia. The cause of the hydrocephalus in carotid dolichoectasia is less certain. It is possible that carotid dolichoectasia causes hydrocephalus through this effect rather than by direct pressure. Because of the episode of right sided weakness, cerebral infarction may contribute to the appearance of hydrocephalus in our case. However the cases described by Little et al. (1981) had only features of dementia and unsteady gait, explicable by hydrocephalus alone.

Diagnosis of dolichoectasia is now possible with CT scans, with isodense or calcified mass seen on plain CT scan and fusiform aneurysm on contrast medium infusion (Peterson et al., 1977; Scotti et al., 1978; Deek et al., 1979; Moseley and Holland, 1979). In view of the clinical deterioration seen in our patient after angiography and in one patient described by Little et al. (1981), it would appear

unnecessary and undesirable to do angiograms on these patients, when CT scans demonstrate the lesions.

Four of the patients described had shunting of the hydrocephalus with improvement in their dementia (Ekbom et al., 1969b; Rozario et al., 1978; Moseley and Holland, 1979). Information on the long term prognosis however is lacking. Our patient's family refused shunting and postmortem examination. Although it is likely that the dolichoectasia, hydrocephalus, and dementia are related, exact proof is lacking in this and other cases.

While uncommon, dolichoectasia of the carotid or basilar arteries may be another cause of treatable dementia in elderly patients, secondary to hydrocephalus. Pathological study of further cases is needed to delineate the cause of the hydrocephalus in carotid dolichoectasia.

Summary

A 65-year-old hypertensive man presented with progressive dementia, and bilateral lower limb weakness. Computerised tomography revealed carotid ar-

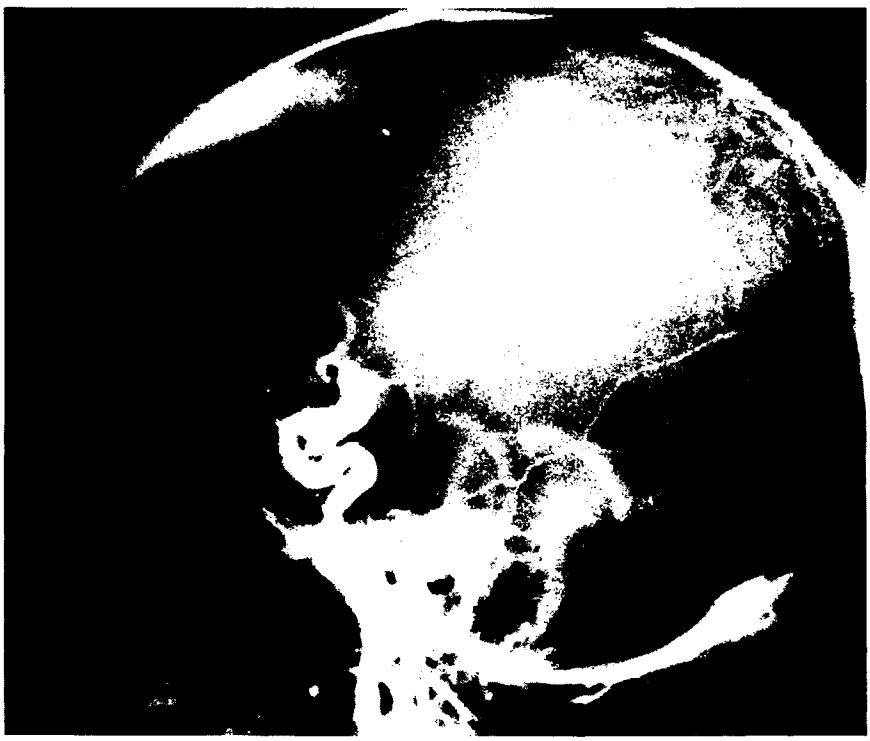

Fig. 4. Angiogram showing elongated dilatation of the right carotid artery.

terial dolichoectasia and hydrocephalus. This uncommon entity may constitute another form of surgically treatable dementia in the elderly.

References

Bladin, P.F. and Donnan, M.G.F.: Cerebral arterial ectasia. Clinical Radiology 14: 349-352 (1963).

Breig, A.; Ekbom, K.; Greitz, T.; Kugelberg, E.: Hydrocephalus due to elongated basilar artery. A new clinicoradiological syndrome. Lancet 1: 874-875 (1967).

Deek, Z.L.; Jannetta, P.J.; Rosenbaum, A.E.; Kerber, C.W. and Drayer, B.P.: Tortuous vertebrobasilar arteries causing cranial nerve syndromes: Screening by computed tomography. Journal of Computer Assisted Tomography 3 (6): 774-778 (1979).

Ekbom, K.; Greitz, T.; Kalmer, M.; Lopez, J. and Ottosson S.: Cerebrospinal fluid pulsations in occult hydrocephalus due to ectasia of basilar artery. Acta Neurochirugia (Wien) 2: fasc. 1: 1-8 (1969a).

Ekbom, K.; Greitz, T. and Kugelberg, E.: Hydrocephalus due to ectasia of the basilar artery. Journal of Neurological Science 8: 465-477 (1969b).

Little, J.R.; St Louis, P.; Weinstein, M. and Dohn, D.F.: Giant fusiform aneurysm of the cerebral arteries. Stroke 12: 183-188 (1981).

Moseley, I.F. and Holland, I.M.: Ectasia of the basilar artery: The breadth of the clinical spectrum and the diagnostic value of computed tomography. Neuroradiology 18: 83-91 (1979).

Peterson, N.T.; Duchesneau, P.M.; Westbrook, E.L. and Weinstein, M.A.: Basilar artery ectasia demonstrated by computed tomography. Radiology 122: 713-715 (1977).

Rozario, R.A.; Levine, H.K.; Scott, R.M.: Obstructive hydrocephalus secondary to an ectatic basilar artery. Surgical Neurology 9: 31-34 (1978).

Scotti, G.; De Grandi, C.; Colombo, A.: Ectasia of the intracranial arteries diagnosed by computed tomography. Megadolichobasilar artery: CT diagnosis. Neuroradiology 13: 183-184 (1978).

Thompson, J.R.; Weinstein, P.R. and Simmons, C.R.: Cerebral arterial dolichoectasia with seizure. Journal of Neurosurgery 44: 509-512 (1976).

Carotid Plaques and Retinal Emboli: A Clinical, Angiographic and Morphological Study

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Carotid endarterectomy has become an accepted method of preventing major strokes in patients presenting with retinal or cerebral ischaemic events (Barnett 1980). Transient ischaemic attacks (TIAs) in the carotid territory may frequently be due to causes other than carotid bifurcation plaques (Reinmuth, 1978). The importance of internal capsule lacunae (Donnan et al., 1982), cardiac embolisation (De Bono and Warlow, 1981) and migrainous events (Fisher, 1980) has recently been emphasised in this regard. The demonstration of angiographic lesions in patients with carotid territory TIAs does not necessarily imply that the lesions are symptomatic, as 14 to 24% of patients undergoing angiography for unrelated reasons have atheroma at the carotid bifurcation (Harrison and Marshall, 1976; Kollaritis et al., 1972).

The pathogenesis of TIAs due to carotid plaques is probably embolisation, rather than haemodynamic factors (Barnett, 1980; Reinmuth, 1978). In individual cases the identification of retinal emboli (Hollenhorst, 1961) provides strong evidence for an embolic mechanism.

The present study was to investigate the likelihood of embolisation as the pathogenetic mechanism in patients with symptomatic carotid lesions.

Methods

All patients judged to have symptomatic carotid disease and who were subjected to carotid endarterectomy over 6 months were prospectively studied. Thirty-

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Table I. Clinical features of 32 patients with symptomatic carotid plaques

Patients (n)	Clinical presentation	Ischaemic events[1]	Retinal emboli	Ipsilateral carotid bruit
8	Amaurosis fugax	4.2 (1-12)	4	4
17	Cortical event	3.5 (1-10)	3	8
7	Cortical event plus amaurosis fugax	7.8 (3-20)	0	6
32		4.6 1-20	7	18

1 Mean number of ischaemic events/patient in each category. Range is shown in brackets.

two patients were eligible, representing 16% of the total admissions to the Austin Hospital Stroke Unit over that period.

Ischaemic events were judged to be due to carotid disease if there was monocular amaurosis fugax with or without ipsilateral cerebral hemispheric ischaemia, or hemispheric ischaemia alone with adequate evidence of involvement of the cerebral cortex (dysphasia, dyspraxia, agnosia, focally disturbed EEG or cortical infarction on CT scan). Patients with potentially embolic cardiac lesions, patients with asymptomatic carotid bruits, and patients with no definite cortical involvement were excluded. Carotid bruits were noted but not used as a criterion of carotid disease.

Biplanar angiography of both carotid arteries was performed and the films were evaluated by a radiologist who was unaware which side was symptomatic. Optic fundi were examined through dilated pupils pre-operatively and daily for 5 days after endarterectomy. The carotid plaques were examined at operation and photographed.

Results

Relevant clinical features of the 32 patients are shown in table I. Eight patients had amaurosis fugax alone, 17 had cortical hemispheric events alone and 7 had hemispheric events plus amaurosis fugax. The mean number of ischaemic episodes per patient was 4.6, and only 5 cases had a single event. Of the 24 patients with hemispheric events, 6 had significant neurological signs pre-operatively while the remaining 18 cases had transient ischaemic attacks or subtle neurological signs.

Retinal emboli were seen in 7 cases (22%), 3 of whom had no history of amaurosis fugax. The emboli were often evanescent and present in the periphery of the retina and would have been overlooked without dilatation of the pupil. In 1 case an embolus not seen preoperatively was noted postoperatively.

At operation the carotid lumen was narrowed in all cases and in 24 patients the stenosis was 70% or more of the luminal diameter (table II). In only 3 cases

Table II. Morphology of the carotid bifurcation plaque at operation

Patients (n)	Clinical presentation	Stenosis > 70%	Smooth stenosis	Complicated plaques[1]		
				ulcers	intraplaque haemorrhage	luminal debris
8	Amaurosis	7	2	6	3	3
17	Cortical	11	1	13	13	10
7	Cortical plus amaurosis	6	0	6	6	5
32		24	3	25	22	18

1 Total of 29 of 32 plaques were complicated.

was a smooth stenosis found, the remaining 29 plaques being complicated by ulceration, intraplaque haemorrhage and/or intraluminal debris.

Correlation of the operative findings with angiography is shown in table III. The degree of carotid stenosis could be accurately predicted by angiography in most cases. Intraplaque haemorrhage could not be diagnosed angiographically and the presence of ulceration or intraluminal debris could not be accurately predicted. These findings will be presented in detail at a later date.

Discussion

A symptomatic and correctable carotid bifurcation lesion was found in 16% of patients admitted with suspected cerebrovascular disease. This figure is in agreement with that of the Harvard stroke registry (Mohr, 1978). Retinal emboli were seen in 7 of the 32 cases (22%). Repeated examination of the ocular fundus through a dilated pupil may be required to maximise the chance of detecting retinal emboli. Emboli were seen in 3 cases who presented with hemispheric events without a history of amaurosis fugax. In such cases the detection of emboli greatly increases the suspicion of a significant carotid lesion.

The operative specimens were complicated by ulceration, intraplaque haem-

Table III. Correlation of morphological features of plaques with angiographic interpretation. Numbers refer to cases

	Carotid stenosis	Ulceration	Intraplaque haemorrhage	Intraluminal debris
Angiographic estimate of stenosis within 20% of operative estimate	24			
Present at operation		25	22	18
False positive angiogram		5	0	3
False negative angiogram		9	22	15

orrhage and/or intraluminal debris in 29 cases (91%). These complicated plaques clearly have the potential to embolise and this was probably the mechanism of symptom production; in 6 cases actual emboli were seen. Imparato et al. (1979) also found a high frequency (80%) of complications in plaques that were removed at operation. In that study, however, plaques were analysed retrospectively where photographic records were available. Harrison and Marshall (1977) found intraluminal thrombus in 66% of cases operated on within 4 weeks of the most recent ischaemic event but in only 21% when operation was delayed.

The importance of carotid stenosis in producing symptoms is debated. Some authors regard a luminal diameter reduction of more than 50% as 'haemodynamically significant' (Thiele et al., 1980). Other authorities believe that haemodynamic mechanisms are rarely, if ever, the cause of focal neurological symptoms in the carotid territory (Barnett, 1980). In the present series all patients had carotid stenoses; in 24 patients the luminal reduction was 70% or more and in 8 cases it was 95% or more, as judged at operation. If haemodynamic factors were important, it is likely that the group with stenosis of 95% or more would have been affected most. In these 8 cases, retinal emboli were seen in 2 and the plaques were complicated in 7. Thus, evidence of embolism was present in all but 1 case where carotid stenosis was very marked.

The smooth uncomplicated nature of the plaque in 3 cases would suggest that haemodynamic factors were responsible for symptoms in these patients. These plaques had stenoses of 70%, 75% and 99% extent. In 1 case a retinal embolus was seen. It is possible that small ulcers were missed at operation or that intraluminal debris was removed by suction at operation before it was identified. Alternatively, other lesions in the heart or great arteries may have been responsible for the symptoms.

Serial angiograms may sometimes directly indicate intracranial emboli in cases of carotid stroke (Bladin, 1964; Blaisdell et al., 1974). Intracranial emboli are rarely seen angiographically in patients with transient ischaemic attacks. The diagnosis of a symptomatic carotid lesion rests on the clinical features and special investigations coupled with the angiographic demonstration of carotid bifurcation plaque. Unfortunately, angiography is an insensitive method of demonstrating plaque complications that lead to embolisation, as seen here (table III) and by others (Blaisdell et al., 1974; Croft et al., 1980).

In the present prospective series of patients with symptomatic carotid bifurcation disease, analysis of the excised plaque suggested that embolisation was the likely mechanism of symptoms in most cases, and retinal emboli could be seen in 22% of patients. Angiography showed the presence of carotid disease but could not accurately predict complications of plaques leading to embolisation. Angiography is essential in the management of stroke but the angiographic criteria for the significance of a carotid lesion remain to be defined. In cases of cerebrovascular disease where a carotid lesion is suspected, retinal emboli should be sought carefully and ancillary investigation used (CT scan, EEG, etc.) to establish the likelihood of embolic cortical ischaemia. In this way, the patients most likely to benefit from carotid endarterectomy can be identified and subjected to carotid angiography.

Summary

The angiographic criteria for the significance of a carotid lesion and the contribution of embolic versus haemodynamic factors in stroke pathogenesis are currently unresolved. This study evaluated correlations between the clinical features, presence of retinal emboli, angiographic appearance of the carotid bifurcation and morphology of the surgically excised plaque in 32 consecutive patients with symptomatic carotid lesions.

