Clinical and Experimental Neurology

Proceedings of the Australian Association of Neurologists, Volume 23, 1986

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WILLIAMS & WILKINS, and ASSOCIATES PTY LTD
Sydney • Baltimore • London

Clinical and Experimental Neurology

ISSN 0-196-6383

Authors are requested to consult the Instructions to Authors p.251–252

Published for the Australian Association of Neurologists by:

WILLIAMS & WILKINS, and ASSOCIATES PTY LTD
404 Sydney Road, Balgowlah, NSW 2093, Australia

Printed in Hong Kong by Caritas Printing Training Center

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The Graeme Robertson Memorial Lecture, 1985
Neurology of the Sphincters

*M. Swash**

Dr E.G. Robertson, to whose memory this lecture is dedicated, was a neurologist of wide ranging interests. He made many contributions to clinical neurology and is perhaps best remembered, by those who were in practice before the advent of computerized scanning, for his work in delineating the scope and role of air encephalography in clinical practice. In addition to his neurological interests he was a skilled photographer and used this to preserve, in several books, the architectural heritage of cast iron decorative work on the houses of his native Melbourne. Early in his career, when working with Denny-Brown at Queen Square in London, he wrote two papers that have acquired lasting significance.[1,2] In the first, published in 1933, he and Denny-Brown investigated the pressure and flow relationships of the urinary bladder in a series of experiments carried out on themselves. This work formed the basis for the cystometrogram, an essential part of the investigative methodology of gynaecology and urology. Two years later, again with Denny-Brown, he reported observations of the function of the anal sphincter using a technique involving volume and pressure relationships within the sphincter zone in the anal canal. This method, now called anorectal manometry, has found a role in the every-day practice of coloproctology. Although Robertson and Denny-Brown thus recognized, 50 years ago, the importance of understanding sphincter function in relation to the nervous system, most of the subsequent investigations of the pelvic sphincters have been carried out by urologists, gynaecologists, or coloproctologists. Neurologists have tended to restrict their interest in incontinence to the sphincter disturbances accompanying lesions in the central nervous system, although treatment for incontinence of this type is largely ineffective.

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Incontinence of urine or faeces is a devastating disability. It is responsible for social embarrassment of such a degree that it frequently produces isolation as severe as that associated with paraplegia. People with incontinence are reluctant to go out, are fearful of making social contact, and frequently become housebound. The symptom is itself not a subject that can generally be brought into the open with friends and family and thus often remains hidden before being brought to medical attention, perhaps years after its onset. Incontinence is a particularly common problem in aged people but cannot be regarded as an invariable consequence of normal aging. Surveys of the incidence of incontinence suggest that incontinence, either of urine or of faeces, may be much commoner than has previously been supposed.[3] As many as 10% of women over the age of 50 may have experienced incontinence of urine, and in elderly populations in nursing homes a prevalence of incontinence of more than 50% is common. Faecal incontinence is less frequent than urinary incontinence but the observation of Leigh and Turnberg[4] that 51% of patients presenting to gastroenterological clinics with the complaint of diarrhoea are in reality incontinent suggests that the incidence of faecal incontinence has been greatly underestimated. All surveys of this problem have confirmed the commonly held view that incontinence is more frequent in women than in men.[3–5]

Incontinence and Sphincter Competence

Incontinence of urine, and of faeces, has long been known to be associated with weakness of the sphincter musculature but there has been controversy as to the reason for this weakness. Indeed, concepts of the aetiology of this type of incontinence, stress incontinence, are largely related to the special viewpoints of different specialists, particularly urologists, gynaecologists and coloproctologists. It has variously been held that stress incontinence, either of urine or faeces, is due to weakness of the voluntary striated sphincter musculature, to weakness of the pelvic floor muscles as a whole, to weakness of the smooth involuntary sphincter musculature, or to stretching of the muscles and ligaments of the pelvic floor itself.

Our investigations of this problem began with the observation that the external anal sphincter musculature was weak in patients presenting with idiopathic anal incontinence. The latter is a disorder of insidious onset, particularly in early middle life, in which there is no evidence of any local cause or of any neurological disorder. About 15% of patients with this disorder also experience typical stress incontinence of urine.[6]

Functional Anatomy of Continence

Both the urinary and anal sphincters consist of functionally and anatomically related smooth and striated sphincter muscle mechanisms. The involuntary smooth muscle sphincter of the anal canal consists of a thickened ring of smooth muscle derived from the longitudinal layer of the rectum and anal canal. Tonic contraction of this smooth muscle ring holds the inner layers of the anal canal in apposition. The

squamous lining membrane of the anal canal is replete with sensory receptors subserving discriminative sensation. The smooth musculature may be particularly important in modulating the sensitivity of these receptors by maintaining apposition of the anal canal, which is usually empty.

The striated anal sphincter musculature consists of a complex ring of external anal sphincter muscle fibres, the superficial layers of which insert into the skin of the anal margins. In addition there is a larger sling of muscle tissue, the puborectalis or pubo-anal muscle sling, that holds the anal canal forwards towards the pubis, thus maintaining a sharp anorectal angulation. This angulation is such that intra-abdominal pressure results in apposition of the mucosae of the anterior and posterior walls of the rectum, against the resistance of the puborectalis contraction, thus maintaining a flap–valve mechanism (Figure 1). Parks[7] suggested

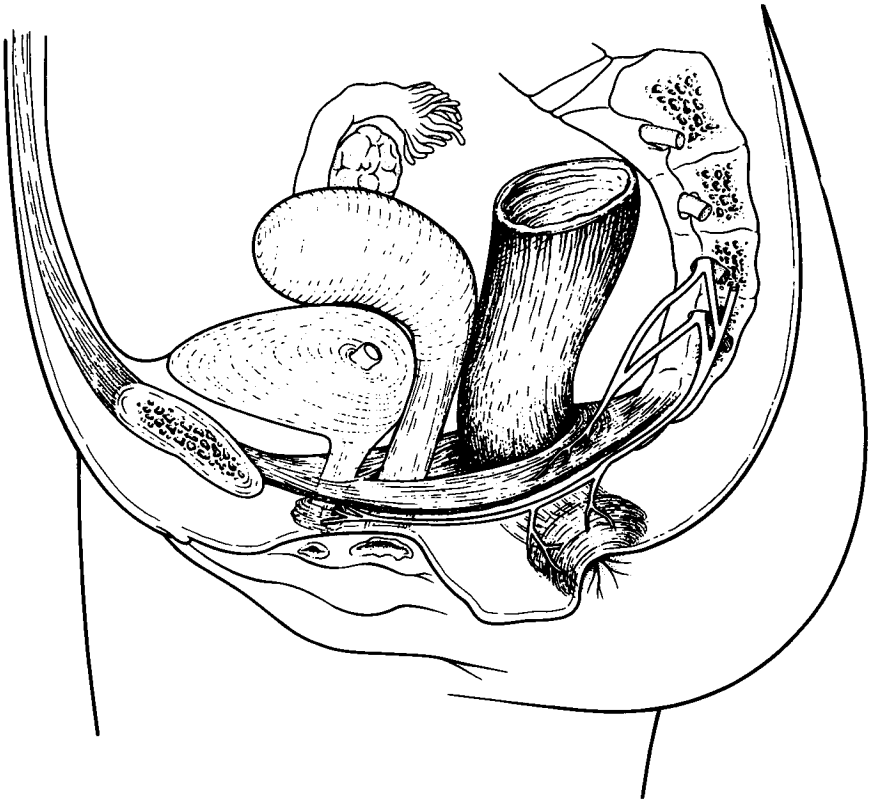

Figure 1. The anatomy of the muscles of continence. Note that the puborectalis muscle sling acts to sharpen the angle between the anal canal and rectum so that intra-abdominal pressure closes the flap–valve between the anterior and posterior mucosal walls of the rectum. This muscle must relax before defaecation can commence.

that this flap–valve at the level of the puborectalis muscle was the major mechanism of faecal continence in man. The external anal sphincter and puborectalis muscles are in a state of continuous low-level activity during ordinary activities, at rest, and during sleep, and relax only during the act of defaecation. Increased contraction will occur during periods of increased abdominal pressure, as in straining against a closed anal canal, in coughing, or in changes of body posture. The flap–valve mechanism is thus maintained at all times in the normal subject. Only in patients with tabes dorsalis is resting activity of the external anal sphincter abolished.

Urinary continence is less well understood. It is probably maintained by tonic contraction of the periurethral striated sphincter musculature resulting in a sharply angled bladder neck. However, tonic contraction of the intra-mural component of the striated bladder sphincter is also important and it may be that combined contraction of these two muscles results in slight kinking of the proximal urethra, and thus in continence. Relaxation of these muscles is necessary before micturition can commence. The role of the involuntary smooth musculature of the bladder neck in the maintenance of urinary continence is uncertain, but this component appears to be more important in urinary continence than in faecal continence. The periurethral striated sphincter musculature, like the external anal and puborectalis muscles, is in a state of continuous resting basal activity. It is interesting to note that the only other muscles in which this basal activity has been recorded in man are the cricopharyngeal sphincter muscles, responsible for closure of the oesophagus in the pharynx, and the abductor muscles of the larynx, necessary for maintenance of an airway.

The anatomical relationships of the striated pelvic floor sphincter muscles are illustrated in Figure 1. These muscles derive their innervation from branches of the S2 and S3 sacral motor roots. The external anal sphincter muscle is innervated by inferior rectal branches of the pudendal nerves. The pudendal nerves leave the pelvis beneath the sacrospinous ligaments and travel in Alcock's canal before passing through ischiorectal fat to reach the sphincter muscle. The periurethral striated sphincter musculature is innervated by perineal branches of the pudendal nerves. The puborectalis muscle, however, is innervated not by branches of the pudendal nerves but by direct motor branches from the S2 motor roots that enter it from its peritoneal surface. The intramural component of the urethral striated sphincter musculature is also innervated by motor branches travelling in the pelvic nerves, rather than from pudendal branches.

Sphincter Denervation in Incontinence

Histopathological studies of the striated anorectal sphincter musculature,[6,11] particularly of the external anal sphincter, the puborectalis, and the lowermost fibres of the levator ani muscles, have shown marked loss of muscle fibres in subjects with incontinence. The puborectalis and external anal sphincter muscles are particularly severely affected. There is marked fibrosis and fatty replacement of muscle tissue with hypertrophy of some of the remaining muscle fibres. Clusters of

tiny fibres with pyknotic nuclei are also seen and some fibres show features suggestive of degeneration or regeneration. Non-specific abnormalities, including rod body inclusions, were seen in some muscle fibres. Enzyme histochemical studies of these muscles showed fibre-type grouping involving both histochemical fibre types with grouped denervation atrophy, and scattered pointed atrophic NADH-dark fibres. These changes, characteristic of a neurogenic disorder, were accompanied by fibrosis, and by loss of myelinated nerve fibres in biopsies of twigs of small nerves entering the puborectalis and external anal sphincter muscles.[6] In a histometric study of these 3 muscles,[11] there was marked hypertrophy of the remaining muscle fibres in subjects with incontinence. This particularly affected type 1 muscle fibres. Further, type 1 fibre predominance was the major feature of these 3 muscles in normal subjects, especially in the external anal sphincter and puborectalis muscles. Type 1 fibre predominance would be an expected feature in a muscle in a state of resting basal activity. In human striated muscles type 2 fibres are invariably slightly larger than type 1 fibres but in the female levator ani this size distribution was found to be reversed, the type 1 fibres being larger than the type 2 fibres. It is not known at what age this sexual dimorphism is acquired but, clearly, this functional specialization within the pelvic floor diaphragm may be an important aspect of this muscle.