Retinal emboli were found in 22% of patients, including some without a history of amaurosis fugax. The carotid plaques were complicated by ulceration, intraplaque haemorrhage and/or intraluminal debris in 91% of cases. The degree of carotid stenosis seen at operation correlated well with the angiographic estimate. Plaque complications could not be accurately predicted angiographically, however. The high frequency of plaque complications, and the presence of retinal emboli, suggested that embolisation was the likely pathogenetic mechanism of stroke in most of these patients.

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References

Barnett, H.J.M.: Progress towards stroke prevention: Robert Wartenburg lecture. Neurology (Ny) 30: 1212-1225 (1980).

Bladin, P.F.: A radiological and pathological study of embolism of the internal carotid-middle cerebral axis. Radiology 82: 615-625 (1964).

Blaisdell, F.W.; Glickman, M. and Trunkey, D.D.: Ulcerated atheroma of the carotid artery. Archives of Surgery 108: 491-496 (1974).

Croft, R.J.; Ellam, L.D. and Harrison, M.J.G.: Accuracy of carotid angiography in the assessment of atheroma of the internal carotid artery. Lancet 1: 997-1000 (1980).

de Bono, D.P. and Warlow, C.P.: Potential sources of emboli in patients with presumed transient cerebral or retinal ischaemia. Lancet 1: 343-345 (1981).

Donnan, G.A.; Tress, B.M. and Bladin, P.F.: A prospective study of lacunar infarction using computerized tomography. Neurology (Ny) 32: 49-56 (1982).

Fisher, C.M.: Late-life migraine accompaniments as a cause of unexplained transient ischaemic attacks. Canadian Journal of Neurological Sciences 7: 9-17 (1980).

Harrison, M.J.G. and Marshall, J.: Angiographic appearance of carotid bifurcation in patients with completed stroke, transient ischaemic attacks and cerebral tumour. British Medical Journal 1: 205-207 (1976).

Harrison, M.J.G. and Marshall, J.: The finding of thrombosis at carotid endarterectomy and its relationship to the timing of surgery. British Journal of Surgery 64: 511-512 (1977).

Hollenhorst, R.W.: Significance of bright plaques in retinal arterioles. Journal of the American Medical Association 178: 23-29 (1961).

Imparato, A.M.; Riles, T.S. and Gorstein, F.: The carotid bifurcation plaque: Pathological findings associated with cerebral ischaemia. Stroke 10: 238-245 (1979).

Kollaritis, C.R.; Lubow, M. and Hissong, S.L.: Retinal strokes. Incidence of carotid atheroma. Journal of the American Medical Association 222: 1273-1275 (1972).

Mohr, J.P.: Transient ischaemic attacks and the prevention of strokes. New England Journal of Medicine 299: 93-95 (1978).

Pessin, M.S.; Hinton, R.C.; Davis, D.R.; Duncan, G.W.; Robertson, G.H.; Ackerman, R.H. and Mohr, J.P.: Mechanisms of acute carotid stroke. Annals of Neurology 6: 245-252 (1979).

Reinmuth, O.M.: Transient ischaemic attacks; in Tyler and Dawson (Eds) Current Neurology 1, pp.166-195 (Houghton Mifflin, Boston 1978).

Thiele, B.L.; Young, J.V.; Chikos, P.M.; Hirsch, J.H. and Strandness, D.E.: Correlation of arteriographic findings and symptoms in cerebrovascular disease. Neurology (Ny) 30: 1041-1046 (1980).

Steady-state Valproate Pharmacokinetics during Long Term Therapy

*M.J. Eadie, V. Heazlewood, L. McKauge and J.H. Tyrer**

Valproate (n-propylpentanoate, di-n-propylacetate) may be given as the free acid or its sodium salt, and has been proven an effective anticonvulsant for generalised and, less often, for partial epilepsy (Simon and Penry, 1975; Jeavons et al., 1977). Valproate is being increasingly used in treating human epilepsy. Single dose pharmacokinetic studies on the drug in healthy volunteers, or at the start of therapy, have been reported on several occasions (Schobben et al., 1975; Eadie et al., 1977; Gugler et al., 1977; Klotz and Antonin, 1977; Perruca et al., 1978b). However, little has been published on the pharmacokinetics of the drug after long term administration.

As a preliminary to marketing a new formulation of valproic acid, a bioavailability study was planned comparing this new formulation with a widely used sodium valproate preparation. Because of recent reports of serious liver (Suchy et al., 1979) and pancreatic (Coulter and Allen, 1980) toxicity from valproate, it was considered unwise to carry out the bioavailability study in the usual way, viz. by administering single doses of both preparations to healthy volunteers. It was thought more ethically acceptable to administer both preparations to epileptic patients already established on valproate therapy and showing no evidence of toxicity from the drug. Thus, the study became, in effect, a steady-state bioavailability one, and allowed determination of the pharmacokinetic parameters of the drug during long term therapy, when there had been abundant time for any induction of drug eliminating capacity to have occurred. Pharmacokinetic parameters in these circumstances may be more relevant for therapeutic decisions than parameters determined after the first dose of the drug.

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Table I. Personal details of 8 epileptic subjects studied

Subject	Age (years)	Sex	Weight (kg)	Type of epilepsy	Duration of epilepsy (years)	Duration of VPA therapy (years)	Therapy (mg/day)					
							valproate	phenytoin	carbamazepine	methyl-phenobarbitone	phenobarbitone	clonazepam
1	23	M	73	Generalised	20	3	1200		1200	600		6
2	42	F	57	Generalised	13	0.1	1600				90	
3	33	F	52	Partial	13	0.7	1000			230		
4	16	F	54	Generalised	5	3.5	1600	370				
5	31	F	61	Generalised	21	0.7	1800	400	1200		60	
6	11	F	40	Generalised	7	3	1000	125				
7	33	F	53	Generalised	21	7	3200	460			150	8.5
8	34	F	54	Partial	22	2.5	1200	360		150		

Hence the interest in the study here reported lies more in the pharmacokinetic than in the comparative bioavailability aspect.

Material and Methods

Patients

Eight long term epileptic patients (aged 11 to 42 years) were studied. Personal details of these patients are set out in table I. The duration of valproate therapy prior to the time of study ranged from 0.1 to 7 years (mean 2.6 years) and in all but 1 subject was over 0.5 years. All patients were also taking at least 1 other anticonvulsant drug long term.

Study Design

The study was an open cross-over one, comparing a marketed sodium valproate (200mg) tablet and a new valproic acid (175mg) formulation. The preparations contained equivalent valproate doses on a molar basis. Order of administration of the preparations was randomised so that 4 subjects took each preparation first. Doses of all anticonvulsants remained unaltered throughout the study in all subjects. At the end of 1 week's oral therapy with 1 preparation, serial blood collections were carried out across the dosage interval following the patient's usual morning dose of valproate. In each subject the procedure was repeated following the next week's therapy with the other valproate preparation.

Since valproate has a half-life of 8 to 15 hours, all patients should have been in the steady state during the studies.

Blood Sampling

In each test period, venous blood sampling via an indwelling cannula was performed at 0,1,2,3,4, and 6 hours. The blood was collected into lyophilised lithium heparin tubes and centrifuged with the minimum of delay to separate off the plasma.

Assay Procedure

Standard and assay tubes were prepared, adding 40μl of methanolic internal standard solution (1.944 mg/ml) and thus delivering 77.76μg cyclohexanecarboxylic acid to each tube. Volumes of 0μl, 10μl, 20μl, 40μl and 80μl methanolic sodium valproate solution (2.04 mg/ml) respectively were added to each of 5 standard tubes. These tubes thus contained 0μg, 20.4μg, 40.8μg, 81.6μg and 122.4μg of sodium valproate. Having dried off the methanol under a stream of nitrogen, 1ml HCl (0.2M) and 5ml chloroform were added to each tube. Then blank plasma (1ml), or patient plasma (1ml), was added to each of the standard or assay tubes respectively. After shaking for 2 minutes, followed by centrifugation,

the aqueous layer was aspirated off and the chloroform layer was transferred to clean conical-based test tubes.

Evaporation of the chloroform was accomplished by shaking the samples under the water vacuum of a Vacu-mix machine. Fifty μl of N, N-dimethylacetamide, 10μl of tetramethylammonium hydroxide (4% in methanol) and 10μl iodobutane were then added to each tube to produce methyl derivatives of the drug and the internal standard. Samples of the supernatants obtained after centrifugation were injected into a gas chromatograph (Varian 2100) and run on a 3% OV-17 column at 95°C, the injector temperature being 265°C and the detector temperature 290°C.

Steady-state Pharmacokinetics – Theoretical Considerations

The theoretical background for determining pharmacokinetic parameters in the steady state is discussed in detail by Gibaldi and Perrier (1975). In brief, a

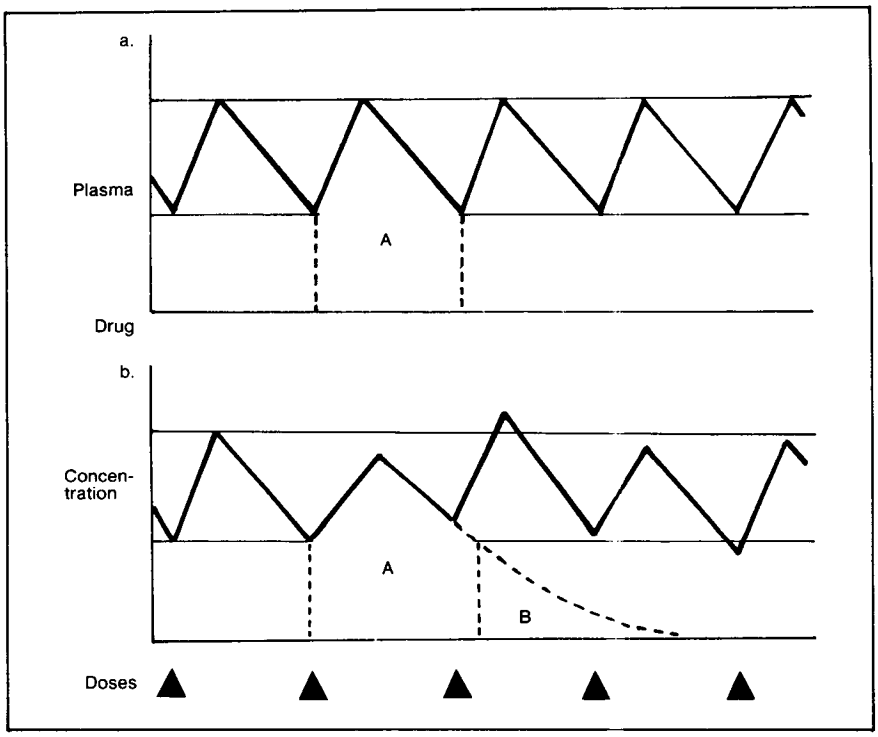

Fig. 1. (a) Theoretical behaviour of plasma drug concentrations under steady-state conditions. (b) Likely actual behaviour of plasma drug concentrations under steady-state conditions, though with dosage intervals kept constant. A = area under the plasma level curve over a dosage interval. B = additional area under the curve that would apply if no further drug were given.

Table II. Calculated pharmacokinetic parameters for valproate preparations in 8 epileptic patients

Preparation	Weight (kg)	Dose (as mg of sodium valproate)	AUC_{ss} (mg·hour/L)	CL (L/kg/hour)	k (hour)	T½ (hour)	V_D (L/kg)	Kabs (hour)
Sodium valproate	73	400	319.34	.0172	.0917	7.56	.1876	1.88
	57	400	793.85	.0089	.1006	6.89	.0885	.992
	52	400	817.03	.0094	.0449	15.43	.2094	2.444
	54	600	642.17	.0173	.835	8.30	.2072	1.523
	61	600	425.42	.0231	.986	7.03	.2343	1.838
	40	400	775.85	.0129	.1248	5.55	.1034	1.424
	53	800	395.69	.0381	.1202	5.77	.3170	2.866
	54	400	661.05	.0114	.0980	7.07	.1163	2.623
Mean	55.4		603.80	.0173	.0953	7.95	.1830	1.941
± SD			197.11	.0097	.0246	3.15	.0771	.648
Valproic acid	73	403	497.07	.0113	.0620	11.18	.1877	2.561
	57	403	798.90	.0089	.1054	6.57	.0844	2.253
	52	403	785.94	.0099	.0500	13.86	.1980	3.233
	54	604	602.84	.0186	.1147	6.04	.1617	1.112
	61	604	391.42	.253	.1262	5.49	.2004	1.792
	40	403	653.35	.0154	.0662	10.47	.2329	7.863
	53	806	365.92	.0415	.1557	4.45	.2665	1.045
	54	403	546.94	.0139	.0716	9.68	.1941	6.595
Mean	55.4		580.30	.0181	.0940	8.47	.1907	3.307
± SD			162.83	.0108	.0371	3.30	.0532	2.549
Paired t =			.7706	.7825	.1095		.3450	1.670
df (degrees of freedom)		=	7	7	7		7	7
p (probability)		=	> .40	> .40	> .90		> .70	> .10
Overall mean value of parameter				.0177	.0946	8.21	.1868	2.624
± SD				.0099	.0309	3.13	.0641	1.930

steady state applies when a drug has been taken regularly for long enough for its amount eliminated to equal its amount absorbed over each dosage interval. In the steady state the plasma drug concentrations at the start and end of the dosage interval are equal, and the mean concentration across each dosage interval, and the peak concentration, should be identical from one dosage interval to the next (fig. 1a). The total area under the plasma level curve ($AUC_{o\rightarrow t}$) during a dosage interval is proportionate to the amount of drug absorbed (and of necessity eliminated) during each dosage interval, a relationship which permits the estimation of plasma drug clearance, as set out below. Other pharmacokinetic parameters can be determined from the clearance.

In practice, when steady-state conditions should apply, there may be some departure from the theoretical situation described above. Drug doses may not always be taken at exactly regular intervals, and drug absorption rate may vary

from dose to dose in response to differing physiological factors. Hence plasma drug level at the start of a dosage interval (C_o) may not be exactly the same as the concentration at the end of that interval (C_t) (fig. 1b). Therefore, in practice, to apply steady-state kinetics, it may be more exact to determine area under the plasma level curve from time 0 (at the start of the dosage interval studied) to the time after dosing when the plasma drug level has again fallen to C_o, rather than to measure the actual area under the curve during that dosage interval. In effect one can use the polyexponential equation of best fit to the plasma level data to calculate the area under the curve from the outset to infinity (assuming no further dose was given); from this area one subtracts the area under the tail of the curve beyond the stage when the plasma level concentration has fallen to C_o. Thus, in (fig.1b), area B would be subtracted from areas A + B, to determine area A.

Analysis of Data

Preliminary estimates were obtained for the parameters of a polyexponential equation of best fit to the plasma concentration – time data ($C = \Sigma a_i e^{-b_i t}$), using

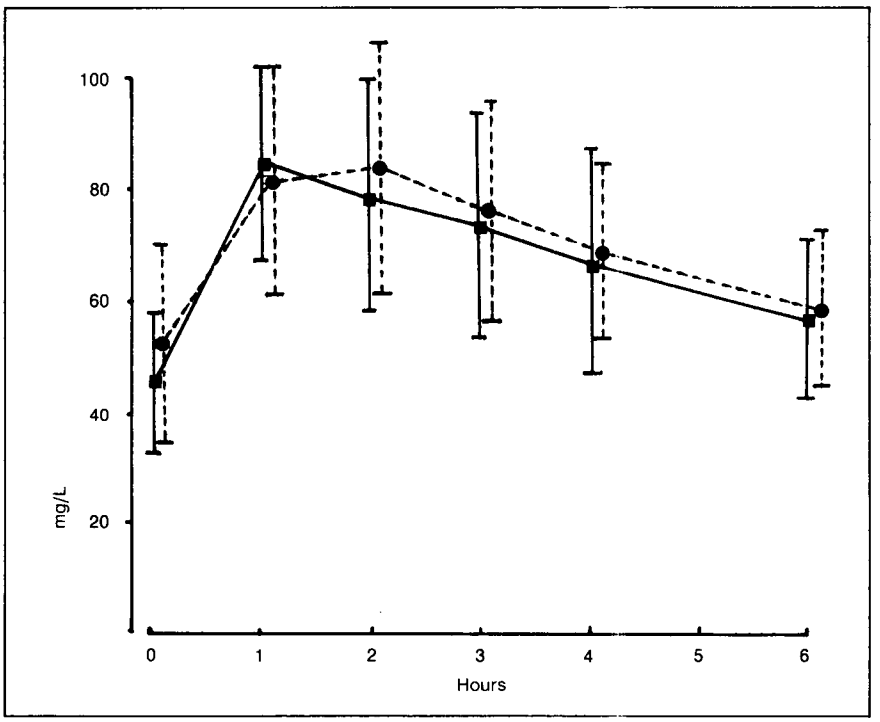

Fig. 2. Time courses of the plasma concentrations of valproate (means ± standard deviations) over 6 hours after sodium valproate (■——■) and valproic acid (●---●) in the same 8 subjects.

the computer program ESTRIP (Brown and Manno, 1978). The estimates were then refined, using the iterative non-linear least squares program of Horwitz and Homer (1970) as modified by Peck and Barrett (1979), run on an Apple II Plus microcomputer. Area under the plasma level curve at steady state (AUC_{ss}) was determined as explained above by calculating $AUC_{o\rightarrow t}$ from the relation $AUC_{o\rightarrow\infty} = \Sigma\, a_i/b_i$, and subtracting from this $AUC_{t\rightarrow\infty}$ (i.e. C_t/k or C_t/β) where t = the time at which the plasma level concentration had fallen again to equal the initial concentration (C_o).

Other pharmacokinetic parameters were calculated, employing the following relationships:

$$CL = Dose/AUC_{ss}$$
$$V_D = CL/k \text{ or } CL/\beta$$
$$T_{1/2} = .693/k \text{ or } .693/\beta$$
$$T_{1/2(abs)} = .693/k_{(abs)}$$

where CL = plasma clearance
V_D = apparent volume of distribution
k or β = terminal elimination rate constant
$k_{(abs)}$ = absorption rate constant
$T_{1/2}$ = elimination half-life
$T_{1/2\,(abs)}$ = absorption half-life

Paired Student's *t* testing was used to compare the mean values for the pharmacokinetic parameters obtained from the 2 drug preparations.

Results

A plot of the mean plasma concentration – time profiles for each preparation is shown in fig. 2. A 1-compartment open pharmacokinetic model provided an adequate fit to the plasma level-time data.

Table II sets out the various calculated pharmacokinetic parameters for each valproate preparation studied. There was no statistically significant difference between the 2 preparations in respect to any of the parameters listed. The data were pooled, therefore, to obtain better estimates of the population values of the parameters.

The mean elimination half-life was 8.21 ± SD 3.13 hours. Plasma valproate clearance was 0.0177 ± 0.0099 L/kg/hour (or 16.34 ± 9.14 ml/minute, if not corrected for body weight) assuming 100% bioavailability for the orally administered drug, which seems reasonable in view of published data (e.g. Perucca et al., 1978a) and the relatively high absorption rate constant (2.624 ± 1.930/hour) found in the present patients. The apparent volume of distribution had a mean value of 0.1868 ± 0.0641 L/kg/hour.

Bioavailabilities of the 2 preparations were, for practical purposes, equal.

Discussion

A moderate amount of information is available regarding the pharmacokinetics of valproate given in a single dose at the start of therapy, but with the

exception of the recently published investigation of Hoffman et al. (1981) using tritiated drug and mass spectrometry, little has been published on the pharmacokinetics of the drug after its prolonged administration in treatment of human epilepsy. This is the situation in which the drug is usually employed in clinical practice, and it would be helpful to know the dispositional parameters of the drug in these circumstances, and whether the parameters were changed to a significant extent by time-related factors, e.g. the autoinduction of biotransformation capacity, and by the concurrent intake of other drugs. It would usually be unethical to withdraw valproate therapy, even temporarily, during the long term treatment of human epilepsy to follow the time course of the decline in plasma level and thus to determine the pharmacokinetic parameters. The present study, however, has shown that it is practicable to determine the pharmacokinetic parameters of the drug under steady-state conditions, when it is unlikely that control of the patient's epilepsy will be compromised by the method of study.

As determined in the present study, the values of the pharmacokinetic parameters of valproate after long term therapy have generally proved similar to those obtained by other workers after the first dose of the drug. Thus, published values of the elimination half-life have been in the range 8 to 15 hours (Loiseau et al., 1975; Eadie et al., 1977; Gugler et al., 1977; Perucca et al., 1978b), but with a value of 5.88 ± 0.47 hours in epileptic patients pretreated with other anticonvulsants (Richens et al., 1976). The present study yielded a mean half-life value of 8.21 ± 3.13 hours. The mean plasma clearance in the present study (0.0177 ± 0.0099 L/kg/hour) was in accord with the general range of published values for this parameter after single doses of valproate (0.0064 ± 0.0011 to 0.018 ± 0.008 L/kg/hour); similarly, the apparent volume of distribution found in the present study after long term therapy (0.1868 ± 0.0641 L/kg) fell within the range of values published for this parameter (0.147 ± 0.004 to 0.198 ± 0.029 L/kg) following single doses of the drug (Richens et al., 1976; Eadie et al., 1977; Gugler et al., 1977; Klotz and Antonin, 1977; Perucca et al., 1978a; 1978b). The findings of the present study are also in agreement with the work of Hoffman, et al. (1981), also carried out in patients on long duration valproate therapy.

It appears that long continued valproate intake in epileptic patients who are often receiving other anticonvulsants is associated with little change in the dispositional parameters of the drug when compared with the parameters determined in other patients after the initial dose of the drug. This is unlike the situation with other anticonvulsants, e.g. carbamazepine, where autoinduction of metabolism occurs (Eichelbaum, et al. 1975). This knowledge may be reassuring to those who have to manage valproate therapy in epileptic patients over months or years.

Summary

As part of a comparative bioavailability investigation, the steady-state pharmacokinetics of the anticonvulsant valproate (given as the sodium salt and the free acid) were studied in 8 epileptic patients who had received long term therapy

with the drug. Mean elimination half-life was 8.21 ± 3.13 hours, mean apparent volume of distribution 0.1868 ± 0.0641 L/kg and mean plasma clearance 0.0177 ± 0.0099 L/kg/hour. The magnitudes of these parameters are similar to those reported for single dose studies in patients at the start of valproate therapy. Thus, long term therapy with valproate does not appear to be associated with significant alterations in the human body's disposition of the drug, unlike the situation with certain other anticonvulsants, e.g. carbamazepine.

References

Brown, R.D. and Manno, J.E.: ESTRIP, a BASIC computer program for obtaining initial polyexponential parameter estimates. Journal of Pharmaceutical Science 67: 1687-1691 (1978).

Coulter, D.L. and Allen, R.J.: Pancreatitis associated with valproic acid therapy for epilepsy. Neurology 7, 92 (1980).

Eadie, M.J.; Tyrer, J.H.: Smith, G.A. and McKauge, L.: Pharmacokinetics of drugs used for petit mal absence epilepsy. Clinical and Experimental Neurology 14: 172-183 (1977).

Eichelbaum, M.; Ekbom, K.; Bertilsson, L.; Ringberger, V.A. and Rane, A.: Plasma kinetics of carbamazepine and its epoxide metabolite in man after single and multiple doses. European Journal of Clinical Pharmacology 8: 337-341 (1975).

Gibaldi, M. and Perrier, D.: Pharmacokinetics (Dekker, New York 1975).

Gugler, R.; Schell, A.; Eichelbaum, M.; Froscher, W. and Schulz, H.U.: Disposition of valproic acid in man. European Journal of Clinical Pharmacology 12: 125-132 (1977).

Hoffman, F.; von Unruh, G.E. and Jancik, B.C.: Valproic acid disposition in epileptic patients during combined antiepileptic maintenance therapy. European Journal of Clinical Pharmacology 19, 383-385 (1981).

Horwitz, D.L. and Homer, L.D.: Analysis of Biomedical Data by Time-sharing Computers. I. Non-linear Regression Analysis. Project No MR 005, 20-0287. (Naval Medical Research Institute, National Naval Medical Centre, Bethesda, Maryland, 20014, 1970).

Jeavons, P.M.; Clark, J.E. and Maheshwari, M.C.: Treatment of generalized epilepsies of childhood and adolescence with sodium valproate ('Epilim'). Developmental Medicine and Child Neurology 19: 9-25 (1977).

Klotz, U. and Antonin, K.H.: Pharmacokinetics and bioavailability of sodium valproate. Clinical Pharmacology and Therapeutics 21: 736-743 (1977).

Loiseau, P.; Brachet, A. and Henry, P.: Concentration of dipropylacetate in plasma. Epilepsia 16: 609-615 (1975).

Peck, C.C. and Barrett, B.B.: Nonlinear least-squares regression programs for microcomputers. Journal of Pharmacokinetics and Biopharmaceutics, 7: 537-541 (1979).

Perucca, E.; Gatti, G.; Frigo, G.M. and Crema, A.: Pharmacokinetics of valproic acid after oral and intravenous administration. British Journal of Clinical Pharmacology 5: 313-318 (1978a).

Perucca, E.; Gatti, G.; Frigo, G.M.; Crema, A.; Calgetti, S. and Visintine, D.: Disposition of sodium valproate in epileptic patients. British Journal of Clinical Pharmacology 5: 495-499 (1978b).

Richens, A.; Schoular, I.T.; Ahmad, S. and Jordan, B.J.: Pharmacokinetics and efficacy of Epilim in patients receiving long term therapy with other anticonvulsants; in Legg, N.J. (Ed) Clinical and pharmacological aspects of sodium valproate ('Epilim') in the treatment of epilepsy pp.78-88 (MCS Consultants, Tunbridge Wells 1976).

Schobben, F.; van der Kleijn, E. and Gabreels, F.J.M.: Pharmacokinetics of di-n-propylacetate in epileptic patients. European Journal of Clinical Pharmacology 8: 97-105 (1975).

Simon, D. and Penry, J.K.: Sodium di-n-propylacetate (DPA) in the treatment of epilepsy. A review. Epilepsia 16: 549-573 (1975).

Suchy, F.J.; Balistreri, W.F.; Buchino, J.J.; Sondheimer, J.M.; Bates, S.R.; Kearns, G.L.; Stull, J.D. and Bove, K.E.: Acute hepatic failure associated with the use of sodium valproate. Report of two fatal cases. New England Journal of Medicine 300: 962-966 (1979).

Hepatotoxicity of Sodium Valproate

*S.F. Berkovic, P.F. Bladin, D.B. Jones, R.A. Smallwood and F.J.E. Vajda**

Sodium valproate is a valuable anticonvulsant for the treatment of most forms of generalised epileptic seizures (Browne, 1980). Relative freedom from side effects is a major advantage of this drug, but reports of fatal hepatotoxicity have appeared recently (Lancet editorial, 1980).

Abnormal liver function tests were infrequently detected in the early clinical studies with the drug (Lance and Anthony, 1977), but recent studies have found that up to 44% of patients on valproate have abnormal liver function tests (Coulter et al., 1980). The relevance of these tests to the risk of serious hepatotoxicity is not known. The appropriate management of patients stabilised on valproate who are found to have abnormal liver function tests has not been defined.

The present study was designed to evaluate the frequency of clinical and biochemical liver dysfunction in patients receiving valproate. Patients taking valproate were evaluated prospectively and a group of patients started on the drug 6 years previously (Vajda et al., 1978) was followed up.

Methods

Prospective Evaluation

Sixty patients attending an epilepsy clinic who were taking sodium valproate were studied. The patients had diagnoses of common generalised epilepsy (25), Lennox-Gastaut syndrome (6), temporal lobe epilepsy (12) and miscellaneous forms of epilepsy (17).

A detailed history of drug and alcohol intake was taken and an examination

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for clinical evidence of liver disease was performed. Blood was taken for estimation of anticonvulsant levels, albumin, bilirubin, alkaline phosphatase, aspartate transaminase (AST), gammaglutamyl transpeptidase (GGT), prothrombin time, partial thromboplastin time and fibrinogen. Fibrinogen was estimated by both a functional assay (Lancer Fibrinogen Analyser, Sherwood Instruments) and by a physicochemical method (sodium sulphite precipitation – Rampling and Gaffney, 1976). Fibrin monomers were sought in cases where fibrinogen was low (protamine sulphate method, Dade Diagnostics Kit).

Repeated clinical and biochemical evaluations were performed over the following 6 to 11 months. Each patient was assessed 2 to 5 times (mean 3.7) throughout this period.

A control group of 18 patients on phenytoin monotherapy and 22 patients on carbamazepine monotherapy was studied similarly. Patients taking other drugs or alcohol were excluded from the control group.

Retrospective Study

Twenty-four patients who had been started on valproate from March 1975 to May 1976 in an early Australian clinical trial (Vajda et al., 1978) were traced in January 1982 and evidence of liver disease was sought in them.

Results

Prospective Study

Sixty patients aged 10 to 69 years (mean 29 years) were taking sodium valproate (0.4 to 4.4 g/day) for 0.5 to 6.7 years (mean 3.3 years). Twenty-three patients received valproate monotherapy while 37 patients were taking other anticonvulsants as well (mainly phenytoin or carbamazepine).

No patient showed hepatomegaly, splenomegaly or the peripheral stigmata of chronic liver disease.

Serum albumin, bilirubin, prothrombin time and partial thromboplastin time were normal in all patients. Alkaline phosphatase was transiently raised in 1 patient. AST was raised in 4 patients; 3 of these were alcoholics and the level fluctuated with alcohol intake. The fourth patient had an AST level about twice the upper limit of normal but there was no other clinical or biochemical evidence of liver disease over 9 months of follow-up.