Cause of Sphincter Denervation and Incontinence

Anorectal incontinence is largely a disorder of women. It is particularly common in women who have borne children, especially those in whom there is a history of a prolonged or difficult labour, often involving the use of forceps. There is also an association between the development of idiopathic anorectal incontinence and a history of intractable constipation, or straining at stool, during a period of many years.[6,7] Sometimes this abnormal bowel habit appears to be acquired after childbirth but commonly it has been present since adolescence.[12] These factors led us to consider the processes and mechanisms of damage to the pelvic floor innervation that seemed to be responsible for producing weakness of the striated sphincter musculature, and so stress incontinence. We have evaluated these hypotheses for stress incontinence, in terms of both anorectal incontinence and stress urinary incontinence, using electromyographic and nerve conduction methods.

Methods

The degree of weakness of the pelvic floor sphincter muscles can be assessed by anorectal manometry, a technique in which the pressure developed in the sphincter zone in the anal canal at rest and during voluntary squeeze contraction of the sphincter musculature is measured, and also by cystometrograms. These were the 2 techniques developed by Robertson and Denny-Brown 50 years ago.

Conventional concentric needle electromyography has long been used in the

assessment of disorders of the urinary and anal sphincters but these techniques are difficult to quantify in these muscles in routine investigations. We have preferred to use single fibre electromyography to measure the fibre density, a measure which indicates the packing density of muscle fibres innervated by branches of the same motor unit in the uptake area of the recording electrode. An increased fibre density in a disorder known to be neurogenic is an indication of the effectiveness of reinnervation. This method has been validated in neuromuscular disorders. It does not, however, give a measure of the extent of denervation except in so far as higher values of fibre density imply that there has been more extensive denervation before the compensatory reinnervation response.[13,14]

In order to assess the innervation of the pelvic and pudendal components of the innervation of the anorectal sphincter mechanism, and the perineal component of the periurethral striated sphincter musculature, it was necessary to devise new electrophysiological methods.[15] By using electrodes mounted on the tip of a glove similar to the finger gloves used by surgeons in the routine digital examination of the anal canal and rectum, together with a pair of recording electrodes mounted at the base of the finger bearing the stimulating electrodes, it is possible to stimulate the pudendal nerves in the pelvis through the lateral wall of the rectum and to pick up the evoked muscle action potential in the external anal sphincter muscles with the electrodes at the base of the finger. This technique gives precise manual control of the position of the stimulating electrodes at the tip of the finger, and of the recording electrodes at the base of the finger. Since the distance between these stimulating and recording electrodes is constant, the latency derived represents the terminal motor latency of the pudendal nerves *via* their inferior rectal branches.[16,17] Using an identical stimulating procedure, but with catheter-mounted surface electrodes in the urethra, it is possible to pick up the evoked muscle action potential response in the periurethral or striated sphincter muscles, representing the perineal nerve terminal motor latency.[18–20]

To evaluate the proximal component of the innervation of these muscles, together with the innervation of the puborectalis muscle, we used the high voltage, low impedance stimulator developed by Merton and Morton[21] for transcutaneous cortical stimulation in man. By applying this stimulator over the lumbar spine at 2 levels, L1 and L4, and by using glove-mounted recording electrodes to pick up the response in the puborectalis and external anal sphincter, and the catheter-mounted electrode to pick up the response from the periurethral striated sphincter musculature, it is possible to measure the motor latency from the cauda equina at the 2 levels to these muscles.[15,18] Subtraction of the 2 latencies derived from L1 and L4 stimulation sites, or the use of the ratio of these 2 latencies (L1 divided by L4) which we have termed the spinal latency ratio,[18,19] enables us to recognize slowing of motor conduction in the cauda equina motor nerve roots innervating the sphincter muscles. This method thus provides a direct assessment of disorders causing slowing of nerve conduction in the cauda equina.[10] Since many patients with idiopathic stress incontinence are middle-aged or older it would be expected that disc disease, spondylosis, or other cauda equina disorders might co-exist with damage to the nerve supply of the sphincter musculature within the pelvis (Figure 2).[22]

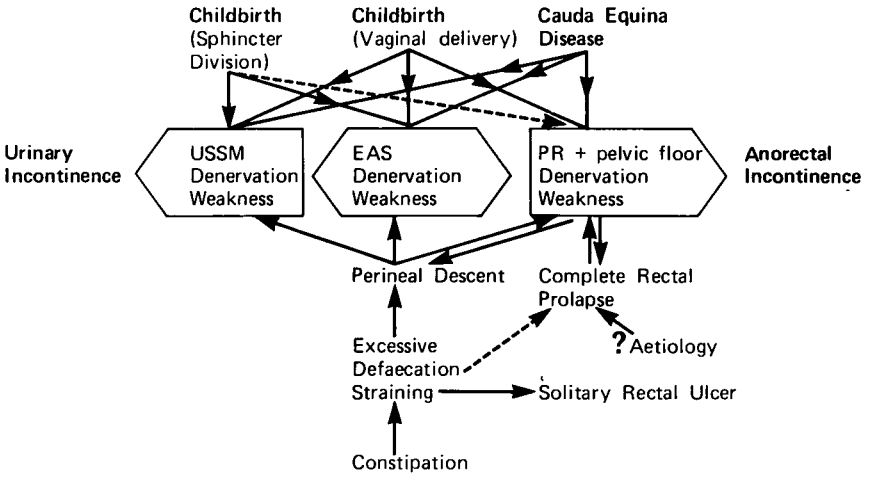

Figure 2. An algorithm for the pathogenesis of faecal incontinence (see ref. 22).

Site of Nerve Damage in Incontinence

In patients with idiopathic anorectal incontinence the single fibre electromyography (EMG) fibre density in the external anal sphincter muscle is increased.[14] The fibre density in this muscle is similarly increased in patients with faecal incontinence associated with rectal prolapse, but in patients with rectal prolapse not associated with faecal incontinence the fibre density is normal.[13] This observation suggests that, although prolapse might be an accompaniment of faecal incontinence when the pelvic floor was weakened by damage to the pelvic floor innervation, in other patients rectal prolapse was not associated with lesion to the pelvic floor innervation but must have some other cause. This observation is consistent with current surgical views that, in some cases of rectal prolapse without incontinence, intussusception of the mucosa and of the viscus might be a factor. About 15% of patients presenting with faecal incontinence of idiopathic stress type also suffer from stress incontinence of urine and a rather larger and undefined number will admit to minor incontinence of urine during stressful manoeuvres such as sneezing, coughing, or turning suddenly. We therefore decided to extend our investigations to include patients with faecal incontinence associated with stress urinary incontinence and, later, patients presenting with genuine stress urinary incontinence alone.

The terminal motor latency of the pudendal nerve is increased in patients with anorectal incontinence.[16,20] In addition, these patients show abnormally long perineal nerve terminal motor latencies when compared with control subjects. However, this increase in perineal nerve terminal motor latency in these patients with anorectal incontinence alone was not associated with symptomatic stress

urinary incontinence. In patients afflicted both by stress faecal and stress urinary incontinence the pudendal nerve terminal motor latency is increased to a similar degree to that found in patients with faecal incontinence alone, but the perineal nerve terminal motor latency in this group of subjects was increased to a much greater extent than in those in whom faecal incontinence was not associated with urinary incontinence.[20] These findings suggest that the relative isolation of faecal incontinence and urinary incontinence of stress type can be explained by the relative predominance of abnormality in the inferior rectal or perineal branches of the pudendal nerves. All the patients studied in these investigations either described difficult or prolonged childbirth, often with forceps delivery, or had had prolonged intractable constipation many years before the development of their incontinence. In addition, perineal descent on straining, often amounting to 3 or 4 centimetres when measured using a technique developed in our laboratory, was a feature of all these patients. These results suggested that the gradual development and inexorable worsening of the incontinence, although initiated by injuries sustained during difficult childbirth, or perhaps by repeated problems associated with prolonged straining of stool, was directly related to recurrent perineal descent during straining.[24] Measurements of the lengths of the pudendal nerve from Alcock's canal to the sphincter musculature suggested that the degree of stretch caused in these nerves by recurrent descent of the perineum during straining was sufficient to result in recurrent stretch injury to these nerves and thus to gradually worsening denervation weakness of these muscles.[25]

Investigation of patients with constipation alone, not associated with incontinence of urine or faeces, revealed that the fibre density in the external anal sphincter and puborectalis muscles is raised, although not to an extent comparable with that found in patients with incontinence. In addition, the pudendal nerve terminal motor latency is also slightly raised in these patients.[12,24] It is difficult to ascertain the duration of a symptom as ill defined as constipation but some indication of the role of defaecation straining in the pathogenesis of damage to the pudendal nerves, and to the direct pelvic somatic efferent nerve fibres innervating the puborectalis muscle, can be obtained from consideration of patients with the solitary rectal ulcer syndrome. The latter is a disorder characterized by intermittent slight anal bleeding, together with intractable straining at defaecation, that frequently occurs in men. In these patients, although there is no incontinence, the pudendal nerve terminal motor latency was raised and the degree of abnormality could be correlated with the duration of symptoms measured on the first occasion on which anal bleeding was recognized.[26] In another investigation it was noted that there was evidence of damage to the pudendal nerves, as shown by pudendal nerve terminal motor latency measurements, and fibre density measurements in the external anal sphincter, in patients in whom traumatic childbirth had resulted in an anterior tear in the external anal sphincter.[27] These patients were incontinent but the incontinence resulted not solely from obstetrical trauma to the external anal sphincter muscle but from the combination of this injury and coincidental damage to the innervation of the anal sphincter muscle that seemed to have been associated with the traumatic childbirth. These investigations indicated that damage to the

pelvic floor innervation could result in denervation of the pelvic floor striated sphincter muscles and indicated that this nerve injury was commonly due either to injury sustained during childbirth, or to recurrent straining at defaecation with pelvic floor descent. Sometimes the 2 factors were inter-related. The abnormality revealed by these investigations was quantitatively related to the functional disturbance so that incontinence was associated with pudendal nerve terminal motor latencies of greater than 2.5 ms and fibre density measurements in the external anal sphincter muscle of greater than 1.8.[28] Incontinence was unlikely in patients with less severe abnormality. In an investigation of aged people resident in a geriatric hospital it was found that the fibre density in the external anal sphincter muscle was usually higher than 1.8, and this also was associated with incontinence, suggesting that cumulative damage to the pudendal nerves, either from the effect of aging, or from the effects of injury of other types, had resulted in incontinence in these elderly subjects.[29]

The question as to the role of a lesion in the proximal part of the innervation of the pelvic floor sphincter muscles, that is, a lesion in the cauda equina motor nerve roots, either in the cauda equina or at their exit through the intervertebral foramina of S2 and S3, was addressed by using the method of transcutaneous lumbar stimulation of the cauda equina nerves roots at the L1 and L4 levels. It was found that in a proportion of patients with the syndrome of idiopathic anorectal incontinence the spinal latency ratio, that is, the ratio between L1 and L4 latencies to the external anal sphincter, puborectalis, and external periurethral striated sphincter musculature, was increased indicating that the L1 latency was more abnormal than the L4 latency. In many of these patients there was also an abnormality in the pudendal and perineal nerve terminal motor latencies suggesting that there was damage to the innervation both proximally and distally. However, in others, the lesion appeared to be restricted to an increase in the L1 latency to these sphincter muscles, with a normal L4 latency.[30–32] Studies of a group of patients with the neurological features of cauda equina disease provided validation for this technique[33], indicating that it was possible to delineate the presence of lesions within the cauda equina between the L1 and L4 levels that had damaged the S2 and S3 motor roots as they passed through this region from the conus medullaris to their exit foramina in the sacral bony mass. In some patients this lesion was due to disc disease, in others it was due to tumour or trauma, but in a small sub-group there was myelographic evidence of arachnoiditis without treatable surgical cause. In the 15% of patients presenting with idiopathic anorectal incontinence in whom there was electrophysiological evidence of slowing of motor conduction between the L1 and L4 levels in the cauda equina, detailed neuroradiological investigations have not yet been undertaken but there is no indication, on neurological grounds, that these patients suffer from surgically treatable cauda equina disease. Many had radiological evidence of spondylosis on lumbar spine x-rays and in our earlier clinical studies of anorectal incontinence it was noted that there was an excess of patients with a past history of sciatica, so that it appears likely that long standing damage, perhaps associated with arachnoiditis of these lumbar roots, was the cause.