Elevation of GGT was found in 31 patients and depressed fibrinogen in 26 patients. Elevation of GGT was generally 2 to 4 times the upper limit of normal and levels in individual patients were remarkably constant on repeated estimations during the follow-up. Low fibrinogen levels ranged from 1.1 to 1.9 g/L (normal 2 to 4 g/L). Levels fluctuated in most patients, however, and in only 5 cases were they persistently depressed. Fibrinogen estimations by the 2 separate methods agreed closely, indicating that the fluctuations were not due to laboratory error. Fibrin monomers were not detected, suggesting that accelerated consumption of fibrinogen was not occurring.

Table 1. Liver function tests in 100 epileptic patients

	Valproate monotherapy n = 23 (%)	Valproate polytherapy n = 37 (%)	Phenytoin or carbamazepine monotherapy n = 40 (%)
Normal	17 (74)	5 (14)	12 (30)
Abnormal			
high GGT alone	1 (4.5)	11 (30)	20 (50)
low fibrinogen alone	4 (17)	3 (8)	3 (7)
high GGT and low fibrinogen	1 (4.5)	18 (48)	5 (13)

Table I shows the frequency of abnormalities of GGT and fibrinogen in the patients taking valproate monotherapy compared with those on polytherapy and the control group. Most of the patients (74%) receiving valproate monotherapy had consistently normal liver function tests. Fibrinogen depletion was found in 5 patients, while elevation of GGT was seen in only 2 patients, both of whom were alcoholic. In contrast, only 14% of patients in the polytherapy group had normal liver function tests, and nearly half (48%) had both raised GGT and low fibrinogen. Of the patients receiving monotherapy with phenytoin or carbamazepine 70% had abnormal liver function tests, but in this group elevation of GGT (63%) was far more common than fibrinogen depletion (20%).

Retrospective Study

All 24 patients who had started valproate in 1975 or 1976 were traced, the follow-up averaging 6 years. Sixteen patients had remained on valproate (8 of whom were seen regularly at the Austin Hospital and were included in the prospective study). The liver function profiles in these patients were no different from those of patients taking valproate for shorter periods. The other 8 patients taking valproate were treated elsewhere and all had had recent liver function profiles which were normal. Seven patients had ceased valproate owing to lack of effect but none had shown liver dysfunction. One patient had died of a glioma, which was known to be the cause of his seizures.

Discussion

Extensive experience with sodium valproate in Europe during the early 1970s did not result in the detection of significant clinical or biochemical liver disease (Jeavons, 1980). Since 1979 case reports of fatal hepatotoxicity associated with valproate have been accumulating (Lancet editorial, 1980). Recent clinical studies have shown frequent abnormalities of liver function tests in patients receiving valproate. Elevated transaminase levels (Coulter et al., 1980), elevated GGT

(Beran and Rischbieth, 1979) and depressed fibrinogen levels (Sussman and McLain, 1979) have been noted most often. Most patients in these studies were receiving polytherapy, however.

The results here reported indicate that abnormal liver function tests are far more common in patients receiving polytherapy than valproate monotherapy. Moreover, abnormal liver function tests are also common in patients receiving monotherapy with phenytoin or carbamazepine. It should be emphasised, however, that in none of our patients was there sufficient biochemical or clinical evidence of liver damage to warrant further investigation (e.g. liver biopsy) or cessation of therapy.

The occurrence of abnormal liver function tests in patients taking other anticonvulsants has been noted before (Rosalki et al., 1971; Sano et al., 1981), but it does not appear to have been adequately considered in some studies of valproate hepatotoxicity (Coulter et al., 1980; Sussman and McLain, 1979). The high frequency of abnormal liver function tests in patients receiving polytherapy regimens which include valproate may be largely due to the other drugs.

The principal abnormalities of liver function detected in this study were elevated GGT and depressed fibrinogen levels. GGT was raised in only 2 patients taking valproate monotherapy, both of whom were alcoholics. It was raised in 78% of patients taking polytherapy and in 63% of patients receiving monotherapy with phenytoin or carbamazepine. GGT is a sensitive marker of liver enzyme induction and it is unlikely that raised GGT levels reflect significant liver damage in these patients (Rosalki et al., 1971). Depression of serum fibrinogen was noted in patients receiving valproate monotherapy and polytherapy. This change was rarely sustained and levels fluctuated from visit to visit, without variation in valproate dose or plasma level, although other workers have claimed it is a dose-related phenomenon (Sussman and McLain, 1979). There were no haemostatic problems in these patients, and this, together with the fact that fibrinogen levels fluctuated widely, suggests that the liver can still supply adequate quantities of fibrinogen when required.

The biochemical abnormalities did not progress over the 6 to 11-month surveillance of the prospective study. The similarity of the liver function profiles in the patients on valproate for 6 years compared with those on the drug for shorter periods suggests there is no cumulative hepatotoxic effect after 6 years of valproate usage.

Most reports of fatal hepatotoxicity have concerned children (Lancet editorial, 1980). The patient group here examined consisted largely of adults but 14 patients taking valproate were aged 10 to 18 years. Results in this adolescent subgroup were no different from the group as a whole. This study did not examine children under 10 years but Jeavons (1980) has found abnormal liver function tests only rarely in small children. In Europe valproate is frequently used as the sole anticonvulsant. In the United States, where most of the reports finding a high frequency of liver function abnormalities have originated, valproate is usually prescribed in combination with other drugs (Coulter et al., 1980). This difference in experience between European and North American studies may be explained by the findings presented here that show abnormal liver func-

tion tests are more frequently associated with polytherapy than with the use of sodium valproate alone.

Most cases of acute severe hepatotoxicity have occurred within 2 to 3 months of starting valproate therapy. In cases where liver function has been assessed before the acute illness it has been normal (Gerber et al., 1979) or near normal (Dodson and Tasch, 1981). Acute severe liver disease may be an idiosyncratic reaction to valproate and conventional liver function tests do not appear to serve as an adequate predictive guide (Dodson and Tasch, 1981). Conversely, abnormal liver function tests are not usually accompanied by clinical illness, and our findings suggest that they are more likely to be due to drugs other than valproate. Thus, the finding of biochemical evidence of liver dysfunction in patients taking valproate is not necessarily an indication for ceasing treatment.

Summary

Repeated clinical and biochemical evaluations of liver function were performed on 60 patients taking sodium valproate. No clinical evidence of liver disease was found. Biochemical abnormalities were frequently found, but they were far more common in patients treated with multiple anticonvulsants than in patients on valproate alone. A control group of patients taking phenytoin or carbamazepine monotherapy also had a high incidence of biochemical abnormalities.

A group of patients started on valproate therapy 6 years previously was followed up. No evidence of liver disease was found in this group.

It was concluded that biochemical abnormalities of liver function in patients receiving valproate are not progressive, and in many cases relate to the intake of other drugs. The finding of abnormal liver function tests is not necessarily an indication for ceasing valproate.

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References

Beran, R.G. and Rischbieth, R.H.C.: Sodium valproate and hepatotoxicity in epileptics. Medical Journal of Australia 2: 603-604 (1979).

Browne, T.R.: Drug therapy: Valproic acid. New England Journal of Medicine 302: 661-666 (1980).

Coulter, D.L.; Wu, M. and Allen, R.J.: Valproic acid therapy in childhood epilepsy. Journal of the American Medical Association 244: 785-788 (1980).

Dodson, W.E. and Tasch, V.: Pharmacology of valproic acid in children with severe epilepsy. Clearance and hepatotoxicity. Neurology 31: 1047-1050 (1981).

Editorial: Sodium valproate and the liver. Lancet 2: 1119-1120 (1980).
Gerber, N.; Dickinson, R.G.; Harland, R.K.; Houghton, L.D.; Antonias, J.I. and Schimschock, J.C.: Reye-like syndrome associated with valproic acid therapy. Journal of Pediatrics 95: 142-144 (1979).
Jeavons, P.M.: Prophylaxis against febrile convulsions. British Medical Journal 1: 863 (1980).
Lance, J.W. and Anthony, M.: The anticonvulsant action of sodium valproate (Epilim) in 100 patients with various forms of epilepsy. Medical Journal of Australia 1: 911-915 (1977).
Rampling, M.W. and Gaffney, P.J.: The sulphite precipitation method for fibrinogen measurement; its use on small samples in the presence of fibrinogen degradation products. Clinica Chimica Acta 67: 43-52 (1976).
Rosalki, S.B.; Tarlow, D. and Rau, D.: Plasma gamma-glutamyl transpeptidase elevation in patients receiving enzyme-inducing drugs. Lancet 2: 376-377 (1971).
Sano, J.; Kawada, H.; Yamaguchi, N.; Kawakita, M. and Kobayashi, K.: Effect of phenytoin on serum gamma-glutamyl transpeptidase activity. Epilepsia 22: 331-338 (1981).
Sussman, N.M. and McLain, L.W.: A direct hepatotoxic effect of valproic acid. Journal of the American Medical Association 242: 1173-1174 (1979).
Vajda, F.J.; McNeil, J.J.; Morris, P.; Drummer, O. and Bladin, P.F.: Sodium valproate (Epilim) in refractory epilepsy. Australian and New Zealand Journal of Medicine 8: 46-51 (1978).

Absence Status in Adults

*S.F. Berkovic and P.F. Bladin**

Absence status is an uncommon disorder first described in children by Lennox (1945). Clinically the patients are moderately confused, but the mental state can vary from near normality to deep stupor. Ictal manifestations include eyelid flutter and myoclonic jerks of facial and limb musculature. The EEG reveals continuous or discontinuous discharges of spike-wave, polyspike or rhythmic slow waves (Roger et al., 1974; Andermann and Robb, 1972).

The disorder is now recognised in adults (Shev, 1964). It may present *de novo* in adult life (Schwartz and Scott, 1971) or on a background of childhood seizures (Thompson and Greenhouse, 1968). The purpose of the present paper is to draw attention to adult absence status, as it is probably underdiagnosed, and to emphasise various aspects of its diagnosis and treatment.

Methods

The records of the Austin Hospital EEG department were searched for cases of adult absence status. Cases with recurrent episodes of absence status from childhood were excluded.

Twelve cases were found for the period 1975 to 1982, and all were followed up. Case details are summarised in table I, and 4 cases are presented in more detail below.

Case Reports

Case 4

A female aged 57 had an 11-year history of infrequent major tonic-clonic seizures treated with carbamazepine. She was admitted after being found dazed and confused at home. The EEG

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Table I. Details of 12 adult absence status cases

Age[1] (years) sex	Diagnosis	Duration of tonic-clonic seizures (years)	Prior absence status[2]	Behavioural or psychiatric problems	Treatment and follow-up	Follow-up period to Feb 1982 (years)
42F	CGE[3]	15	2	Depression; poor compliance	Controlled on phenytoin and clonazepam; recurrent major seizures and absence status when tablets are forgotten	9
47M	CGE	0	0	Very aggressive; ?depressed	Recurrent attacks of absence status despite phenytoin, diazepam, clonazepam; excellent response to valproate	7
49M	CGE	34	4	Obsessional personality; depressed	Recurrent attacks of absence status; excellent response to valproate	6
57F	CGE	11	3	Depression; delusions	Poor control with phenytoin; excellent response to valproate	6
40M	Undiagnosed encephalopathy	4	10	Dementia; obsessional personality	Severe dementia; institutionalised; drop attacks and major fits continue; partial response to valproate and clonazepam	6
57M	CGE	46	5	'Chronic brain syndrome'	Well controlled on phenytoin and diazepam; apparent dementia has resolved	4
60M	Renal failure	0.4	10	Nil	Died of pneumonia; seizures controlled on valproate	0.4
64F	CGE	57	4	Depressed	Controlled on phenytoin and clonazepam	2
38F	CGE	19	1	Anxiety neurosis	Controlled on phenytoin, carbamazepine and diazepam	0.8
54F	CGE	40	50	Depressed	Attacks controlled with large doses of oral clonazepam	0.6
46F	CGE	10	0	Dependent personality; anxiety	One attack only; started on valproate	0.4
31F	Hypopara-thyroidism	0.8	2	Nil	Vitamin D, calcium; investigation and follow-up incomplete[4]	0.2

1 Age when absence status was first diagnosed.
2 Number of suspected prior episodes of absence status.
3 Common generalised epilepsy.
4 This patient will be reported on separately when investigation is complete.

showed absence status (fig. 1) which responded to intravenous diazepam. Review of her history revealed 3 admissions for undiagnosed confusional states over the previous 2.5 years. In retrospect, these confusional states were probably unrecognised absence status.

The patient was treated with phenytoin but had periods of phenytoin intoxication and poorly documented confusional episodes. Two years later her treatment was changed to valproate monotherapy and she has remained well for the subsequent 4.5 years. She has a history of depression and bizarre delusions that have persisted since the absence status was controlled.

Case 7

A male aged 60 had chronic renal failure due to hypertension. After 6 years of uneventful haemodialysis he began having periods of confusion and occasional major tonic-clonic seizures while on dialysis. The EEG was relatively normal immediately before dialysis. Shortly afterwards continuous spike-wave complexes appeared, associated with confusion and myoclonus of facial muscles (fig. 2). A CT head scan showed cortical atrophy. Valproate was prescribed with good effect. Five months later he died of pneumonia.

Postmortem revealed severe nephrosclerosis. The brain was normal on macroscopic sectioning, but histological examination was not done.

The patient had no previous history of seizures. His brother, who had normal renal function, had had a documented episode of absence status at age 48 years.

Case 10

A 54-year-old woman had a history of major tonic-clonic seizures, occurring about once a year, which were treated with phenytoin and methylphenobarbitone. At the age of 52 her seizure pattern changed and she had bizarre confusional episodes, lasting a few hours, occurring about once a week. During these episodes she would frequently lose contact with her surroundings, twitch around the face and eyes and have repeated tonic seizures with brief elevation of the left arm and extension of the left leg with lesser involvement of the right side. Her husband had noted a change in behaviour with general loss of interest, depression and childish behaviour. Attacks were documented on videotape and EEG. The EEG was normal between attacks. On the days when she became confused the EEG showed continuous spikes at 12Hz which would recruit during the tonic seizures (fig. 3). Neurological and neuropsychological examinations were normal. The CT head scan was normal apart from a small area of focal atrophy in the right parietal region. Carotid angiography was normal. Oral phenytoin, carbamazepine, valproate and small doses of clonazepam were unhelpful. Control of seizures was finally achieved by the self administration of large doses (10 to 12mg) of oral clonazepam whenever the confusional episodes began.

Case 11

A female aged 46 had a 10-year history of infrequent major tonic-clonic seizures treated with phenytoin. She suffered from acute anxiety and has a very dependent personality requiring frequent psychiatric counselling.

Thirty-six hours after receiving a general anaesthetic for minor breast surgery she was brought to this hospital by a friend after she had become confused at home. Eyelid flutter and facial twitching were noted. The EEG showed bursts of well-formed spike-wave complexes occupying over half the trace (fig. 4).

Medication was changed from phenytoin to sodium valproate and she has had no further attacks over a 5-month follow-up.

Results and Discussion

The mental state changes, ictal manifestations and EEGs of most of our patients resembled those of previous larger series (Roger et al., 1974; Andermann and Robb, 1972), and will not be enlarged upon. Case 10 was noteworthy because

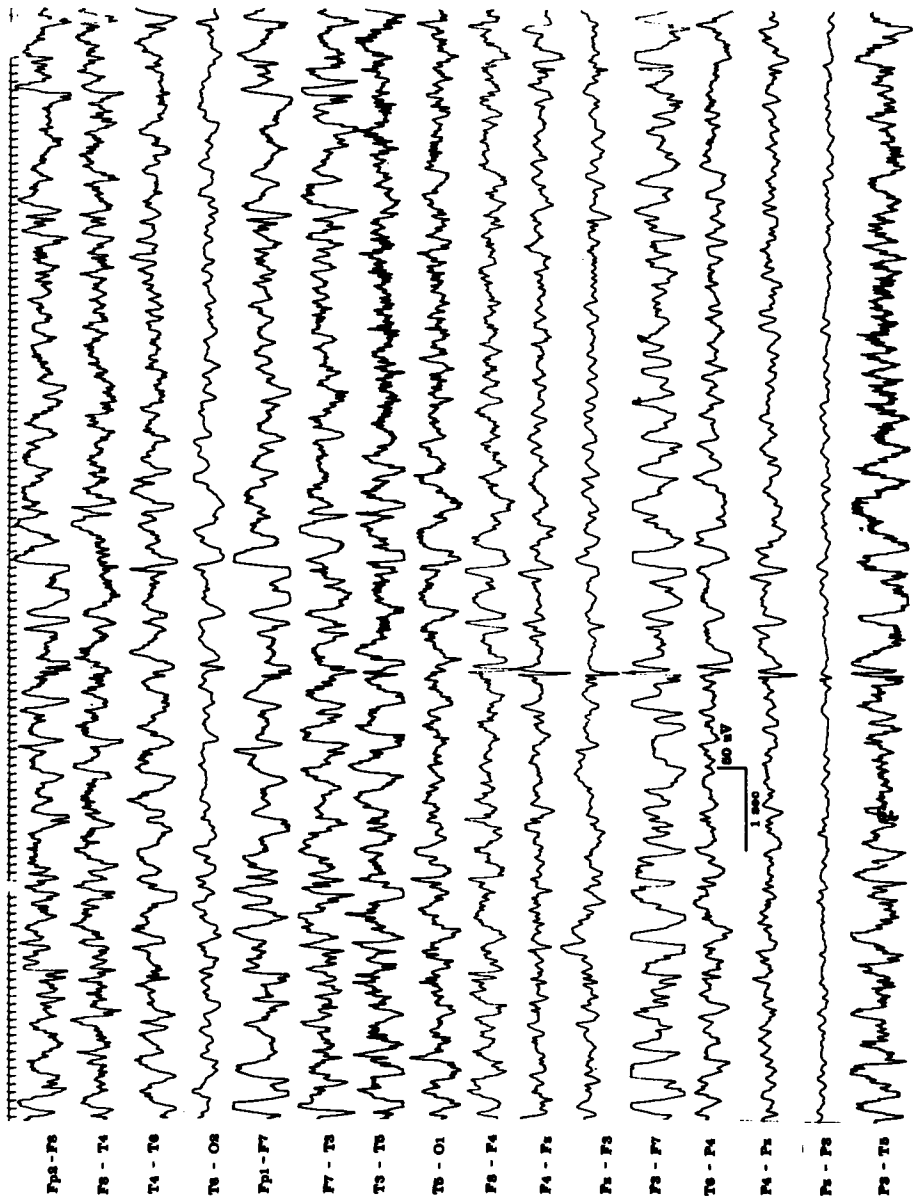

Fig. 1. Absence status (Case 4). Continuous spike and spike-wave intermingled with slow activity.

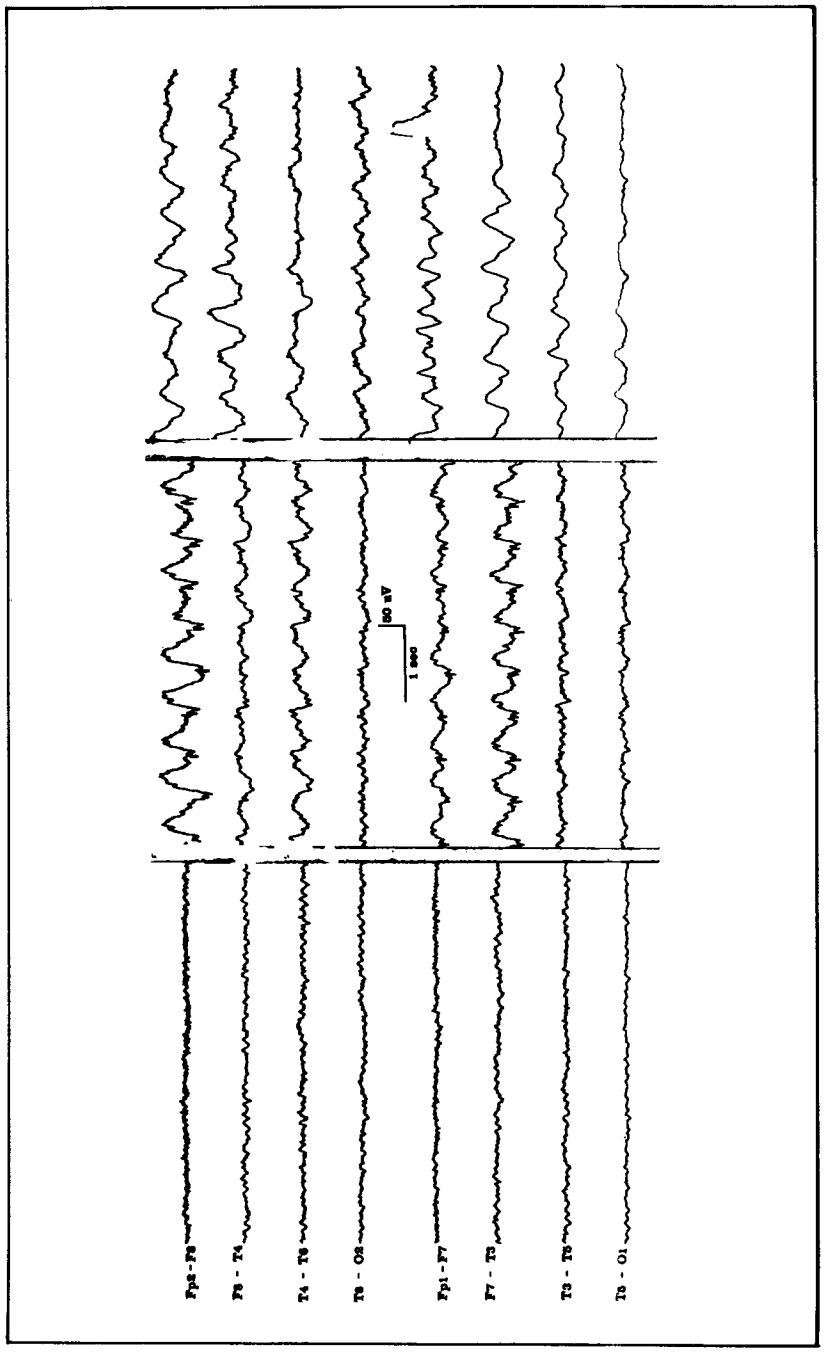

Fig. 2. Absence status due to haemodialysis (Case 7). The first panel shows a relatively normal trace before dialysis. The centre panel shows continuous spike-wave after 1 hour of dialysis. The third panel shows the effect of clonazepam 1 hour later.

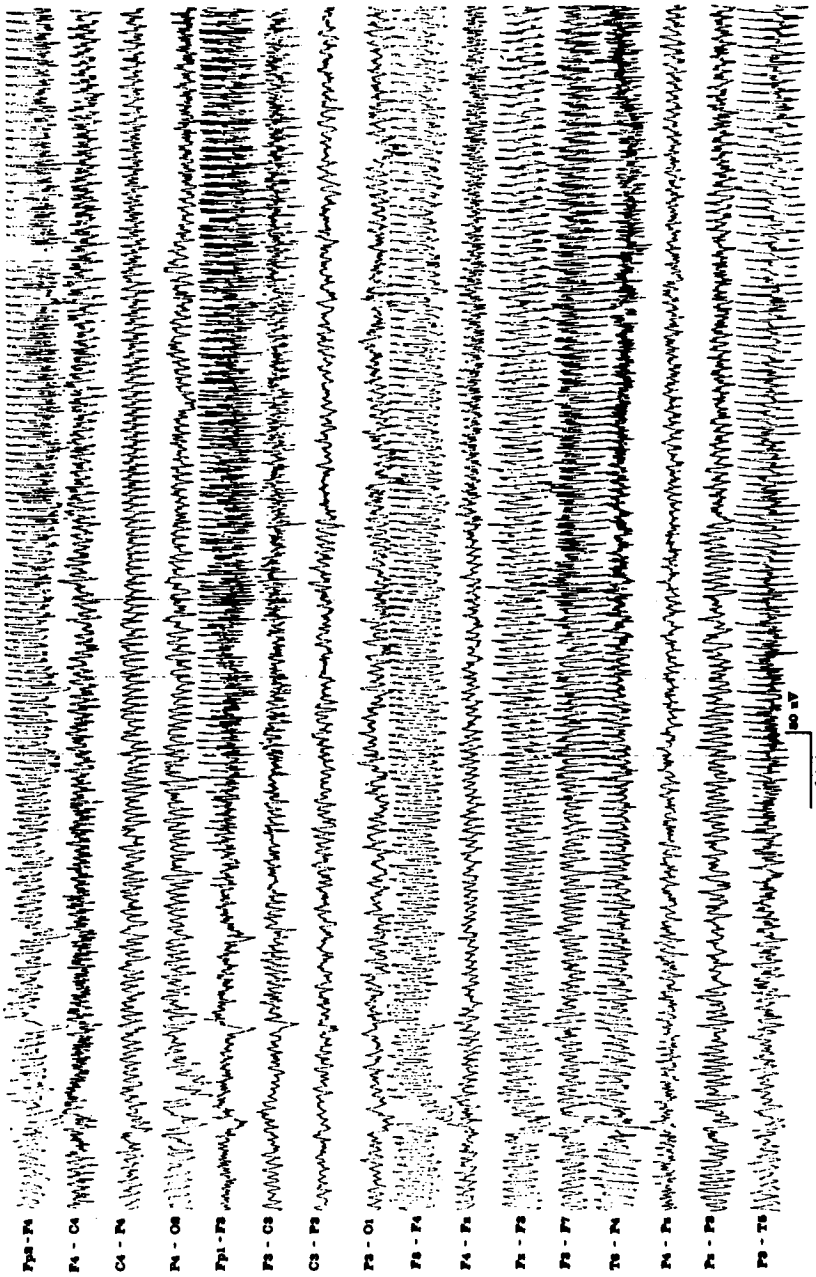

Fig. 3. Absence status associated with hemitonic seizures (Case 10). Continuous bilaterally synchronous spikes at 12Hz. Halfway through the figure there is recruitment of spikes associated clinically with elevation of the left arm.

the fits were bizarre hemitonic seizures that occurred regularly four times a month without obvious precipitating factors. The EEG was also remarkable (fig. 3), with high voltage spikes at 12Hz. Tonic seizures and continuous high frequency spikes have only rarely been described in absence status (Roger et al., 1974).

The primary diagnosis in 9 of the 12 patients was common generalised epilepsy. This was on the basis of family history, the inter-ictal EEG, prior or contemporaneous major tonic-clonic seizures and the lack of dementia, neurological defects, structural brain abnormalities or metabolic disorders. Of the remaining 3 patients, 2 had a family history of epilepsy but the absence status was associated with severe dementia (Case 5) and haemodialysis (Case 7). The other patient (Case 12) had absence status as the presentation of hypoparathyroidism, without a family history of epilepsy. Single case reports of absence status associated with dialysis (Vignaendra et al., 1977) and hypoparathyroidism (Vignaendra et al., 1977) have appeared previously.

The histories of 10 patients (e.g. Case 4) suggested that they had suffered prior unrecognised episodes of absence status. Three factors may have contributed to this. Firstly, clinicians may lack familiarity with this relatively rare condition and some of its more subtle manifestations. Secondly, if the EEG was not done soon after admission to hospital the attacks may have spontaneously terminated before a definitive diagnosis was reached. Finally, the practice of giving oral or intravenous benzodiazepine to epileptic patients who are thought to be 'post-ictal' or confused for no apparent reason, may have resulted in the attacks being aborted; thus, the opportunity for diagnosis was missed.

Ten patients had serious psychiatric problems that antedated or appeared simultaneously with periods of absence status. These psychiatric disturbances were not of uniform type but included depression, personality disorders and anxiety neuroses. In half the cases the psychiatric symptoms remitted with control of the seizures. Psychiatric presentations of absence status have been noted previously (Thompson and Greenhouse, 1968), but they have not been stressed in the major reviews of the subject. The clinical importance of the association with psychiatric disorders is that the uncritical physician may overlook the diagnosis of absence status in a patient with psychiatric illness who presents with confusion.

The reason why common generalised epilepsy should manifest itself as absence status in adults is unknown. Occasionally precipitating factors including drug withdrawal, emotion, photic stimulation or hormonal changes, can be implicated (Andermann and Robb, 1972). Case 7 was of interest, as haemodialysis was clearly the precipitating factor in a man without a past history of seizures but with a family history of absence status. Gall et al. (1978) found minor frontal lobe abnormalities on CT scans of 7 patients and suggested that structural frontal lobe changes had a role in releasing spike-wave discharges. Pneumoencephalograms or CT scans were done on 10 patients in our study. Four patients had no atrophy, 5 patients had mild generalised or focal atrophy and 1 patient had severe atrophy associated with profound dementia. It is difficult to accept that these scattered, and generally minor, changes were responsible for precipitating absence status.