Effect of Childbirth on Pelvic Floor Sphincter Innervation

In a group of 180 women presenting consecutively to the obstetric department at St Bartholomew's Hospital for ante-natal care we investigated the possible role of childbirth in causing damage to the pelvic floor innervation.[34–36] All the patients had single fibre electromyography of the external anal sphincter muscle during the first trimester of pregnancy. They were studied again within 3 days of delivery, and for a third and final time 2 months after delivery. During these 2 later investigations the pudendal nerve terminal motor latency was measured and the fibre density and perineal descent measurements were repeated. This investigation showed that the terminal motor latency of the pudendal nerve was commonly mildly or moderately increased immediately after delivery but that it tended to return towards a normal value 2 months after delivery, although it did not always return to the normal range. Similar changes were observed in the fibre density in the external anal sphincter muscle. Women who had had a previous child showed a much more marked abnormality in the pudendal nerve terminal motor latency immediately after delivery and failed to show as marked a return of this measurement to the normal range 2 months later. Indeed, 2 of these patients developed symptomatic incontinence. Women who experienced a forceps delivery, whether or not they were primiparous or multiparous, showed very marked abnormalities in fibre density and in pudendal nerve terminal motor latency immediately after childbirth. These abnormalities remained, although to a lesser extent, 2 months later and were always much more marked than in women who had experienced a normal vaginal delivery. In addition there was a correlation between birth weight and pudendal nerve terminal motor latency, and between the duration of the second stage of labour and the pudendal nerve terminal motor latency in the whole group of women. Further, women who had pelvic disproportion, and who had a trial of labour, but were delivered by Caesarean section, showed no change in pudendal nerve terminal motor latency or in fibre density either shortly after or 2 months after childbirth. Thus they were protected from developing damage to the innervation of the pelvic floor musculature. Pudendal or spinal anaesthesia had no effect on the electrophysiological investigations.[34]

These prospective studies clearly indicated the role of difficult or prolonged childbirth, particularly when forceps assistance was used, in causing damage to the innervation of the pelvic floor musculature. The amount of residual damage present in women who had had more than one baby was such that it might be appropriate in future to use these investigations as a means of indicating when a woman might be at risk of developing incontinence from damage to the pelvic floor innervation during subsequent deliveries.

An algorithm for the interlocking factors that seem to lead to the development of stress urinary and stress anorectal incontinence is summarized in Figure 2. This algorithm is restricted to factors leading to damage to the motor innervation of these sphincter muscles and does not take account of any possible sensory effects of damage to these nerves, or of any functional inter-relationship between smooth muscle factors with the striated sphincter system.

Central Pathways for Continence

The descending and ascending pathways related to bladder function have been evaluated in neuropathological studies by Smith and Nathan.[37,38] We used transcutaneous electrical stimulation of the central nervous system, together with our method for assessing motor conduction across the cauda equina by transcutaneous stimulation of the motor nerve roots in the lumbar region, to estimate central conduction time to the external anal sphincter, puborectalis and periurethral striated sphincter musculature in a group of normal subjects. In addition, by using transcutaneous stimulation of the cervical spinal cord at C6 we introduced a method for assessment of the motor conduction velocity in the spinal cord with reference to these 3 muscles.[39] This method is also applicable to measurement of central conduction time between cortex and C6 levels, and motor conduction velocity in the spinal cord with reference to other target muscles by placing recording electrodes over the muscles in question. In these investigations we found that the motor conduction velocity in the human spinal cord was 67.4 ± 9.1 m/s and in the cauda equina was 57.9 ± 10.3 m/s. In patients with multiple sclerosis, and in a single subject with radiation myelopathy resulting from treatment of a bronchogenic neoplasm, there was slowing of motor conduction in the spinal cord. This new method allows the assessment of the descending corticospinal pathway for sphincter function in humans and may thus be useful in the assessment of patients with incontinence of central origin. However, we have so far attempted to correlate electrophysiological abnormalities only in patients with stress urinary and stress anorectal incontinence. The central and peripheral mechanisms concerned with the syndromes of detrusor instability, urge incontinence, and sphincter dyssynergia have not as yet been investigated with these new electrophysiological methods.

Implications for Clinical Practice

The abnormalities we have described have relevance both to the understanding of the cause of stress incontinence, particularly for prevention, and in the planning of surgical corrective procedures. Clearly, if incontinence can be prevented by appropriate management of childbirth, or by appropriate management of pelvic floor descent syndromes and constipation syndromes, then it is possible that incontinence of this type might, in some measure, be prevented. The realization that the pelvic floor muscles, and the striated sphincter musculature of the pelvic floor, are denervated in most patients with incontinence implies that attempts to correct the functional disorder of incontinence surgically by tightening up these muscles are unlikely to succeed. Operative procedures that re-fashion these sphincter muscles from unaffected portions of levator ani, like the post-anal repair procedure introduced by the late Sir Alan Parks for correction of anorectal incontinence, are more likely to be successful. It is perhaps unfortunate that urinary and anorectal incontinence fall within the province not only of physicians but also of 3 separate surgical specialties: gynaecology, urology and coloproc-

tology. Since these syndromes overlap, and have a similar pathogenesis, it would be appropriate for the surgical techniques in common use to be rationalized in relation to the physiological and functional disturbance; this might result in more effective treatment.

The neurologist and clinical neurophysiologist have a role not only in the investigation of patients with incontinence before surgical correction but also in the recognition of patients within this large group in whom there is disease in the cauda equina, and in selecting patients for myelography. The electrophysiological tests we have introduced are useful in this problem. These tests will become more widely available when the glove electrodes we have designed have been manufactured commercially. Greater understanding of these disorders, initiated by Robertson's efforts with Denny-Brown to understand pressure and flow relationships within the bladder and bowel, will result in better advice and better treatment for patients afflicted with incontinence.

Acknowledgements

The work described in this lecture represents the results of investigations carried out with the following Research Fellows: Michael Henry, Friedrich Beersiek, Mischel E. Neill, John P. Percy, Tatsuo Teramoto, Max Wunderlich, Edward B. Kiff, Philip R.H. Barnes, Steven J. Snooks, David H.K. Chalmers and David Lubowski. The work has been generously supported by the St Mark's Hospital Research Foundation, the Sir Alan Parks Research Fund of the Royal College of Surgeons of England, the British Council, the Royal Society, the Viennese Academy of Sciences, the Commonwealth Research Trust and The London Hospital Special Trustees.

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Crossed Facilitation and Post-contraction Depression of Abductor Pollicis Brevis Motor Neurons

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The F response is a late muscle potential resulting from antidromic activation of motor neurons.[1-3] Individual F responses arise from a limited number of motor units which represent a small and variable fraction of the motor neuron pool.[3] There is evidence that the number (persistence) and sizes of F responses reflect the excitability of the motor neuron pool.[4-10] It is known that voluntary contraction, either of the muscle being recorded from, or of remote muscles, results in enhancement of the F response[9-11] followed by a period of depression after the contraction.[12] In this study we investigated the degree and time course of F response enhancement in the abductor pollicis brevis (APB) during contraction of the contralateral APB and of post-contraction depression.

Subjects and Methods

Eight normal right-handed volunteers (5 men, 3 women) aged between 22 and 30 years were studied. Recordings were carried out in an electrophysiological laboratory with an ambient temperature ranging between 20 °C and 23 °C. The procedure was explained to each subject who was then allowed to relax in the supine position for 5 minutes before the recording commenced.

F responses were recorded from disc electrodes placed over the motor point and tendon of the right APB. Responses were amplified and analysed with an electromyograph (EMG) (Medelec MS6) interfaced to a PDP 11/23 computer which digitized 50 ms of EMG at 4 kHz, beginning 14 ms after the stimulus. The

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high frequency setting was 8 kHz and a low frequency setting of 8–32 Hz was selected for each subject to optimize the baseline after the M response. The right median nerve was stimulated at the wrist with supramaximal 0.1 ms square-wave pulses at a rate of 0.5 Hz. At the end of each recording session successive sweeps were displayed on a Tektronix 4010 terminal. The operator identified F responses and cursored the onset and offset of each response. The computer then calculated the integrated F response (surface) EMG (ISEMG) by summing individual data points for each digitized response after baseline adjustment. The total ISEMG for each sequence of stimulation was then determined.

The following experiments were performed on each subject.

(i) The responses to 3 sequences of 25 stimuli, each separated by a 90 s interval, were first recorded to establish baseline values. The subject then maintained a maximal isometric contraction of the contralateral APB against a fixed resistance for 2 minutes. Further sequences of 25 stimuli were given 60 s after commencement of contraction, immediately after cessation of contraction, and then at 90 s intervals for 6 minutes.

(ii) Sequences of 10 stimuli were given before, and at 30 s intervals during, a sustained maximal isometric contraction of the contralateral APB for 4 minutes.

(iii) After 3 baseline sequences of 25 stimuli, each separated by a 90 s interval, the subject maintained a maximal isometric contraction of the ipsilateral APB for 2 minutes. Further sequences of 25 stimuli were given immediately after cessation of contraction and then at 90 s intervals for 6 minutes. After 10 minutes the procedure was repeated with a 2 minute period of isotonic contraction of the ipsilateral APB at a rate of 2 Hz.

Results

The number of F responses per trial increased from 11 ± 2 (mean $\pm$ SE) to 15 ± 2 (not significant) during isometric contraction of the contralateral APB (Figure 1). The ISEMG increased from $8.9 \pm 1.6 \times 10^3 \mu$V ms to $35 \pm 3.1 \times 10^3 \mu$V ms ($p < 0.001$) during contraction (Figure 1) and individual F responses showed a greater number of subcomponents and an increased duration. After cessation of contraction, F response numbers fell to 8.3 ± 1.8 ($p < 0.01$) and the ISEMG to $6.4 \pm 0.9 \times 10^3 \mu$V ms, the latter being significantly different from the value during contraction ($p < 0.001$) but not from the pre-contraction value. F response numbers and ISEMG fell further by 90 s after contraction and increased over the next 3 minutes, but these changes were not significant (Figure 1).

The sequential changes in F response numbers and ISEMG during 4 minutes of isometric contraction of the contralateral APB are shown in Figure 2. There was a significant increase in F response numbers from 2.5 ± 0.5 to 4.8 ± 0.6 ($p < 0.05$) and in ISEMG from $1.9 \pm 0.3 \times 10^3 \mu$V ms to $5.7 \pm 0.7 \times 10^3 \mu$V ms ($p < 0.05$) at 30 seconds. The increase in F response numbers was maximal at 120 s and in ISEMG from 30 to 180 s. Subjective fatigue occurred between 150 and 180 s and most subjects were unable to maintain the contraction beyond 4 minutes. Values for both parameters fell during the fourth minute of contraction (Figure 2).