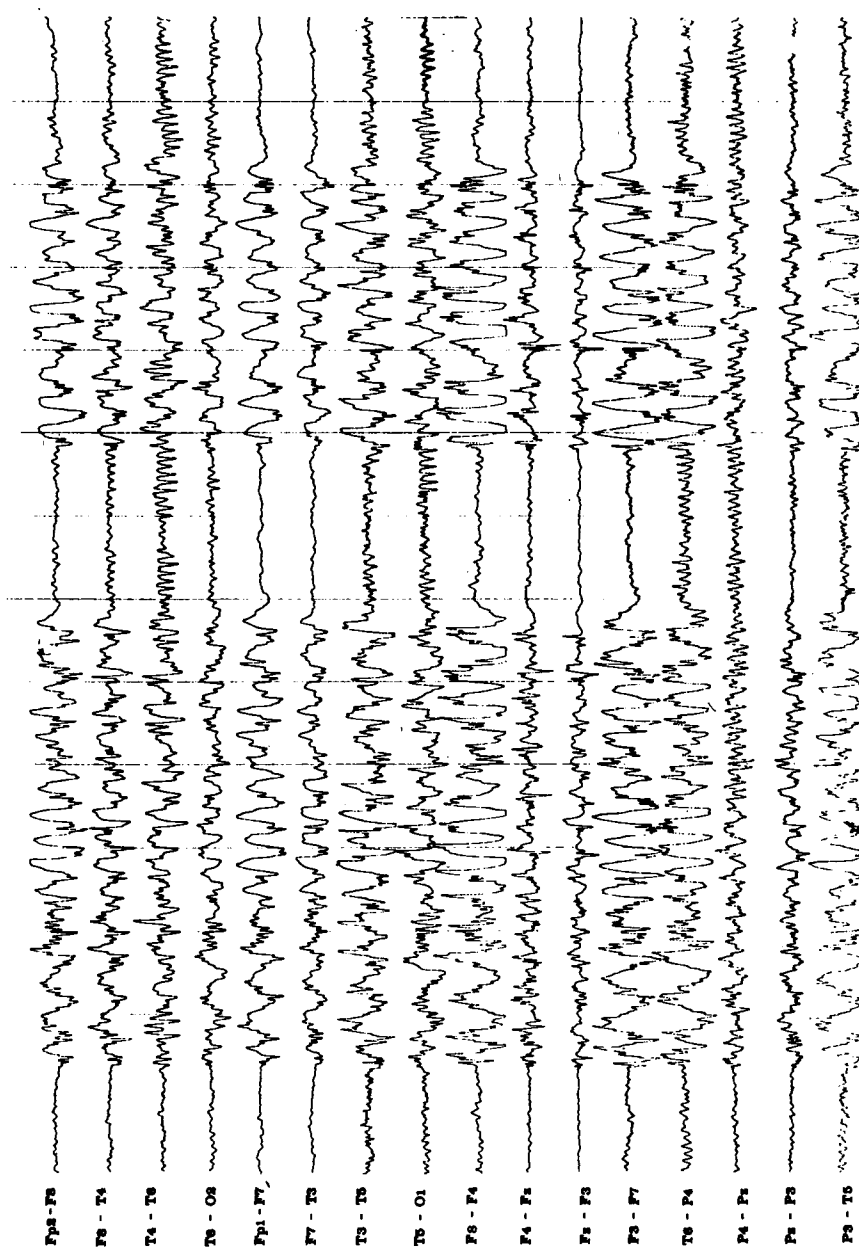

Fig. 4. Absence status (Case 11). Well-formed spike-wave complexes with a fairly normal alpha rhythm interspersed.

Phenytoin, carbamazepine and barbiturates were generally ineffective in preventing attacks of absence status. Ethosuximide and troxidone have been found occasionally useful by some (Andermann and Robb, 1972), but valproate appears to represent a real therapeutic advance. In 5 patients it totally suppressed absences, it caused a partial response in 1 case and failed only in Case 10. Oral clonazepam was useful as a prophylactic agent in 3 patients. In Case 10 numerous combinations of maintenance anticonvulsants failed to control recurrent attacks but a large dose of oral clonazepam taken at the start of an attack was found to be a useful therapeutic manoeuvre.

Conclusion

Absence status is frequently overlooked and is probably more common than realised. The diagnosis should be considered in epileptics with confusional states of any severity. Clinical evidence of eyelid flutter or myoclonus should be carefully looked for. The presence of psychiatric symptoms should not deter the clinician from considering this condition. Therapy with valproate and/or clonazepam is usually very effective.

Summary

Twelve cases of adult absence status were seen over 7 years. Clinically the disorder was characterised by long periods of clouding of consciousness with myoclonic phenomena of varying degrees of severity. The EEGs showed sustained spike-wave, polyspike and rhythmic slow activity. In one exceptional patient bizarre hemitonic seizures were documented clinically and on EEG.

Diagnosis of the condition was frequently delayed and the histories of most patients showed episodes of obscure confusional behaviour, undiagnosed over the previous months or years. Psychiatric disturbances of various types were surprisingly common, contributing to diagnostic difficulty.

Treatment with conventional anticonvulsants was often disappointing. In contrast, sodium valproate and clonazepam were found to be very effective.

References

Andermann, F. and Robb, J.P.: Absence status. A reappraisal following review of thirty-eight patients. Epilepsia 13: 177-187 (1972).

Gall, M.; Scollo-Lavizzari, G. and Becker, H.: Absence status in the adult. New results including computerized transverse axial tomography. European Neurology 17: 121-128 (1978).

Lennox, W.G.: The petit mal epilepsies. Their treatment with tridione. Journal of the American Medical Association 129: 1069-1074 (1945).

Roger, J.; Lob, H. and Tassinari, C.A.: Status Epilepticus; in Vinken and Bruyn (Eds) Handbook of Clinical Neurology, Vol. 15, pp.145-188 (North Holland Publishing Co., Amsterdam 1974).

Schwartz, M.S. and Scott, D.F.: Isolated petit mal presenting *de novo* in middle age. Lancet 2: 1399-1402 (1971).

Shev, E.E.: Syndrome of petit mal status in the adult. Electroencephalography and Clinical Neurophysiology 17: 466 (1964).

Thompson, S.W. and Greenhouse, A.H.: Petit mal status in adults. Annals of Internal Medicine 68: 1271-1279 (1968).

Vignaendra, V.; Frank, A.O. and Lim, C.L.: Absence status in a patient with hypocalcemia. Electroencephalography and Clinical Neurophysiology 43: 429-433 (1977).

Vignaendra, V.; Ghee, L.T. and Lee, L.C.: Petit mal status in a patient with chronic renal failure. Medical Journal of Australia 2: 258-259 (1976).

Demographics of an Epileptic Population

*R.G. Beran, C. Sutton and T. Read**

Those with epilepsy have been stereotyped and stigmatised throughout the ages (Scott, 1973). The term 'epileptic' has negative connotations (Vinson, 1975) and those with epilepsy are frequently considered less intelligent, less socially adequate and are often regarded as inferior to the 'average' or 'normal' person. The present report looks at demographic characteristics of a random sample of people with epilepsy and relates these characteristics to those of the Sydney population as a whole (Australian Bureau of Statistics, 1976).

Method

One hundred people with epilepsy were interviewed in the Sydney Metropolitan Area (SMA). The respondents comprised the first 100 patients referred by a random sample of 50 general practitioners (Beran et al., 1981). Their ages are shown in table I.

Results

Marriage

Of the 100 people interviewed, 38 were male and 62 female. 50% of both the males and females were married for the first time, compared with a figure of 46% for the SMA ($p > 0.05$). A 40 : 60 ratio of males to females is comparable with the rough ratio of 50 : 50 (with a slight preponderance of females) as found in the general population.

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Table I. The ages defined of 100 patients with epilepsy

Age range (years)	Respondents (n)
< 10	9
11-20	16
21-30	22
31-40	19
41-50	13
> 50	21

Area of Dwelling

The SMA was divided into 5 socio-economic sectors using the weightings of Congalton (1969), which were found to be valid a decade later by comparing the socio-economic gradings defined by Gibson and Johansen (1979), for 100 randomly selected Sydney suburbs.

Fifteen of the 100 respondents lived in Area 1; 26 lived in Area 2; 33 lived in Area 3; 19 lived in Area 4, and 7 lived in Area 5. Thus, a cross-section of the community was included in the study and the distribution of socio-economic status compared closely with that expected after analysing the Sydney area (Congalton, 1969; Gibson and Johansen, 1979).

Education

Seven per cent of the sample had tertiary qualifications, compared with approximately 7% of the population of the SMA aged 15 years and over. 20% of the sample had a trade certificate or diploma, compared with 15% of the population of the SMA. 33% of the sample had secondary school qualifications only. (There are no comparable data available from the 1976 census.)

Home Ownership

54% of respondents owned their own homes. If the 25% of the sample aged 20 years or less is excluded from calculations, the percentage of home ownership is 72%, which is not significantly different from the 68.8% of the population of the SMA who are home owners ($p > 0.05$).

Discussion

Public attitudes towards epilepsy have been monitored over the past few decades (Caveness and Gallup, 1980; Ivanainen et al., 1980; Fink, 1980) and such studies have demonstrated an increased acceptance of those with epilepsy. There still exist, however, negative attitudes among not only the public but also

among those with epilepsy and among doctors who treat the condition (Ryan et al., 1980; Beran et al., 1981).

When looking at the areas of education, marital status, socio-economic status (as measured by area of dwelling) and home ownership, parameters frequently used as indications of 'social adequacy', it can be seen that no significant differences are apparent between those with epilepsy cared for by Sydney general practitioners and the population in which they live.

The present survey suggests that people with epilepsy may not differ from the general population and that the negative stereotypes frequently attached to those with epilepsy often result from myths and ignorance. It is these factors which hinder many of those with epilepsy in their right to enjoy all the privileges and responsibilities extended to other members of the community.

Summary

The demographic data of 100 people with epilepsy were compared with established information concerning the community in which they lived. No real difference was identified.

References

A.B.S. (Australian Bureau of Statistics), 1976 Census, A.G.P.S., Canberra.

Beran, R.G.; Jennings, V.R., and Read, T.: Doctors' perspectives of epilepsy. Epilepsia 22: 397-406 (1981).

Caveness, W.E. and Gallup, G.H.: A survey of the public's attitudes towards epilepsy in 1979 with an indication of trends over the past thirty years. Epilepsia 21: 509-518 (1980).

Congalton, A.A.: Status and Prestige in Australia. (F.W. Cheshire, Melbourne 1969).

Fink, M.: Public attitudes towards epilepsy in the Federal Republic of Germany: Trends over the past decade. Abstr. Epilepsia 21: 201 (1980).

Gibson, V.B. and Johansen, A.: The Quick and the Dead: A Biomedical Atlas of Sydney (A.H. and A.W. Reed, Sydney 1979).

Ivanainen, M.; Uutela, A. and Vilkkymaa, I.: Public awareness and attitudes towards epilepsy in Finland. Epilepsia 21: 413-423 (1980).

Ryan, R.; Kempner, K. and Emlen, A.C.: The stigma of epilepsy. Epilepsia 21: 433-444 (1980).

Scott, D.: About Epilepsy (International Universities Press, Inc., New York 1973).

Vinson, T.: Towards demythologising epilepsy: An appraisal of public attitudes. Medical Journal of Australia 2: 663-666 (1975).

Abstract

Muscle Trauma

*Byron A. Kakulas**

Despite the frequency of muscle trauma, there is comparatively little written on this topic. Perhaps this is due to the ability of skeletal muscle to readily compensate for the loss of a substantial part of its bulk. Muscle also appears to show relative resistance to infection and to the formation of metastases. Sports injuries command attention because of their effect on athletic performance.

One cause of muscle pain is minor tearing of muscle fascicles as a result of unaccustomed exertion. Pre-existing muscle disease greatly aggravates the effect of minor injury. Minor trauma may also play a role in the initial stages of polymyositis and myalgic encephalomyelitis.

The following conditions can be defined as clinical entities:

The crush syndrome, penetrating and non-penetrating injuries without fracture, muscle injuries in association with bony fracture, muscle herniae, muscle and tendon rupture, the anterior tibial syndrome, birth trauma, myositis ossificans, pseudotumour, proliferative myositis, and denervation atrophy as a result of trauma.

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Abstract

Localised Toxoplasmosis and Cytomegalovirus Infection in a Renal Transplant Patient

N. Tan, F.L. Mastaglia† and M. Bucens‡*

A 32-year-old woman developed a febrile illness associated with prolonged Jacksonian seizures involving the left side of her body 2 years after renal transplantation for polycystic renal disease. Immunosuppressive therapy during that period consisted of azathioprine, cyclophosphamide and prednisone. The CT scan showed an extensive area of low density in the right parietal lobe which was biopsied and excised. Light and electron microscopic examination disclosed the presence of *Toxoplasma gondii* organisms as well as cytomegalovirus. At about the same time she developed severe bilateral choroidoretinitis which was thought to be due to cytomegalovirus and which led to severe visual impairment. She was treated with amphotericin B, trimethoprim and sulphamethoxazole, pyrimethamine and 5-fluorocytosine and has shown no progression of the infection to date.

Abstract

Eosinophilic Meningitis

David Williams

Two patients with eosinophilic meningitis from areas endemic for *Angiostrongylus cantonensis* are presented.

The cases are presented to discuss the difficulty in diagnosing the syndrome of meningitis, and in an era of increasing international travel to remind us of the above entity, which is common in areas of South-East Asia and Oceania.

The life-cycle of the parasite is described, and the interaction of complex biological and sociological factors which predispose to individual infection is discussed.

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Abstract

F-Response Studies. Computer Analysis and Recovery Cycle

F.L. Mastaglia, W.M. Carroll† and G. Thickbroom‡*

The excitability and refractory properties of the alpha motor neurone pool have classically been studied by the analysis of the orthodromically-evoked oligosynaptic Hoffman (H) reflex. More recently, the F-response, which results from antidromic activation of α motor neurones after peripheral nerve stimulation, has received increasing attention as a means of evaluating conduction in the proximal segment of the motor neurone and as a possible means of assessing motor neurone excitability. A computer based technique for the analysis of the F-response which allows rapid determination of mean latency, amplitude, duration and number of phases of a series of successive responses has been developed and has been applied in normal subjects and patients with neurological diseases. In addition, by using paired stimuli with increasing interstimulus intervals, the recovery cycle of the F-response has been studied in normal subjects and in the rat. These observations indicate that the F-response recovery cycle closely resembles that which has been described for the H-reflex.

Abstract

Neurological Sarcoidosis Presenting as Intramedullary Spinal Cord Tumour

J. O'Neill and D.J. O'Sullivan

Sarcoidosis of the nervous system although uncommon, is a well-recognised clinical entity. Neurological symptoms usually develop late in the course of pulmonary sarcoidosis. Neurological involvement most commonly presents with evidence of diabetes insipidus or multiple cranial nerve palsies. The patient in the following case report presented with a progressive spinal cord lesion, which

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proved to be due to sarcoidosis, with no evidence of involvement outside the nervous system.

A female patient aged 37 presented to St Vincent's Hospital with a 6-month history of perineal numbness, difficulty with micturition and defaecation. For 1 month she had noticed increasing pain in the left buttock, difficulty with walking and paraesthesiae in the feet. Neurological examination indicated signs of a conus lesion. Initial myelogram was negative. However, CSF showed raised protein with pleocytosis. Repeat myelogram confirmed a conus lesion and exploration revealed intramedullary hard mass, which biopsy showed to be sarcoidosis. Post-operatively the patient had papilloedema and right VI nerve palsy. Clinical response was satisfactory to steroids. Chest x-ray was normal throughout.

Abstract

Neurological Complications of Lithium Poisoning: A Case Report

*R. Pamphlett and R.A. Mackenzie**

The present report details clinical and investigative findings in a young man who suffered both central and peripheral nervous system damage following lithium poisoning. A 31-year-old manic-depressive man on oral lithium developed a confusional state and lapsed into a coma while overseas. He was severely lithium toxic. On return to Australia he was bedridden with signs of diffuse cortical and cerebellar damage, as well as a severe peripheral neuropathy rendering him virtually quadriplegic. After 12 months he could walk with aid.

Investigations included CSF analysis, nerve conduction studies, somatosensory evoked potentials, CT scan and sural nerve biopsy.

The findings in this patient will be discussed with reference to known lithium effects on the nervous system, with emphasis on the unusual finding of a peripheral neuropathy.

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Abstract

A Longitudinal Visual Evoked Potential Study of Visual Pathway Demyelination in 116 Patients with Multiple Sclerosis and Isolated Optic Neuritis

W.M. Carroll, A.M. Halliday and G. Barrett†*

Ninety-seven patients with multiple sclerosis and 19 patients with isolated optic neuritis were examined on 6 occasions over periods ranging from 1 month to 7 years (mean 28 months), using wide-field, half-field and central-field stimulation. Fifteen healthy subjects who were examined on average 17 months apart served as controls for P100 latency and amplitude variations. Both qualitative assessments of wave-form and quantitative analyses of P100 latency and amplitude were made.

Between R1 (first VEP) and Rx (last VEP) the incidence of abnormality increased from 65% to 82.5%. Of the 7 different types of VEP abnormality, delayed wide-field P100 components remained the largest single group. Attenuated or absent responses, paramacular-derived negativities and P135 components correlated with recent symptomatic involvement and poor acuity. Seventy VEPs worsened between R1 and Rx and 51% of these were 'new', changing from normal to abnormal or to a more abnormal VEP classification. Improvements were outnumbered 2 to 1 by worsenings but 8 VEPs from 6 patients normalised (7.5%). The P100 latency, however, was remarkably stable with only 4.8% showing a significant decrement of more than 8 msec (range 9 to 10 msec) to re-enter the normal range. A significant P100 latency increment (> 8 msec) occurred in 26% of patients with the mean increase being 17.6 msec.

It is concluded that the visual pathway is frequently and repeatedly affected in multiple sclerosis, particularly in patients with symptomatic lesions, and that the P100 latency is a sensitive index of previous and additional lesions of the visual pathway.

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Abstract

Experimental Demyelinative Optic Neuropathy: A Model for Combined Morphological and Electrophysiological Studies

*W.M. Carroll, F.L. Mastaglia and A.E. Jennings**

A model for electrophysiological and morphological studies of demyelinative optic neuropathy in rats is described. Monocular cortical flash evoked potentials (EP) were recorded before and after unilateral intraneural microinjection of lysophosphatidyl choline (LPC) and galactocerebroside (Gal-C) antiserum. The interocular latency difference (ILD) for the N40 and P60 components of the rat flash EP served to monitor progress. Light and electron microscopic examination showed that with LPC there was nonselective damage to myelinated fibres with considerable axonal degeneration. The lesion produced by Gal-C antiserum also exhibited some axonal degeneration, but in addition there was evidence of primary demyelination.

Abstract

Peripheral Nerve Demyelination Induced by Serum from Patients with Guillain-Barré Syndrome

L.A. Hansen, J.D. Pollard and J.G. McLeod†

Rat sciatic nerves were injected subperineurally with 50μl of serum obtained from 8 patients with Guillain-Barré syndrome (GBS) and from 8 control subjects. The amplitude of the muscle action potentials in the foot, and conduction velocities in the sciatic nerve were measured serially at intervals from 24 hours to 33 days after injection. Conduction block resulted from injection of fresh GBS serum, or GBS serum stored at −70°C, with recovery commencing at about 9 days and return to normal by 24 days. GBS serum stored at −20°C did not differ in effect from control serum.

The findings suggest that a demyelinating factor is present in the serum of patients with GBS.

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Abstract

Visuo-vestibular Interaction in Patients with Cerebellar Disease

*D.G. Milder and S.M.J. Hunt**

The visual tracking performance of normal subjects and cerebellar patients with and without clinically detectable eye movement abnormalities has been investigated under 3 conditions: with the subject stationary, and during vestibular inputs designed to either assist or oppose visual tracking. Phase versus frequency responses were consistent with a constant tracking time delay. The delay did not differ during a stationary condition in normal subjects and cerebellar patients with normal eye movements, but was increased in cerebellar patients with abnormal eye movements. During an assisting input, the delay decreased equally in normal subjects and cerebellar patients with normal eye movements, but did not change during an opposing input. In cerebellar patients with abnormal eye movements, the delay was reduced to the level of the other groups during an assisting input but increased with an opposing input. These results indicate a disinhibition of the vestibulo-ocular reflex in cerebellar patients with abnormal eye movements during visual tracking.

Abstract

Factors Determining the Frequency Content of the Electromyogram

A.M. Williams, H. Kranz, D.J. Caddy and R.B. Silberstein†

The contribution of central and peripheral factors to the frequency content of the electromyogram of thenar muscles was examined in 10 subjects. Compound action potentials had similar spectral content to the electromyogram early in contractions. Following 45 seconds of maximal voluntary contraction the mean decrease in the centroid frequency of the power spectra was 39% for the electromyograms, and 35% for the compound potentials ($p < 0.3$). As compound potentials reflect only peripheral changes in electrical properties, most (mean

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89%) of the fall in the centroid frequency of the electromyogram can be attributed to peripheral factors. Only 1 of the 5 subjects showed evidence of increasing synchronisation of motor unit discharge as the contraction progressed. The centroid frequency of the electromyogram at the onset of contractions was inversely related to initial force. No consistent peaks which might correspond to motor unit firing rate were evident in the power spectra of the electromyograms. Motor unit firing characteristics thus did not appear to make a significant contribution to the frequency content of the electromyogram. There was a mean increase of 5% ($p < 0.02$) in the distal latency of the compound response over the period of voluntary contraction. Nerve stimulation produced a change in the frequency content of the evoked muscle compound potentials. This was related to the rate and duration of stimulation. In cat experiments, direct muscle stimulation, in the presence of neuromuscular blockade, produced a similar change in the compound response to that induced by nerve stimulation. The findings indicate that the spectral content of muscle electrical activity, and its shift during contraction, primarily reflect intrinsic muscle properties.

Abstract

Somatosensory Evoked Potentials as a Diagnostic Tool in Brachial Plexus Injuries

*V.M. Synek and J.C. Cowan**

Somatosensory evoked potentials were recorded in the upper arm, above the clavicle, at the cervical spinal cord and the contralateral scalp during stimulation of median, ulnar or radial nerves in a group of 13 patients with post-traumatic lesions of the supraclavicular part of the brachial plexus. The results were compared with a group of normal individuals and with results from the unaffected arm. It was found that in patients suffering from upper trunk lesions the results are normal during stimulation of the median nerve. In patients with avulsion of C5/6 roots the responses were normal, delayed or absent at the cervical cord and cortex, depending on the presence of a complicating lesion distal to the dorsal root ganglion. In patients with particular involvement of C7 root the results were abnormal during stimulation of the radial nerve and normal using stimulation of the median or ulnar nerves. In 5 patients with flail anaesthetic arms the potentials were absent at the cervical cord and contralateral cortex level during stimulation of all nerves. It is suggested that in patients with injuries limited to a certain area of the brachial plexus, nerve stimulation should be

*Department of Clinical Neurophysiology, Auckland Hospital, Auckland (New Zealand).

chosen according to the clinical problem. The routine stimulation of only median nerves should be avoided.

Abstract

Dominantly Inherited 'Ophthalmoplegia Plus' (Reductio Ad Absurdum?)

D. Williams

The index case is a 64-year-old female who had a progressive history of poor vision, drooping eyelids and impaired eye movements and who presented with an inability to walk.

Examination revealed primary optic atrophy, bilateral ptosis, external ophthalmoplegia, proximal and distal weakness, cerebellar and pyramidal tract signs and signs of peripheral neuropathy.

Examination of family members showed a dominant pattern of inheritance, with 2 out of 3 definitely affected children, one brother probably affected, and another possibly affected.

Muscle biopsy showed a mitochondrial myopathy and nerve biopsy active axonal neuropathy.

This family is presented because:

1) There are no previously well-documented cases of inherited chronic progressive external ophthalmoplegia, and

2) It provides an opportunity to discuss the problems of classifying diseases according to phenomenology when the aetiology and pathophysiology is unclear.

Abstract

Congenital Fibre Type Disproportion

*R.B. Fitzsimons and R.A. Ouvrier**

The classical clinical picture of congenital fibre type disproportion is that of a benign non-progressive congenital myopathy. Additional features may include macrocephaly and short stature. The disease is defined by the relative

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disproportion in size between the large Type II fibres and small Type I fibres in skeletal muscle, in the absence of other recognised causes of this phenomenon, such as spinocerebellar degeneration and myotonic dystrophy.

We present a further 7 cases, whose protean clinical manifestations suggest that this myopathy cannot be regarded as a single disease entity. As a diagnosis of exclusion 'fibre type disproportion' may simply be a common form of pathological response to different neuromuscular disorders. We also demonstrate, however, that fibre type disproportion is present in muscle from different members of the same family, with different clinical forms of neuromuscular disease, e.g. the first cousin of the mother of a 'floppy infant' with fibre type disproportion has classical clinical features of facio-scapulo-humeral dystrophy. This patient's biopsy confirmed the presence of fibre type disproportion.

Abstract

Retinitis Pigmentosa, Ataxia and Peripheral Neuropathy

*R.R. Tuck and J.G. McLeod**

Refsum's syndrome appears to be extremely rare in Australia. The clinical features of 4 patients initially suspected of suffering from the condition are described; they had retinitis pigmentosa, ataxia, peripheral neuropathy and, in 2 cases, sensorineural deafness but normal serum phytanic acid levels. There was no family history. Nerve conduction studies demonstrated impaired sensory conduction but normal or only mildly slowed of motor conduction. Reduction of myelinated fibres, but no onion bulb formations, were found on sural nerve biopsy. Other recognised conditions, such as Kearns-Sayre syndrome, α-beta lipoproteinaemia, Cockayne's syndrome, Hallgren's syndrome and lipidoses associated with these clinical features were excluded. It seems likely that the patients suffered from an unusual type of spinocerebellar degeneration.

*Department of Medicine, University of Sydney, Sydney (Australia).

Abstract

Rhinocerebral Mucormycosis

*C.J. Kilpatrick, A.G. Speer, B.M. Tress and J.O. King**

Mucormycosis is a frequently fatal fungal infection caused by the genera Rhizopus, Mucor and Absidia within the family of Mucoraceae. These organisms are ubiquitous saprophytes which, rarely, may produce an acute, rapidly progressive, necrotising infection. Clinically, the infection may be characterised as rhinocerebral, pulmonary, disseminated, gastrointestinal or cutaneous. Regardless of anatomical site the infection is distinguished pathologically by a predilection of the fungus to invade blood vessel walls with subsequent thrombosis and tissue infarction. Rhinocerebral mucormycosis is the common form typically presenting in a diabetic with ketoacidosis. Reported cases demonstrate a remarkably consistent clinical picture with facial swelling, sinusitis and a unilateral orbital apex syndrome. Despite these characteristic physical findings it would appear that recognition of this condition is not yet widespread, for often the diagnosis is made at postmortem. Awareness of this condition is important because of the need for early diagnosis and immediate aggressive treatment if patients are to survive. Two cases of rhinocerebral mucormycosis are reported. Both patients were diabetic and in each case the diagnosis was made during life. The patients were treated aggressively with orbital exenteration, intravenous amphotericin B and control of diabetes. The first patient died 3 days postoperatively and the second patient is alive and free of disease 6 months after presentation. At the time of presentation, both patients had CT scans which showed characteristic changes not previously reported.

Abstract

Determinants of Patient Compliance with Anticonvulsant Therapy

G.M. Peterson, S. McLean and K.S. Millingen†

Poor patient compliance is the most frequent reason for therapeutic failure

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in epilepsy in general and possibly for life threatening status epilepticus and sudden death in particular.

Determinants of patient compliance were examined in 101 hospital outpatients being treated for epilepsy. The patients were drawn from the neurology and neurosurgery outpatient clinics of the Royal Hobart Hospital over 6 months. All were responsible for their own medication and were interviewed according to a Standard Questionnaire by one of us (G.M.P) who was not involved in their prescribing. Five measures of patient compliance were: self-reported compliance, plasma anti-convulsant levels, prescription refill frequency, pill count, appointment keeping.

The factors independently related to patient compliance with anticonvulsant therapy were: worry about one's health, having generalised major seizures and the absence of barriers to compliance. Seizure frequency was indirectly contributing to patient compliance through worry about one's health. Perceived barriers to compliance or appointment keeping were, in the case of the former, inconvenience of taking medication, forgetfulness, sleeping in late. The major hindrances to appointment keeping were: transport difficulties, obtaining time off work, forgetfulness.

The study suggests that patient compliance can be represented as a balance between stimulators and inhibitors of compliance. Disclosure and modification of these stimulators and inhibitors should help to promote patient compliance.

Abstract

Diurnal Variation in Anticonvulsant Levels

*R. Goldsmith, R.A. Ouvrier and P.G. Procopis**

The diurnal variation of serum and salivary anticonvulsant levels was studied in 9 children aged 6 to 16 years. The results were summarised as follows:

Anticonvulsant	[1] > 50% Trough value		[1] < 50% Trough value	
	No. of studies	Patients	No. of studies	Patients
Carbamazepine	10	(6)	2	(2)
Phenytoin	2	(2)	3	(3)
Phenobarbitone	–		6	(3)
Primidone	5	(3)	–	
Valproate (Plasma)	1	(1)	–	
Carbamazepine (Plasma)	1	(1)	–	

1 Represents maximum diurnal variation.

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Of the drugs studied, phenobarbitone and phenytoin were the most, and primidone and valproate, the least stable. This is expected from the recognised half-lives of these drugs.

Carbamazepine levels varied widely. In 6 patients, the levels rose during the day, peaking in the afternoon or early evening. All 6 had levels outside the therapeutic range at some stage during the day. In 1 patient evidence of clinical toxicity in the afternoon corresponded with peak levels. Except for phenobarbitone and phenytoin isolated blood or saliva levels are not reliable indicators of anticonvulsant activity – they are only a rough guide.