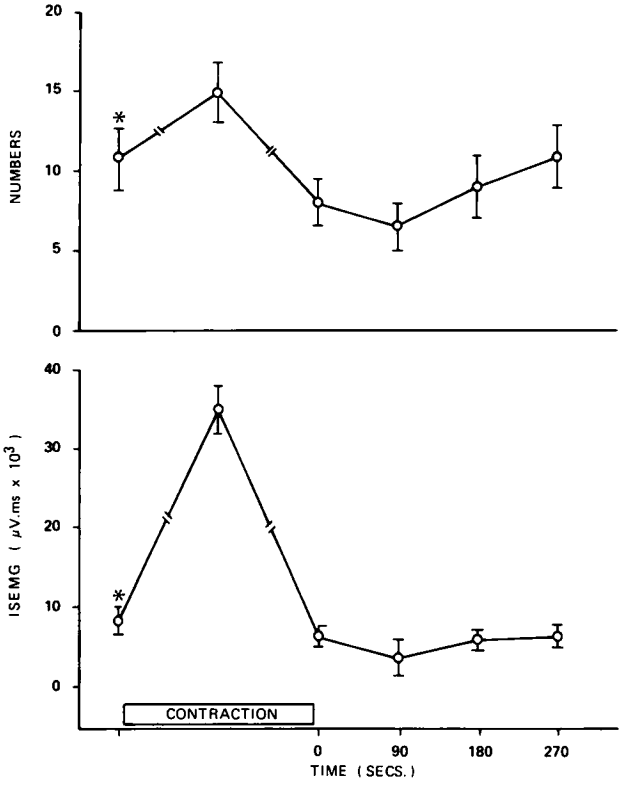

Figure 1. F response numbers and integrated surface EMG before (asterisk), during and after 2 minutes of maximal voluntary isometric contraction of the contralateral APB. Pooled data from 8 subjects. Bars represent standard error of the mean.

The changes in F response numbers and ISEMG after a 2 minute period of isometric contraction of the ipsilateral APB are shown in Figure 3. The ISEMG fell from $8.9 \pm 1.6 \times 10^3 \mu$V ms to $4.4 \pm 1.3 \times 10^3 \mu$V ms ($p < 0.05$), but the decrease in F response numbers from 11 ± 2 before contraction to 7 ± 1.5 immediately after contraction was not significant. Values for both parameters returned progressively towards normal over the next 6 minutes. Similar changes were found after 30 s and 60 s periods of isometric contraction and after a 2 minute period of isotonic contraction.

Discussion

The findings indicate that F responses from the APB are markedly enhanced by voluntary contraction of the contralateral APB. This was shown particularly by an increase in the size and complexity of individual F responses, indicating activa-

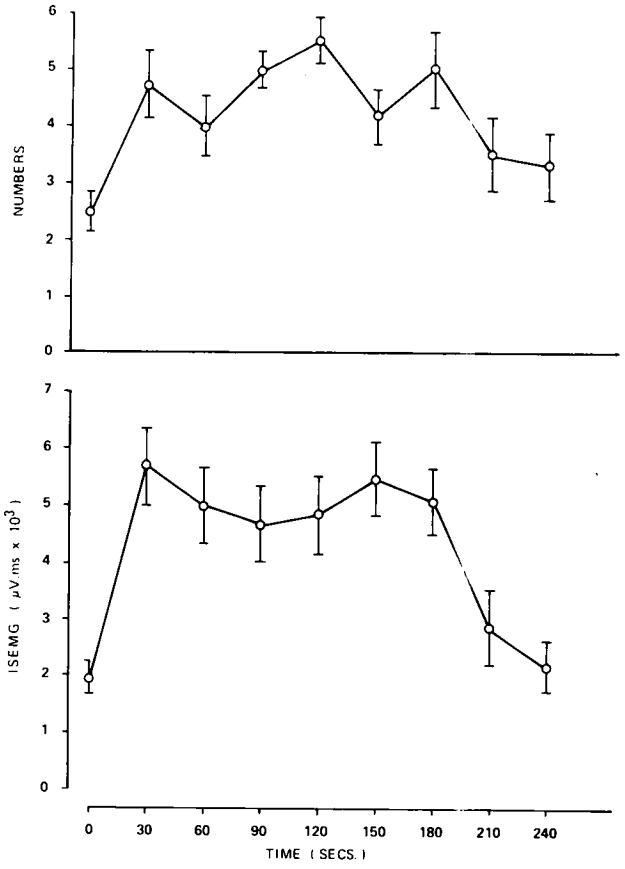

Figure 2. Changes in mean F response numbers and integrated surface EMG during 4 minutes of sustained voluntary isometric contraction of the contralateral APB. Pooled data from 8 subjects. Bars represent standard error of the mean.

tion of a larger number of motor neurons, and to a lesser extent by an increase in response numbers. Crossed facilitation of the motor neuron pool has been demonstrated previously in studies of the soleus H reflex[13] and the quadriceps tendon reflex, which is facilitated contralaterally as well as ipsilaterally by contraction of upper limb muscles.[14] The pathways subserving crossed facilitation are not known. In the case of reflex facilitation by contraction of muscles with a different segmental innervation, a long-loop pathway has been postulated comprising peripheral 1a afferents, a spinal ascending pathway, a supraspinal relay at bulbar or cortical level, and bilateral descending spinal pathways.[14] When the homologous muscle in the opposite limb is used, as in the present study, a purely segmental spinal interneuronal circuit may also be involved.

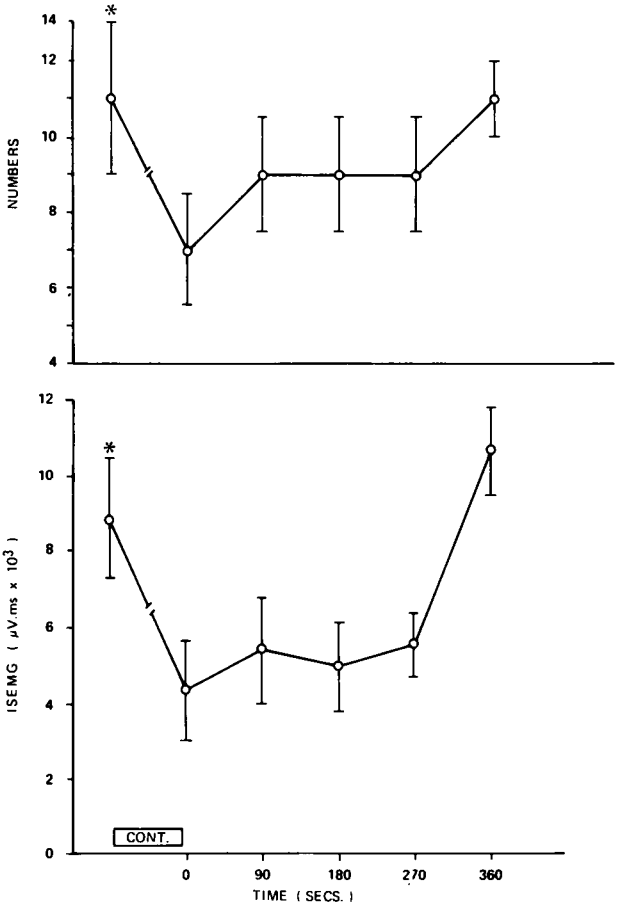

Figure 3. F response numbers and integrated surface EMG before contraction (asterisks), immediately after cessation of 2 minutes of maximal voluntary isometric contraction of the ipsilateral APB (CONT.), and at 90 s intervals for the next 6 minutes. Pooled data from 8 subjects. Bars represent standard error of the mean.

The finding that the enhancement of the F response by contraction of the contralateral APB was not maintained once subjective fatigue developed is pertinent to the role of central factors in muscle fatigue. The evidence suggests that fatigue is due principally to peripheral factors such as depletion of high-energy compounds, impaired excitation–contraction coupling and neuromuscular transmission but there is also some evidence for a reduction in neural drive.[15–21] The present findings suggest that with the onset of fatigue there is a reduction in motor neuron excitability even on the side opposite to the contracting muscle, and support the concept of a reduction in central motor 'drive'.

The depression of F responses after a period of voluntary contraction points to a resetting of the level of motor neuron excitability after completion of the contraction. It was notable that this depression occurred even with short periods (30 s) of contraction, indicating that it is not a fatigue phenomenon. Recovery was complete only after a period of several minutes, suggesting that it is not due to any of the forms of motor neuron inhibition at spinal level (for example pre-synaptic inhibition) which have been invoked to account for the more short-lived depression of the soleus H reflex after cessation of voluntary contraction.[22] A more likely explanation is that it is supraspinal in origin and represents a reduction in central motor 'drive' following a period of intense voluntary muscle contraction. It may therefore be regarded as the converse of the Jendrassik phenomenon.

Summary

Crossed facilitation of abductor pollicis brevis (APB) motor neurons by voluntary contraction of the contralateral APB was investigated using F response analysis. The integrated F response EMG showed a mean 4-fold increase during contraction. This enhancement was maintained until the onset of subjective fatigue and then declined. After isometric or isotonic contraction of the ipsilateral APB there was a significant depression of F responses with a progressive return to baseline values over a 6 minute period. The significance of the findings is discussed.

Acknowledgements

The study was supported by a grant from the Australian Brain Foundation. Mrs P. McBryde provided secretarial assistance.

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Unusual Paraspinal Muscle Lesions in Ankylosing Spondylitis

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Recently recognized and unusual pathological changes in the paraspinal muscles in ankylosing spondylitis (AS) deserve greater attention than they have received so far. Myopathic changes were first reported by Roux *et al.* in 1975.[1] They described small angulated fibres and central nucleation in patients with AS and suggested that the abnormalities were neurogenic in origin.

In 1976, Berman *et al.*[2] described 'core-targetoid' fibres in histochemical preparations and correlated these appearances with the typical electron microscopic changes of central cores. These consisted of loss of organelles and Z line streaming with disarray of sarcomeres in the central regions of the fibres. In their first patient 'tubular aggregates' with 'moth-eaten' and 'target' fibres occurred in type I fibres and a reduced number of histochemical type II fibres were present. In their second and third patients the changes were similar but tubular aggregates were lacking. In 1983 Hopkins *et al.*[3] confirmed the histochemical abnormalities described by Berman *et al.*[2], but did not perform electron microscopy. Carrabba *et al.* in 1984[4] reported similar muscle changes in ankylosing spondylitis, describing core-targetoid appearances within the sacrospinalis muscles which affected only type I fibres. Electron microscopy confirmed the presence of typical core-targetoid features.

These reports are of some interest as they resemble the ultrastructural lesions found in at least 3 of the congenital or 'structural' myopathies: central core, minicore-multicore and rod body (nemaline) myopathies. Target fibres are also a

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feature of denervation or, more probably, reinnervation. It is also of interest that all these changes may occur in experimental tenotomy, as shown by Karpati *et al.* in 1972[5] and Chou *et al.* in 1981.[6]

To gain some insight into the nature of the reported changes in AS within the paraspinal muscles, 10 of our patients with ankylosing spondylitis underwent muscle biopsy. It was found that the sacrospinalis muscle in these patients showed changes similar to those previously reported. Ultrastructural lesions consisting of Z band streaming, rod body formation, minicores, multicores, and core-targetoid fibres, singly or together, were found in the majority, but only a small proportion showed histochemical abnormalities.

Clinical Materials

The patients selected for biopsy fulfilled the diagnostic criteria for AS. Brief clinical details are given below. The muscle biopsies were obtained from the erector spinae muscle using a Kellog all-purpose needle[7] guided by x-ray fluoroscopy to avoid penetrating the dura. The muscle tissue was prepared using standard methods for light microscopy, histochemistry and electron microscopy.[8]

Clinical Data

Case 1 was a man of 62 years who had had AS for 36 years. He was treated with naproxen and diclofenac. The entire spine was involved, with marked limitation of movement but with no point of tenderness.
Case 2 was a man of 44 years who had had AS for 22 years. He was treated with piroxicam and suffered recurrent uveitis. The entire spine was involved, with extreme limitation of movement but without tenderness.
Case 3 was a man of 32 years who had suffered from AS for 16 years. The sacroiliac and hip joints were involved in addition to the thoracic and lumbar spine.
Case 4 was a 33 year old man who had had AS for 3 years and psoriasis. He was treated with indomethacin.
Case 5 was a man of 29 years who had had AS for 9 years and iritis and who was treated with naproxen and steroid eyedrops.
Case 6 was a 49 year old man whose ankylosing spondylitis had been present for 29 years. There was widespread spinal disease with fusion and limitation of motion and he had had a left total hip replacement.
Case 7 was a 32 year old man who had had AS for 16 years and who was being treated with naproxen.
Case 8 was a 36 year old man who had had AS for 14 years and who had been treated intermittently with indocid and diclofenac.
Case 9 was a man of 43 years who had had AS for 28 years and who had restricted lumbar and thoracic mobility.
Case 10 was a 37 year old man who had had AS for 21 years but still had good spinal mobility.

Results

Light Microscopy

In only 3 patients were the muscle fibres within the normal range of size and shape. In the remainder, there was excessive variation in muscle fibre diameter and outline, usually associated with atrophy. One patient showed myopathic changes with necrosis and regeneration. There was no evidence of grouped atrophy of denervation in any patient.

Histochemistry

In 8 patients type I fibres predominated, which is the normal finding for the erector spinae muscle. However, the very small number of type II fibres was probably significant in 3 patients. In the other 2 patients, the specimen was too small for quantification. In 2 patients target fibres were present and 2 others showed 'moth-eaten' fibres in oxidative enzyme preparations.

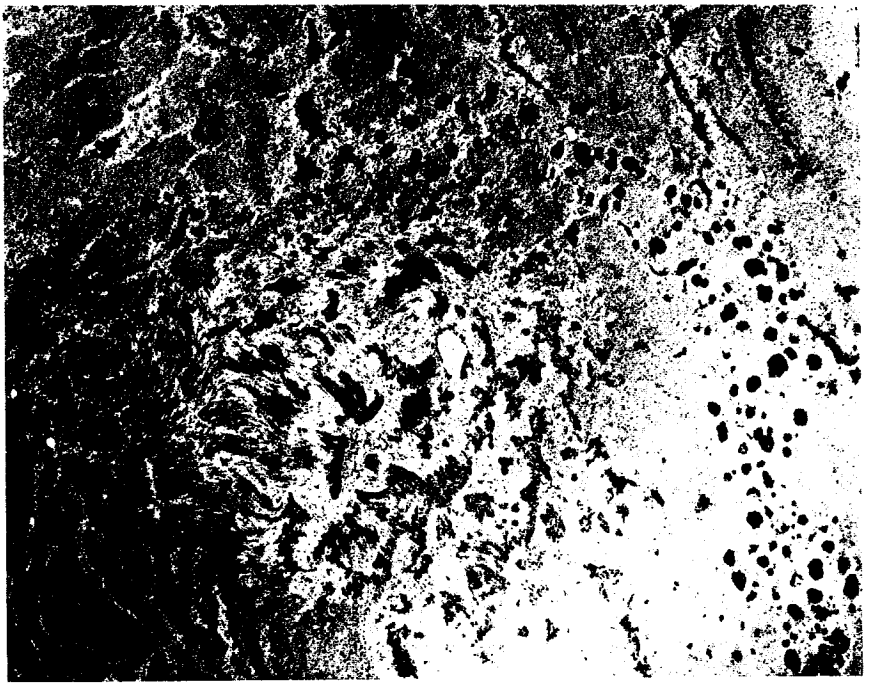

Figure 1. Cross section of central core in ankylosing spondylitis. There is a central area of disorganization of sarcomeres with thickening of the Z bands and absence of mitochondria. EM × 12000.

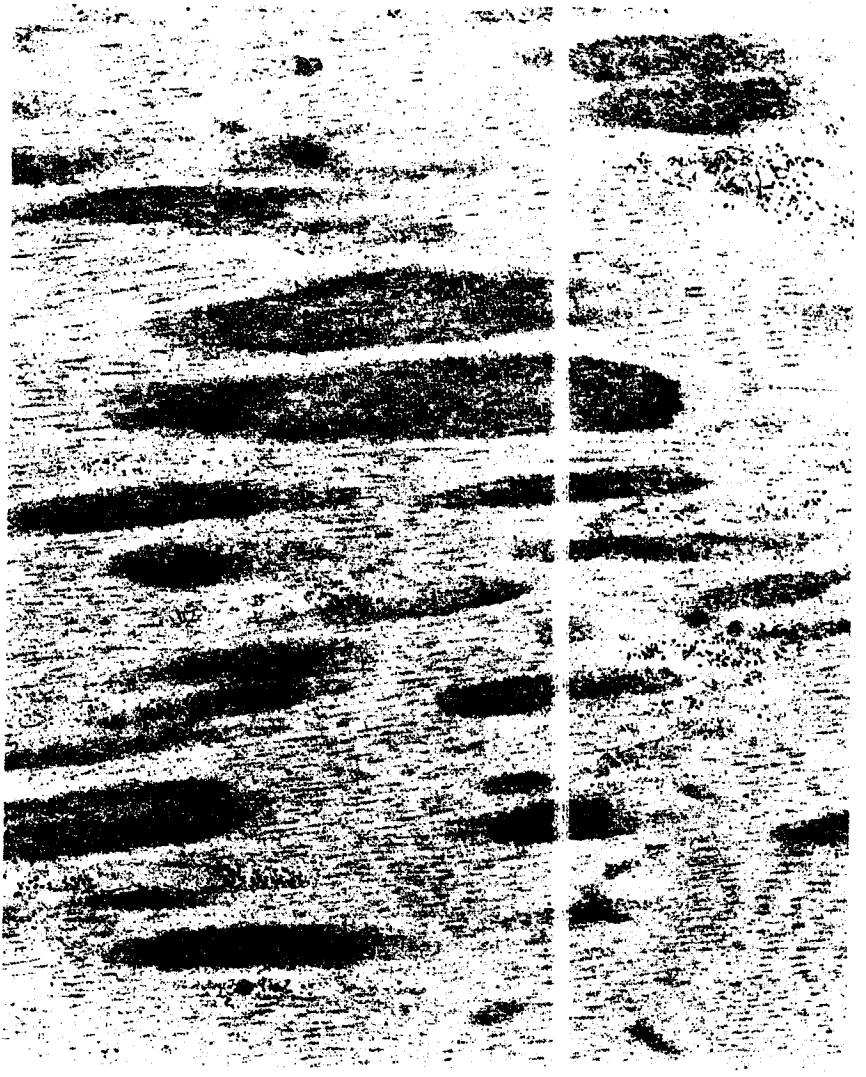

Figure 2. Rod body formation in ankylosing spondylitis. Note the dark-staining bodies which also show regular cross-banding and appear to arise from the Z lines. EM × 52 700.

Electron Microscopy

In 5 patients the erector spinae showed typical core-targetoid fibres (Figure 1), 3 of which were also associated with rod-body formation (Figure 2). One patient showed a filamentous inclusion, 1 showed Z band streaming, 2 showed simple

atrophy and 1 was normal. The most extensive ultrastructural abnormalities were present in those patients with the greatest degree of immobilization of the spine.

The core-targetoid fibres were typical, with loss of mitochondria and other organelles in the centre of the fibres in association with disarray of myofilaments and Z band streaming. All the cores were of the 'unstructured' type with the Z, A and I bands being out of register or in various degrees of disorganization. The nemaline rods were seen to arise from the abnormally thickened Z bands. In 1 patient the cores were small and numerous, being similar in appearance to minicores and multicores.

The findings are summarized in Table 1.

Discussion

The electron microscopic findings were quite remarkable and unexpected since only a few changes were observed with light microscopy and histochemistry. There were only 4 patients with possible target or 'moth-eaten' fibres in the histochemical preparations but 6 showed significant EM changes.

When first described, rod (nemaline) bodies were considered to be pathognomonic for a congenital myopathy characterized by generalized hypoplasia of muscles and nemaline rod formation. Clinically, these patients suffered from slowly progressive or non-progressive muscle weakness and some had Marfanoid features.

Table 1. Clinical and pathological findings

Case	Biopsy	Age (years)	Light microscopy	Histochemistry*†	Electron microscopy
1	X86/28	62	XS variation in size and shape with slight atrophy	I > II Target fibres	Core-targetoid fibres and nemaline bodies.
2	X86/29	44	"	I > II	Z band streaming
3	X86/39	32	"	– 'Moth-eaten' fibres	Core-targetoid fibres and nemaline bodies
4	X86/42	34	"	I >> II	Atrophy
5	X86/43	29	Minimal changes.	I > II	Filamentous inclusion
6	X86/70	49	XS variation in size and shape with slight atrophy	–	Core-targetoid fibres
7	X86/97	33	"	I > II	Core-targetoid fibres and minicores
8	X86/98	37	Minimal changes	I > II 'Moth-eaten' fibres	Normal
9	X86/118	43	Myopathic changes	I >> II Target fibres	Central cores and nemaline bodies in AS
10	X86/119	39	Minimal changes	I > II	Atrophy

*– =specimen too small for quantification. †I > II = Histochemical type I fibre predominance (normal for erector spinae).

It was later shown that rod bodies could also be found non-specifically in polymyositis and, rarely, in muscular dystrophy or other myopathies. The congenital 'muscle fibre disproportion' myopathy may also contain small numbers of rods. Similarly, central cores were at first believed to be the primary lesion of a congenital myopathy which was again characterized by congenital hypotonia, weakness and muscle underdevelopment and designated 'central-core disease'.

It also became known with the development and wider use of muscle histochemistry that target fibres were common in chronic denervation, especially in larger histochemical type I fibres. It was later appreciated that target fibres were more abundant in patients recovering from denervation so that the change was considered more likely to be due to reinnervation.

The significance of these changes became even more difficult to interpret when it was discovered that tenotomy[5,6] also caused very similar changes. It is of great interest that the experimental production of nemaline rods and core-targetoid, minicore, and multicore fibres by tenotomy requires the nerve supply to be intact. In experimental controls it was shown that division of the nerve resulted in simple atrophy without the appearance of such distinctive ultrastructural changes.

The findings in the paraspinal muscles in AS, showing features in common with the congenital myopathies on the one hand, and reinnervation or experimental tenotomy on the other, adds a new dimension to myopathology.

Other unusual reactions of the paraspinal muscles are known. For instance, patients with idiopathic scoliosis have shown virus-like particles. These were later considered to be due to glycogen.[8] Whether this finding points to unusual properties of the paraspinal muscles or is a mere coincidence is yet to be determined.

It is pertinent that the degree of ultrastructural disorganization in our patients correlated with the degree of severity of the disease and thus, presumably, with the degree of immobility. Similar electron microscopic changes do not occur in other diseases within the rheumatic group. Type II fibre atrophy and focal myositis are the recognized changes of rheumatoid arthritis. Otherwise there may be group atrophy due to denervation when peripheral neuropathy is associated with rheumatoid arthritis. However, rod bodies and core-targetoid or minicore changes are not reported.

We suggest that the unusual ultrastructural changes in AS are the result of a disordered metabolic process which has something in common with the mechanisms responsible for similar electron microscopic lesions in experimental tenotomy. It is probable that tension provides the normal stimulus for expression of genes responsible for the organization of sarcomeres and when the tension is absent the controlling mechanisms go awry. It is well known that tension is a necessary factor for the maintenance of normal structure and function of muscle and, even when denervated, tension may stimulate muscle hyperplasia.[9]

It is postulated that as a result of the reduced spinal mobility (even to the extent of complete ankylosis with no joint movement whatever) AS produces an effect equivalent to tenotomy. That is to say the repeated daily stretching of muscle, as part of normal joint movement, is lacking and regressive changes occur. However, because of the lack of lysosomes or other electron microscopic evidence

of necrosis, it is more likely that the disarray of sarcomeres, rod bodies, Z line streaming and other changes are the result of abnormal synthesis rather than being due to simple breakdown of myofilaments.

In addition to providing information important in AS, the muscle lesions reported here provide a further demonstration of the relative non-specificity of histochemical or ultrastructural changes in muscle biopsy diagnosis.