Abstract

Urinary Retention as the Sole Sign of Viral Infection of the Cauda Equina

*M. Anthony and R. Sakellariou**

Five patients, 3 female and 2 male, aged 21 to 42 years, presented with urinary retention which was preceded by dysuria for 2 to 14 days. Only 1 patient had systemic symptoms consisting of headache, mild neck stiffness and raised temperature for 2 days before the onset of retention, while the remainder were symptom-free. Neurological examination revealed no signs but lumbar puncture disclosed a variable mononuclear CSF pleocytosis in all patients (11 to 297 WBC/mm^3), with a slight rise in CSF protein in 3 patients (0.59 to 0.77 g/L). CSF viral studies were performed in 3 patients. No virus or raised viral titres were demonstrated in 2, while in the third patient there was a significant rise of varicella-zoster and measles viral titres. Urodynamic studies were performed in 4 patients. They were normal in 3 and in the fourth patient there was impairment of bladder sensation, which was attributed to previous prolonged catheterisation. Clinical improvement paralleled progressive reduction of the cell count in the CSF and all patients recovered fully within 4 weeks.

It is suggested that these patients had suffered a viral infection of the cauda equina and that such a cause should be suspected in young patients presenting with unexplained retention, rather than attributing the symptom to hysteria, as has frequently been the case.

*Department of Neurology, Prince Henry Hospital, Sydney (Australia).

Abstract

Loss of Ability to Perceive Motion in Depth Following Occipital Infarction

*G.A. Nicholson, J.G. Morris and L. Lim**

Animal studies suggest that ability to perceive motion in depth is a specific integrative function of vertical cell columns in the peristriate cortex.

A case of selective loss of ability to perceive motion in depth with preservation of ability to perceive motion across the visual field, is presented. The patient complained of persistent visual problems following open heart surgery with inability to see the direction of travel of motor vehicles. Several accidents resulted from attempting to cross roads. On examination there was gross reduction in the visual fields to a small area of macular vision. Uncorrected visual acuity was 6/12 right, 6/24 left. On confrontation testing there was loss of ability to perceive direction of motion of a finger in a plane along the visual axis but there was preservation of ability to perceive motion of the finger at a plane across the visual fields at right angles to the visual axis. Computed tomography showed inferomedial infarction of the left occipital lobe.

Experiments on control subjects wearing glasses, with equivalent reduction in visual fields and acuity, demonstrated that the field and acuity defects were not responsible for the defect in perception.

It is concluded that ability to perceive motion in depth is a specific visual modality which can be simply tested at the bedside.

Abstract

The Experience of Sydney Eye Hospital with Ocular Myasthenia

M. Hely, J. Pollard and D. Campbell†

Eleven patients presenting to Sydney Eye Hospital from 1974 to 1981 with ocular myasthenia are described.

Difficulty with diagnosis was noted in many. Duration from onset of symp-

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†Sydney Eye Hospital, Sydney (Australia).

toms to diagnosis ranged from 2 days to 23 years. Two patients presented with ptosis, 4 presented with diplopia and 5 presented with both ptosis and diplopia. Edrophonium chloride relieved ptosis to a marked degree in all cases where present. In 2 of 4 cases with diplopia alone, and in 3 of 5 cases with ptosis and diplopia, there was no improvement in ocular movement.

Acetylcholine receptor antibody was, therefore, performed in all suspected cases. Receptor antibody was positive in 6 of 11 cases, including 2 cases with negative edrophonium chloride tests, and the 2 cases who developed generalised disease.

Other investigations included skeletal muscle antibody, chest x-ray, mediastinal tomograms or CT scan and, non-routinely, EMG.

If therapy was required pyridostigmine was commenced. Two patients were unresponsive from the onset and 6 patients showed an improvement lasting from 1 month to 36 months. Where pyridostigmine was inadequate, prednisone was introduced in a dose of 30 to 60 mg/day. Nine patients required prednisone and 7 had a dramatic response. Of these 7, 1 is off all therapy and 5 are maintained on 5 to 7.5 mg/day or 10 to 15mg on alternate days. One developed transient generalised disease when steroids were commenced.

It is concluded that ocular myasthenia is difficult to diagnose, particularly when ptosis is absent. It may be severely incapacitating and when a trial of pyridostigmine fails, ocular myasthenia is often very responsive to steroids that can be maintained at low dose.

Abstract

End-plate, Muscle Fibre-type and Retina Specific Monoclonal Antibodies

P. Darveniza, D.J. O'Sullivan,* D. Trissler* and M. Nirenberg†*

The aim of this work is to understand the molecular mechanisms of cell communication and recognition, and ultimately their genetic regulation, which result in the formation of highly organised and differentiated functional and structural units. Two mammalian models have been under study: (i) rat retina and (ii) rat neuromuscular junction. The strategy taken has been to identify specific molecular markers, especially of the cell surface, with the hybridoma technique using end-plate enriched rat diaphragm and the clonal hybrid cell line

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†Laboratory of Biochemical Genetics, NIH, Bethesda (USA).

N18RE-103 (Fisher rat embryo retina x N18TG-2 mouse neuroblastoma) as immunogens. By this method a panel of 46 cell lines has been obtained secreting monoclonal antibodies which recognise N18RE-103 (but not fibroblast cell lines from the same parents) and/or rat diaphragm. The preliminary inter- and intratissue specificities of these antibodies, determined by indirect immunofluorescence of cryostat tissue sections, showed a wide variety of patterns including 11 which recognise specific muscle fibre types (type 1, 2 and 2B), 18 which recognise only 1 or 2 elements within retina, 4 which recognise end-plates, 12 which recognise peripheral nerve, 1 which recognises only glomeruli in kidney and 4 tumour specific antibodies.

Abstract

Tremor, the Cogwheel Phenomenon and Clonus in Parkinson's Disease

*L.J. Findley, M.A. Gresty and G.M. Halmagyi**

Resting and postural tremor, intention and action tremor, clonus and the cogwheel phenomenon in Parkinson's disease have been characterised in terms of frequency content using spectral analysis. Typical resting tremor ranged in peak frequency from 4 to 5.3Hz with tremor in each individual varying only by 0.2 to 0.3Hz. The peak frequency of postural tremor ranged between 6 and 6.2Hz. Intention tremor appeared to be an exaggeration of postural tremor. Clonus evoked by active or passive stretch at the wrist had a frequency of 6Hz and appeared to be a continuation of postural tremor. The cogwheel phenomenon was found at frequencies between 6 and 6.5Hz and between 7.5 to 9Hz. Action tremor was indistinguishable from the cogwheel phenomenon. Some patients had either a symptomatic resting tremor with a concurrent 6Hz component of smaller amplitude, or a symptomatic postural tremor with a 4 to 5Hz component of smaller amplitude. These combinations would produce 2 peaks in the power spectrum. When this occurred EMG studies showed that individual muscles had 2 types of rhythmical activation suggesting that the tremors have separate mechanisms. Likewise some patients had a symptomatic 6Hz tremor on posture with a second peak at 8 to 10Hz in the physiological band. Therefore, the 6Hz postural tremor is not an exaggeration of physiological tremor. On the basis of wave form and frequency similarities postural tremor, the low frequency type of active or passive cogwheeling, intention tremor and clonus possibly involve a common spinal mechanism. Higher frequency cogwheel phenomenon and action tremor

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may be an exaggeration of physiological tremor. More than 80% of patients with Parkinson's disease manifest tremors at both 4 to 5Hz and 6Hz. This combination would appear to be the strongest objective criterion for the diagnosis of basal ganglia disease.

Abstract

Fluctuations in Parkinson's Disease: The Effect of Withdrawal of Levodopa Therapy

*J.G.L. Morris, D. Madden and D.N. Wade**

Motor performance was assessed at hourly intervals throughout the day by means of a peg test in 16 patients suffering from idiopathic Parkinson's disease and in 11 control subjects. Patients were first assessed on a dosage regimen of levodopa and benserazide tailored in each case to give optimal control of symptoms. They then participated in a double blind crossover study in which they were given levodopa and benserazide for 3 days followed by placebo for 3 days or vice versa. Controls were studied in the same way. In 9 patients in whom fluctuations throughout the day were greater than normal, significant deterioration occurred on placebo. The amplitude of the fluctuations, as expressed in the coefficient of variation, was proportional to the deterioration which occurred on placebo. Seven patients did not deteriorate on placebo. Fluctuations in this group fell within the normal range. In 2 of these patients it was possible to demonstrate, from assessments made prior to the commencement of levodopa therapy, that benefit had accrued from this treatment.

These findings suggest that in patients who fluctuate, the effect of levodopa is relatively short-lived, persisting in some patients for a few hours only. In those who do not fluctuate the effect of levodopa can be shown to persist for at least 3 days. Possible mechanisms for these findings are discussed.

*St Vincent's Hospital, Department of Clinical Pharmacology, Sydney (Australia).

Abstract

Upbeat Nystagmus in the Primary Position of Gaze: Clinico-Pathological Observations

*A. Fisher, C. Harper and S. Wallis**

Electro-oculographic examination of the eye movements in a chronic alcoholic patient manifesting large amplitude primary position upbeat nystagmus was undertaken following his clinical recovery from Wernicke's encephalopathy.

The upbeat nystagmus increased in amplitude on upgaze, and diminished on downgaze but not in total darkness. The velocity of downward saccades was greatly reduced and there was defective upward pursuit, particularly at faster target velocities. Vestibulo-ocular responses were preserved.

Some months after examination death occurred from peritonitis following perforation of a colonic diverticulum. Postmortem revealed an old superficial cerebellar hemisphere infarction and chronic Wernicke's encephalopathy with an unusual distribution of lesions.

The clinicopathological findings in this case throw doubt on the anatomical specificity of the current classification of upbeat nystagmus.

Abstract

An Evaluation of Thermography and Palmar Sweat Prints in Disorders of the Peripheral Nervous System

S. Bajada†

Autonomic nervous function may be affected by a number of conditions involving the peripheral nervous system. Standard evaluation of autonomic function includes tests of postural vasomotor function, sudomotor function and pupillary function. Many of these tests have limited and nonspecific value. A need exists for the development and assessment of new techniques, and for new applications of existing methods. Thermography has received some attention from investigators in this field. Palmar sweating has been previously used in diagnosis of peripheral nerve injuries.

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†Department of Clinical Neurophysiology, Fremantle Hospital, Western Australia.

In the present study the 2 techniques have been reassessed and examples of their value in diagnosis are presented. Thermography may be used to examine the limbs or trunk. Examples are given of peripheral entrapment syndromes, radiculopathy, and sympathetic dystrophy. Palmar sweat prints have been recorded using a silver chromate technique developed in 1959. The technique may be adapted for use at other sites in the body and provides a permanent record of sudomotor function.

Abstract

Serum Prolactin Levels in the Diagnosis of Epilepsy*

S. Bajada†

The problem of diagnosis in epilepsy and clinically similar disorders is well known to neurologists and electroencephalographers. In 1978 Trimble reported an increase in serum prolactin levels following grand mal seizures with little increase after hysterical seizures. This increase was confirmed in work by Abbott et al. (1980) who suggested further studies were required in different types of clinical epilepsy. Prolactin release has been studied in perfusion studies of animal models and has been demonstrated following electrical stimulation of the amygdala in humans. We have studied serum prolactin levels in patients attending our epilepsy clinic to assess the potential diagnostic usefulness of the test.

Patients attending the clinic are asked to have a basal prolactin level performed and requested to subsequently attend the hospital or local practitioner as soon after an attack as possible for a further level to be performed. The time between attack and blood collection is noted and in some instances repeated levels are taken. Diagnosis is based on symptoms plus witness' description wherever possible and all patients have an EEG as a minimal investigation. Patient categories include grand mal seizure, petit mal seizure, simple and complex partial seizure, syncope, hysterical fit, narcolepsy and others. The results of this study are presented in the light of known mechanisms of prolactin release.

Reference

Abbott, R.J.; Browning, M.C. and Davidson, D.L.: Serum prolactin and cortisol concentrations after grand mal seizures. Journal of Neurology, Neurosurgery and Psychiatry 43: 163-167 (1980).

*This paper was presented at the AAN meeting in Adelaide, April 1981.
†Fremantle Hospital, Western Australia.

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Manuscript Preparation: Articles will be published in English. Submit two copies of the complete manuscript, including text pages, references, tables, legends, footnotes and figures. Only typed copy, doubled spaced on one side of preferably A4 (206mm × 294mm) typewriter paper, and with liberal margins is acceptable.

Subdivision of Articles: Manuscript should be prepared and paginated in the following manner:

1) Title page
2) Summary
3) Text pages
   - Introduction
   - Methods
   - Results
   - Discussion
4) Acknowledgements
5) List of references
6) Tables
7) Figures and captions
8) Footnotes

Title Page: There should be a separate title page with title, authors and institutions where the work was done, indicating city and country, and a condensed running title of not more than 50 letters including spaces.

The name and address of author to whom reprint requests should be addressed should appear separately as the second page.

Summary: The third page should contain a summary. The summary should not exceed 150 words. It should be factual not descriptive, and should present the reason for the study, the main findings (give specific data if possible), and the principal conclusions.

House Style: Papers reporting clinical studies or experimental work lend themselves to the sectional heading style of presentation and review articles also can be improved by a more limited use of this approach.

Method: Description of the experimental method should be succinct, but of sufficient detail to allow the experiment to be repeated by others.

Results and Discussion: Conclusions and theoretical considerations must not appear in the results section, nor is a recapitulation of the results acceptable for the discussion section. Where relevant, a concise statement of the implications of the experimental results, particularly to the clinical use of drug(s), should appear as a separate section.

References: In the text, reference to published work is cited by author (alphabetically) and year — viz (Brown, 1968, 1969; Brown and Smith, 1967; Brown et al., 1969).

The list of references must be arranged alphabetically by first author's name (and initials if more than one author of the same name) or by second or third etc authors if more than one author of same name and initials. If the sequence of the authors' names and initials is identical, the references should be arranged chronologically by year of publication. Samples of references are listed below. *Note:* titles of journals are *not* to be abbreviated. Supply inclusive pagination for all articles.

Journals: Carruthers, R.K.; Giles, G.R.; Clark, C.G. and Coligher, J.C.: Conservative surgery for bleeding peptic ulcer. British Medical Journal 1: 80-82 (1967).

Book: Keen, H.: Minimal diabetes and arterial disease: Prevalence and the effect of treatment; in Cammerini-Davalos and Cole (Eds) Early Diabetes, p.437-445 (Academic Press, New York 1970).

Supplement: Keen, H.; Jarrett, R.J.; Chlouverakis, C. and Boyns, D.R.: The effect of treatment of moderate hyperglycemia on the incidence of arterial disease. Postgraduate Medical Journal 11(Suppl.): 960-966 (1968).

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Subject Index