Summary

Minicore, multicore, core-targetoid and other ultrastructural lesions were found in the paraspinal muscles of patients with AS. The 10 patients studied, all men with AS, showed varying degrees of muscle fibre atrophy, Z band streaming, rod body formation, minicores, multicores and core-targetoid fibres. Central core disease, rod body myopathy, minicore and multicore diseases are recognized clinical entities within the congenital group of structural myopathies. Target fibres are believed to be a feature of reinnervation. It is also known that experimental tenotomy causes core-targetoid changes, rod bodies, minicores and multicores. Therefore, it seems possible that tension is a necessary stimulus for the correct programming of synthetic muscle enzymes, and without this disorganization occurs. It may also be assumed, but in this case for genetic reasons, that similar biochemical systems are disturbed in the group of congenital myopathies.

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The Pyriformis Syndrome: Review and Case Presentation

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The 'pyriformis syndrome' is a rare entrapment neuropathy in which the sciatic nerve is compromised by the pyriformis muscle. Attention was first drawn to this condition by Yeoman[1] when he stated that 'insufficient attention has been paid to the role of the pyriformis in the causation of sciatica'. The issue was investigated further and defined 50 years ago by Freiberg and Vinke[2] who conducted extensive anatomical studies and found a close relationship between the pyriformis muscle and sciatic nerve, noting that in 10% of cadavers the sciatic nerve passed through the pyriformis muscle. Freiberg of Cincinatti[3] complained that 'an orthopaedic surgeon is likely to see a patient with sciatic pain only after he has run the gamut of physicians, spas, cultists and downright quacks'. He was the first to suggest surgical treatment for this condition, while Thiele[4] was in favour of massage of the pelvic muscles involved through the anal canal. Robinson in 1947[5] also favoured surgical treatment and described two patients in whom he transected the pyriformis muscle and who recovered completely. As Kopel and Thompson[6] noted, 'The reason that the syndrome fell from grace was no doubt the improper selection of cases for surgery or the failure to exclude other bases for a clinical sciatica'. Indeed, over-diagnosis eventually led some neurologists and neurophysiologists to doubt whether the syndrome existed at all. Variations in the relationship between the sciatic nerve and pyriformis muscle are not uncommon;[7] the whole nerve passes through the muscle in 0.8%, the peroneal division alone passes through the muscle in 7.1% and in about 1% of subjects the nerve travels over the muscle. Similar findings were reported by Pecina.[8] These variations are shown in Figure 1.[9]

The pyriformis syndrome is often referred to in the literature as the sciatic notch syndrome, and this disorder has been discussed in more recent literature.[10–15]

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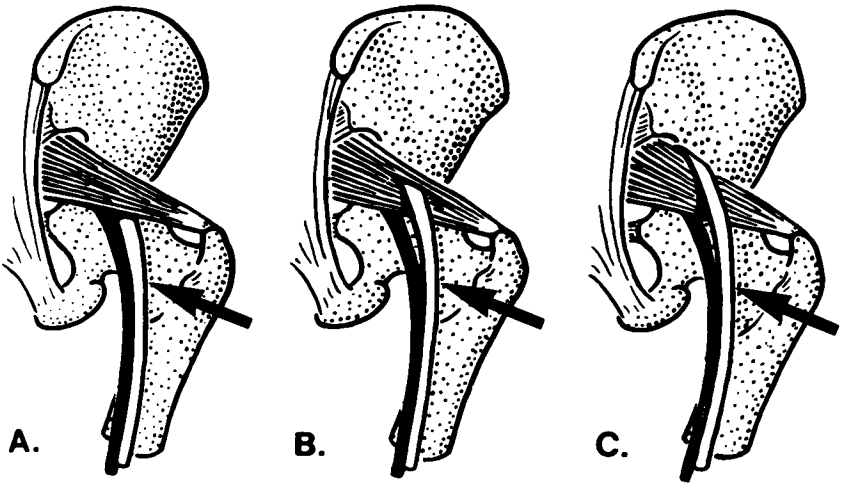


Figure 1. Diagram illustrating the relationship of the sciatic nerve to the pyriformis muscle. (a) In most cases it passes inferior to the muscle. (b) In 10% to 12% of cases the sciatic nerve divides before entering the gluteal region and the common peroneal nerve passes through the muscle. (c) In 0.5% of cases the common peroneal division passes superior to the muscle (arrows). Reprinted with kind permission from Moore KL. Clinically oriented anatomy. Baltimore: Williams & Wilkins, 1980.

Symptoms may be triggered by blunt injury to the buttock region, particularly by a fall in the sitting position, when a sudden upward pressure can injure the sciatic nerve by pulling it against the sciatic notch which has a relatively sharp edge. Hip flexion with compensatory lordosis may approximate the nerve to the edge of the sciatic notch. This can occur after episodes of prolonged stooping, sitting and squatting. Compression resulting from wound scars, injections, gluteal abscesses, heterotopic endometriosis, spasm, hypertrophy or contracture can also cause focal compression of the sciatic nerve at this site.

The clinical presentation consists of pain or paraesthesia extending to the hip and the back of the thigh as in sciatica. Women may experience dyspareunia. Symptoms are more commonly unilateral and are associated with limping and pain increased by prolonged walking. On physical examination the pyriformis muscle is tender, particularly on palpation through the rectum or vagina. There is weakness on voluntary abduction and external rotation of the thigh. There is no tenderness or limitation of movement in the lumbar spine and the patients are able to bend forward with extended knees. Straight leg raising may be restricted and there is usually some atrophy in the gluteus maximus with sparing of the tensor fasciae latae and gluteus medius and minimus muscles. The disparity of involvement of the glutei is due to the fact that the inferior gluteal nerve supplying the gluteus maximus muscle takes part in the entrapment syndrome. There is a variable degree of weakness and atrophy involving the hamstring and peroneal nerve innervated muscles, while muscles innervated by the posterior tibial nerve are less affected.

The ankle jerks may be preserved. There is usually hypoaesthesia or dysaesthesia in the whole sciatic nerve distribution.

Clinical diagnosis is assisted significantly by the EMG findings which show a normal EMG pattern in the paravertebral lumbar muscles, tensor fasciae latae, and gluteus medius and minimus, while there is variable chronic partial denervation in the gluteus maximus, hamstrings and peroneal innervated muscles. The posterior tibial nerve innervated muscles are less affected. Nerve conduction studies are usually within normal limits apart from delayed F waves and H reflexes. A computerized tomography (CT) scan of the pelvis gave evidence of heterotopic endometriosis in one reported case.[16] Examination of cerebrospinal fluid and myelogram reveal no abnormalities.

In the differential diagnosis, lumbosacral radiculopathy, spinal stenosis, lesions primarily involving the sacroiliac or hip joints, coccygodynia, ischio-gluteal bursitis and gout should be considered.

Initial enthusiasm for surgical treatment, suggested in the early reports from Freiberg and Robinson, is still maintained.[3,5] The surgery consists of division or section of the pyriformis muscle and leads to a minor motor deficit only. Very few patients, however, require surgical treatment.[17] Conservative treatments rely on improved anatomical relationships in the region produced by support or exercise, and on the use of anti-inflammatory drugs. Pace and Nagle[12] suggested the injection of local anaesthetic in the pyriformis muscle, which should result in a decrease in pain without anaesthesia of the sciatic nerve. If the pyriformis muscle is correctly identified and the needle is outside sciatic nerve territory, corticosteroids may be injected.

Case Report

A previously fit and healthy woman, aged 42 years, presented in mid-1979. She complained of tingling in the left lower leg, particularly in the big toe, which started after a blunt injury to the left buttock. Over the previous 18 months she had also noticed an ache in the left sciatic distribution aggravated by bending forward. There was no history of other illnesses. She had been a competitive squash player. Significant wasting and weakness of the left gluteus maximus muscle and minor weakness in the hamstrings and foot extensors were found. The flexors appeared normal. A diagnosis of a left pyriformis or sciatic notch syndrome was suggested after she was seen at an EMG clinic. To exclude other possibilities she was admitted for myelogram in 1981, three years after the onset of symptoms. At that time power in her arms and right lower limb was normal. There was grade 4 power[18] of hip flexion and abduction on the left and of plantar flexion of left foot, while knee flexion, hip abduction and rotation and dorsiflexion of the left foot were all grade 3.[18] The knee jerks were symmetrical, the left ankle jerk was sluggish, while the left thigh was 2.5 cm and the left calf 1.5 cm smaller in circumference than the right. Sensation was diminished for pin-prick on the left posterior thigh, left posterior calf and sole of the left foot. Rectal and bimanual pelvic examinations were normal. Straight leg raising on the left was painful from 60 degrees of hip flexion. No abnormality was found on testing the lumbar and cervical spine. Lhermitte's test was negative. There were no significant changes in objective signs over the five years of follow-up. Complete blood count, routine biochemical analysis of CSF, and x-ray examination of pelvis, thoracic and lumbar spine were all normal. A thoraco-lumbosacral myelogram (17 mL 'Amipaque') showed good delineation of the lower thoracic and lumbar subarachnoid space, with filling of all of the lumbo-sacral root sheaths; the distal spinal cord and the conus region were also normal. No evidence of a retroabdominal mass lesion was found on abdominal ultrasound.

Neurophysiological Investigations

Electromyography (EMG) was performed three times: when the diagnosis was established in 1979, again in 1981 and finally in 1984. The EMG pattern did not change significantly over the 5 years and in particular there was no progressive loss of motor units in the affected area. Detailed EMG investigations of the right lower limb as well as of the left lumbosacral paraspinal muscles bilaterally, the left gluteus medius, gluteus minimus, tensor fasciae latae and muscles in the territories of supply of the left femoral and obturator nerves were all normal. EMG of the left gluteus maximus, hamstrings and muscles in the left peroneal nerve territory showed a small amount of fibrillation. During voluntary effort there was a moderate loss of active units, which were all polyphasic with prolonged durations, amplitudes of 3–6 mV and low firing rates. The muscles in the left posterior tibial nerve distribution showed only a few abnormally large polyphasic units while some units were normal. All EMG abnormalities were thus confined to a level below the left sciatic notch in the distributions of the left inferior gluteal and sciatic nerves, with major involvement of the nerve to the hamstrings and the peroneal division.

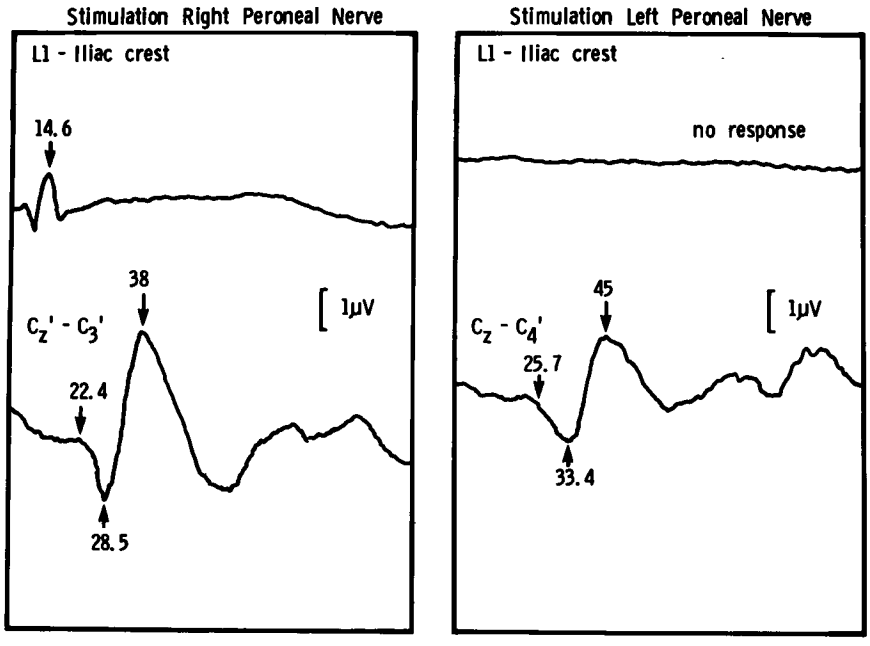
Motor and sensory nerve conduction velocities in the unaffected right lower limb were normal. On the left, the following abnormalities were found: peroneal nerve motor conduction velocity was 40 m/s (right 47 m/s), posterior tibial 38 m/s (right 46 m/s), left superficial peroneal nerve 41 m/s (right 49 m/s), sural nerve 27 m/s (right 48 m/s), and latency of H reflex on the left 36 ms (29 ms on the right).

Somatosensory Evoked Potentials (SEPs)

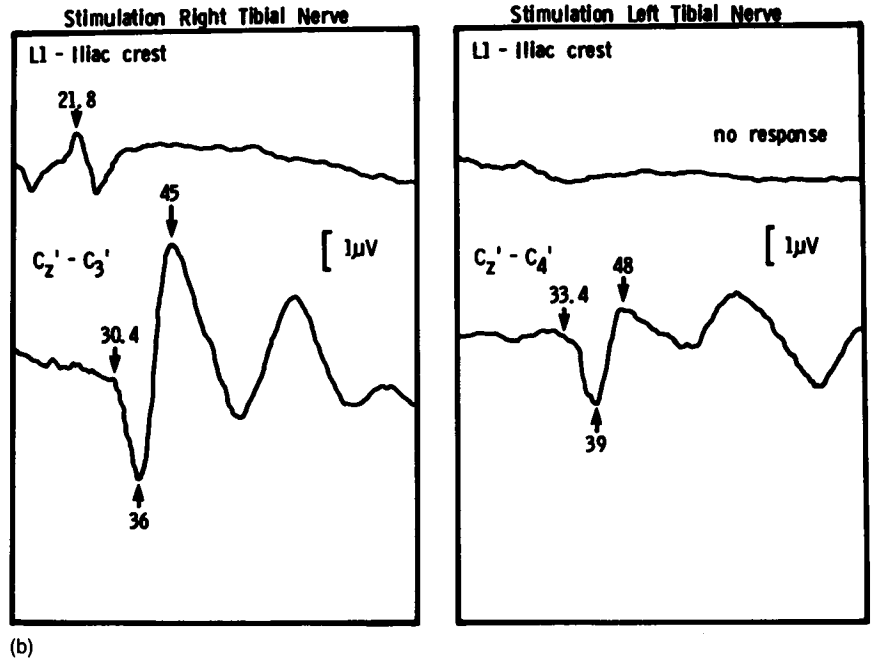
The peroneal nerves were stimulated at the knee and the tibial nerves medial to the ankle according to the technique reported previously.[19,20] The nerves were stimulated electrically at a rate of 1.9 per second and the stimulus level was adjusted to produce a visible twitch in the relevant muscles. Evoked potentials were recorded from the first lumbar vertebra (reference – contralateral anterior iliac crest) and from scalp electrodes 2 cm posterior to C_z referred to C_3, C_4 respectively (10–20 international electrode system). Five hundred responses were averaged twice and superimposed to ensure reproducibility. Cortical evoked potentials after stimulation of the peroneal and tibial nerves on the left were delayed, more so after peroneal nerve stimulation. They were also attenuated in amplitude when compared with the opposite (right) side. No potentials were recorded at the lumbar area (Figure 2a,b). All specialists involved in the case agreed about the diagnosis of pyriformis syndrome.

Since the diagnosis was established in 1979 the problem has been repeatedly discussed with this intelligent woman. As the wasting did not progress over the years, she did not develop further limitations to her lifestyle and the EMG abnormalities remained stable, she declined surgery. She takes analgesics for pain, and is able to maintain her occupation.

Figure 2. (a) SEPs after stimulation of the peroneal nerves at the knee with recordings from lumbar and contralateral scalp area. In the box on the left are SEPs after stimulation of the non-affected right side: the potentials at the level of the first lumbar vertebra and contralateral scalp are normal both in amplitude and latency. In the box on the right are SEPs after stimulation of the peroneal nerve on the affected side. The potential is absent at the level of the first lumbar vertebra and the first positivity from the contralateral scalp is delayed by 4.9 ms. (b) SEPs after stimulation of the tibial nerve at the ankle from the unaffected side (left box) are normal. After stimulation of the left posterior tibial nerve (right box) no reproducible potential was present at the level of first lumbar vertebra and the cortical potentials were attenuated with the first positivity delayed by 3 ms, when compared with the opposite side. The figures indicate latencies in ms after the stimulus. Negativity is upwards, positivity downwards, and all traces start 4 ms after onset of the stimulus.


Stimulation Right Peroneal Nerve
L1 - Iliac crest
14.6
38
$C_z' - C_3'$
1μV
22.4
28.5
Stimulation Left Peroneal Nerve
L1 - Iliac crest
no response
45
$C_z - C_4'$
1μV
25.7
33.4

(a)


Stimulation Right Tibial Nerve
L1 - Iliac crest
21.8
45
$C_z' - C_3'$
1μV
30.4
36
Stimulation Left Tibial Nerve
L1 - Iliac crest
no response
$C_z' - C_4'$
1μV
48
33.4
39

(b)

Discussion

The clinical presentation and neurophysiological investigations were typical of the pyriformis syndrome. The patient presented with pain in the sciatic nerve distribution after blunt injury to the buttock and the pain was aggravated by bending forward. She had a sedentary occupation as an accountant and could have aggravated the symptoms and signs by prolonged pressure on the sciatic nerve while working. The sciatic notch area was painful to palpation. There was striking wasting of the gluteus maximus muscle with minor wasting in the hamstring and in the left peroneal nerve distribution. Abduction against resistance caused maximal pain. There was hypoaesthesia in the distributions of the posterior cutaneous nerve of the thigh and of the sural nerve and in the plantar nerve divisions. The symptoms had progressed initially, before she was seen, but later became stable. X-ray examination of the pelvis and thoraco-lumbar spine, myelogram, abdominal ultrasound examination and CSF analysis were normal and there was no associated somatic illness. EMG findings were of great diagnostic value and showed evidence of a chronic partial neurogenic lesion particularly affecting the gluteus maximus, the hamstrings and the peroneal nerve innervated muscles, while changes in the tibial nerve distribution were mild. This correlates with the fact that peroneal division is much more often compromised by the pyriformis muscle than the rest of the sciatic nerve. There was a minor delay in the H reflex and both sensory and motor nerve conduction velocities were slowed on the affected side. These delays *per se* are not diagnostic and similar changes could have been caused by compression of lumbosacral roots.

We have previously shown the importance of somatosensory evoked potential investigations in the diagnosis of proximal nerve lesions in the lower limbs.[19–21] In this patient the evoked potentials after peroneal and tibial nerve stimulation of the affected side were absent in the lumbar area, while potentials recorded from the scalp were delayed, more so after peroneal nerve stimulation. This again raised the possibility that the peroneal nerve fibres were more severely compromised than those from the tibial nerve. However, similar changes could have occurred in lumbosacral root lesions and therefore SEPs were supportive but not diagnostic. As the patient has refused operative treatment and did not show deterioration over the years, it is possible that the pyriformis syndrome may, in some patients, arrest spontaneously, leaving an acceptable limitation of function. As Nakano suggested[17] surgical exposure of the sciatic notch for neurolysis is rarely necessary.

Summary

The pyriformis syndrome is a rare entrapment neuropathy in which the sciatic nerve is compromised by the pyriformis muscle or other local structures. It usually presents with sciatic pain and hypoaesthesia and a limp caused by weakness of the gluteus maximus muscle. Peroneal nerve innervated muscles and hamstrings are also usually affected. The diagnosis relies on the clinical presentation and the EMG

findings. Other causes of symptoms should be excluded by careful examination, detailed x-ray studies of the lumbosacral spine (including myelogram), sacro-iliac and hip joints. A case of this syndrome occurring in a previously healthy 42 year old woman and her follow-up investigations are reported.

Acknowledgements

I thank Dr B.J.L. Synek for helpful criticism.

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Clonic Perseveration

J.G.L. Morris and J. Leicester†*

The term 'perseveration' was first used by Neisser[1] to describe the behaviour of a delirious patient who repeatedly caused his eyes to converge, having been made to do so once during the course of a clinical examination. Since then the term has been used in different ways by different authors. For the purposes of this study perseveration is defined as a disturbance of behaviour which results in an inappropriate repetition or persistence of an action in response to a given stimulus. Liepmann[2] recognized three types of perseveration which he named intentional, clonic and tonic.

Intentional perseveration is the common type in which a previous response is repeated when, and only when, a new response is *intended* (hence the name). Thus one of Liepmann's patients, having correctly named a windowsill, used the same label for each new object he was shown. Wilson and Walshe[3] disliked the term 'intentional' as it implied that the patient behaved in this way on purpose. The term 'intention perseveration' would avoid this ambiguity. Luria[4] referred to this entity as 'inertia of a previously recorded programme of action'.

In clonic perseveration a response is repeated many times but is changed when a new response is appropriate. For example the patient may respond 'spoon, spoon, spoon, spoon' when shown a spoon and 'knife, knife, knife, knife, knife' when shown a knife. Liepmann observed it in writing and called it clonic perseveration to describe 'the alternating change between contraction and relaxation of the perseverated movement'. Luria referred to this entity as 'efferent perseveration'.

In tonic perseveration a muscle contraction, once initiated, cannot readily be terminated. Liepmann's patient was unable to throw away a used match. Wilson

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and Walshe,[3] preferring the term 'tonic innervation', described 3 cases in detail. One of their patients was unable to let go of a dumbbell with his left hand and most cases of tonic perseveration involve an inability to release the grip. This behaviour is now called the grasp reflex.[5] Such patients however may show sustained contraction of other muscles: Wilson and Walshe's third case, when asked to put out her tongue, kept it protruded 'as though she had forgotten it was out'.

In this paper we describe 2 patients with clonic perseveration following infarction of the midbrain and thalamus. In one patient perseveration was confined to movements by one side of the body. In the other patient the tendency to perseverate was evident in most activities including speech. Evidence is presented that in the second patient perseveration was, to some extent, under voluntary control. In discussing the mechanism of perseveration the case is made that psychological factors have been underestimated in the past.

Case Reports

Case 1

A 48 year old housewife was admitted to Westmead Hospital on 11 October 1983 following the abrupt onset of headache. Her spinal fluid was moderately bloodstained and 4 vessel angiography revealed a large aneurysm of the distal basilar artery. A CT scan showed the aneurysm but was otherwise normal. She had no abnormal neurological signs. On 28 October the aneurysm was clipped. Immediately after this she was observed to have bilateral third nerve palsies with fixed dilated pupils, complete ptosis and divergent squint. The ptosis in the left eye improved within a few days. There was cerebellar ataxia of the left arm and leg. She was mute but obeyed simple commands.

Ten days after the operation she began to make rhythmical movements of the right arm and leg. She ran her heel up and down the sheet until the heel bled. She repeatedly rubbed the sole of her left foot with the dorsum of her right foot. When her right arm was examined the leg movements ceased as she pursued the examiner's fingers with the right hand. At times she scratched her nose as though it was itching. Instead of ceasing this activity after a few moments she would continue it for minutes at a time, causing injury to her lips. Passive movement of the leg would initiate rhythmical movement of that limb. She had forced grasping and groping of the right hand. Perseveration was not observed on the left side of the body. A CT scan showed small bilateral thalamic infarcts.

The movements ceased after one month. She was left severely disabled with gross global amnesia.

Case 2

A 62 year old electrician was admitted to Westmead Hospital on 6 July 1984 with sudden onset of confusion and unsteadiness of gait. All movements of his eyes were lost apart from abduction of the left eye. The right pupil was fixed and dilated and there was a complete right ptosis. He was dysarthric and had a left homonymous hemianopia, left hemiparesis and ataxia of the right arm and leg. A cerebral CT scan showed areas of infarction in the right occipital lobe and right thalamus. He had a previous history of hypertension. His mental state had been normal before this illness.

One week after admission he began to make rhythmical movements of his limbs. He would spend much of the day noisily running his right heel up and down the sheet of the bed. If asked to stop the movement he would do so, although after a moment or two the movements would recur. The movements could be induced. If the examiner flexed the patient's right thumb he would repeat the movement for up to two minutes. Perseveration in the leg ceased when the patient's attention

was drawn to his hand. Repetitive movements could also be induced on the left side though these were not as well sustained, possibly because of the left hemiparesis.

He had little spontaneous speech. His replies to questions were relevant but he repeated them again and again. Asked why he did this he replied 'to make sure you heard, you heard, you heard'. When asked to recite the days of the week he did so, six times. His reading was interupted by perseveration: 'a boy had, a boy, a boy had dog, dog, dog, dog, dog, a boy had dog, a boy had dog'. Asked to poke his tongue out, he did so repeatedly.

He was asked to draw a circle, triangle, square and division sign in that sequence, three times. He was able to switch from one drawing to the next without difficulty but drew over the outline of each figure repeatedly. Offered 20 cents for each figure drawn just the once he repeated the task with almost no perseveration. At the end of the test he was paid. As he put the money in his pocket he said 'Thank you, thank you, thank you, thank you'.

Discussion

Wilson and Walshe[3] criticized the term 'clonic perseveration' on the grounds that clonus 'should be reserved for phenomena occurring in the lower levels of the nervous system'. While this criticism is valid, the term nevertheless vividly describes the most striking feature of perseveration in our patients, the rhythmical motion of the limbs. This motion has two features which clearly distinguish it from other abnormal movements with which it may be confused such as tremor, hemiballismus or focal fits (all of these terms had been used at one time or another to describe our patients). The first feature is that the movements can be induced. Thus the hand movements in Case 1 began when the patient scratched her nose. The movement which repeated itself was an echo of the initial movement. In both patients the movement could be initiated by passively moving the limb, the resulting movement always reflecting the initial movement. Even apparently spontaneous movements were probably induced on many occasions. The second feature is that the tendency to repeat an activity is not confined to limb movement but may also be seen in other activities such as speech, drawing, writing and tapping. Case 2 illustrates this well. In Case 1 the intellectual impairment and lack of speech precluded testing of these other functions.

There have been few detailed descriptions of clonic perseveration in the past. Bastian[6] described a sailor who painstakingly wrote long epistles which were unintelligible because letters or combinations of letters repeated themselves. In writing 'Royal Navy' for example he wrote 'ROYENDENDD NAVENDENDD'. Another word, which is unrecognizable, he wrote as 'Innmmmmmmnmmmmmmmmm'. A letter written by a patient of Hughlings Jackson[7] included the sentence 'I keep you first way in Newington Road the poor way is the best way is the best way for me is the best way for me is the best way for me is the best way the way is the best for me for ways kept for me for kept ways kept me for way kept for me'. Another of Jackson's[8] patients said only 'Jimmy Jimmy' or at other times 'Jim Jim'. These words were repeated inappropriately in every setting, almost all other language having been lost. A hospital inpatient of Von Solder,[9] asked to write down where he was, wrote '...Im Im Hossspitapatatal'.

Luria's Case 1[4] is the most carefully documented example of clonic perseveration in recent times. This was most evident in the patient's attempts to write, draw

simple diagrams and tap. It was not apparent in her speech. She had no difficulty changing response when a new task was set, in contrast to a second patient he described who had features of an intention perseveration. Luria emphasized the lack of spontaneous activity in these patients. Clonic perseveration was present in writing and tapping in the patient described by Shahani, Burrows and Whitty.[10] In this patient the most disabling feature, however, was the presence of forced grasping and groping in the right hand. Two similar cases were described by Goldberg, Mayer and Toglia[11] with perseveration again confined to the right side of the body.

Explanations of perseveration generally assume an abnormality in the physiological mechanism which causes the response of the brain to a given stimulus to terminate. This may be due to an abnormally strong[9] or long[2] response to the first stimulus. It may also be due to a lessening in the intensity of the response to subsequent stimuli, perhaps because of a defect in attention.[12,13] Goldstein[14] believed that the threshold for excitation is raised but, once breached, the breaching excitation spreads abnormally and lasts unduly, leading to perseveration. Symonds[15] agreed with this proposition. Werner[16] wrote that intentional perseveration is probably due to functional isolation of sensorimotor activity so that it repeats itself no matter how incongruous it is. Luria[4] believed that intention perseveration is due to pathological inertia of a previously recorded programme of action so the patient is unable to switch tasks. Freeman and Gathercole[17] wrote that clonic and intention perseveration are release phenomena occurring when inhibitory influences are in abeyance. Allison and Hurwitz[18] discussed the possibility of a physiological block in transmission between subcortical and cortical level.

The underlying theme in all of these explanations of perseveration is the presence of unduly prolonged excitation of neuronal pathways. Such a process may well explain perseveration in some cases. Forced grasping associated with tonic perseveration is best explained on this basis, that is, the release of a cutaneous spinal reflex from cortical inhibition.[10] The patient is unable to suppress the activity and indeed may use the other unaffected hand to control the offending hand.[11] The latency of the grasp reflex is consistent with it being a spinal reflex and there is a well established association between the presence of this reflex and lesions of the medial frontal cortex.[11]

No such clear-cut association exists between the site of lesions of the brain and clonic perseveration. Luria's Case 1 had a massive meningioma of the olfactory groove, Von Solder's case had delirium, Freeman and Gathercole[17] have seen it in dementia and schizophrenia while our cases had upper basilar–posterior cerebral artery strokes. Intention perseveration similarly has been described in frontal lobe lesions,[4,13] parietal lesions[19] and in lesions of the posterior third of the brain.[2] Indeed perseveration is readily detected in most healthy children and in the elderly[18] when the task which is set is difficult or the subjects become tired.

A different approach to the mechanism of perseveration was offered by Leicester *et al.*[20] They studied the errors aphasic patients made in performing 'matching to sample' tasks. Intention perseveration was a common type of error. In many cases it was possible to demonstrate that the patient was repeating a previous-

ly correct and reinforced response. One such patient, asked to match auditory digit-name samples to visual digit choices, responded:

Sample	nine	four	eight	three	seven	five	one	nine	two
Response	7	2	7	3 (rewarded)	3	3	3	3	3

Another cause of perseveration in these patients resulted from them responding to irrelevant stimulus parameters (such as the colour or shape of the board on which the numbers were written). In these patients it was demonstrated that perseveration was a voluntary response to a difficult task. There was no need to invoke the concept of persisting neuronal excitation to explain the phenomenon; rather, it was the consequence of the laws of normal stimulus–response behaviour.

It seems likely that perseveration is the end result of a number of different processes, as follows.

(i) Restriction in the diversity of activities of which the patient is capable. The patient of Hughlings Jackson who repeated the words 'Jimmy Jimmy' in all situations had lost all other speech. What little he could say he did say. If the words had no meaning in themselves they at least allowed him to express his feelings by varying the intonation. As Hughlings Jackson put it 'the patient "sings" his recurring utterance'. Perseveration is also common in less severe forms of dysphasia.[18] It seems likely that the more restricted the patient's vocabulary the more likely he is to repeat words or phrases. Such a mechanism might also explain motor perseveration. Both patients of Luria[4] had very large frontal lesions. They had little spontaneous movement and what they could do was severely limited. It is not perhaps surprising therefore that they tended to repeat the few actions of which they were capable. Such a mechanism could not, on its own, explain perseveration for it is not seen in patients with restriction of movement due to diseases of the spinal cord or peripheral nervous system.

(ii) Loss of memory. A characteristic feature of transient global amnesia is the tendency of the patient to repeat questions, for example Q. 'What day is it – Monday?' A. 'No it is not Monday, it is Wednesday'. Q. 'Did I go to tennis?' A. 'No you did not go, it was raining'. Pause. Q. 'What day is it – Monday?' and so on. Sequences like this may be repeated many times. The patient repeats herself because her question remains unanswered, the answer having been forgotten within a few seconds.

The conversation of patients with Korsakoff's psychosis is often littered with recurring names or pieces of information. Here the patient appears to fill the gaps in conversation resulting from loss of short term memory with items from the long term stores. A striking feature of our Case 1, when the patient recovered sufficiently to be able to speak, was a gross loss of immediate and short term memory.

(iii) Difficulty of the task. Normal subjects who are fatigued or set tasks which are beyond them tend to perseverate. This is particularly true in the extremes of age. A brain-damaged patient set a task which would be easy for a normal subject may be in a similar position. Under these circumstances the patient may repeat a

response which was rewarded or pick on an irrelevant stimulus parameter. Perhaps the repetition is a displacement activity which relieves the stress resulting from being given a task which is too difficult.

It is difficult to determine the mechanism of perseveration in our patients. Both patients were restricted in what they could do with their limbs as a result of the stroke. Patient 1 had severe memory loss. By our interest in their movement disorder we may have unwittingly reinforced this behaviour. It is difficult to imagine that either patient derived satisfaction from the perseveration although neither seemed distressed by it. That patient 2 was able, under conditions of positive reinforcement, to abolish the perseveration supports the proposition that this behaviour was, at least to some extent, under voluntary control.

We suggest that, while tonic perseveration is best explained on the basis of persisting excitability of a neuronal pathway, clonic and intention perseveration are often the consequence of the laws of normal stimulus–response behaviour.

Summary

Two patients are described in whom clonic perseveration was observed following infarction of the midbrain and thalamus. In one patient perseveration was confined to movements of one side of the body and was associated with a grasp reflex on the same side. In the other patient perseveration occurred in movements of both sides of the body and involved drawing, writing and speech. It was possible to induce clonic perseveration in both patients by passive limb movements, a feature of this condition which has not been described previously. Evidence is presented that this type of perseveration is, to some extent, under voluntary control. It is suggested that the role of psychological factors in perseveration has been underestimated in the past.

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The Basis for Aspirin Dosage in Stroke Prevention

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In recent times there has been considerable interest in exploring the role of aspirin in the prevention of stroke and other forms of thrombo-embolic arterial disease. There is still much work to be done before the place of aspirin becomes clear. However at this stage it may be useful to assess what is known, and what still needs to be done.

The Use of Aspirin – Theoretical Basis

From the outset it must be made clear that the substance which is believed to be of benefit in certain types of stroke is aspirin (acetylsalicylic acid) itself, and not its hydrolysis product salicylic acid. Salicylate forms fairly readily from aspirin in an aqueous environment, and forms very readily within the animal body, where the hydrolysis of aspirin is catalysed by a variety of esterase enzymes. Until recently, salicylate and aspirin were taken as being more or less equivalent. Salicylate concentrations were measured and regarded as measures of aspirin concentrations. It is now clear, however, that aspirin possesses several very important actions which salicylate lacks. In what follows it is aspirin that is being discussed, unless salicylate is mentioned specifically.

Action of Aspirin on Platelets and Endothelium

There appear to be reasonable grounds for believing that platelet aggregation is an important factor in the mechanism of certain forms of stroke. Therefore

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aspirin, which has an antiplatelet action, has the potential to help in some stroke situations. Aspirin inhibits the enzyme cyclo-oxygenase (prostaglandin synthetase). The normal function of this enzyme is to catalyse the formation of prostaglandin endoperoxides from arachidonic acid. In platelets the endoperoxides serve as substrates for further chemical reactions which produce thromboxane A_2, a short-lived eicosanoid which is a potent vasoconstrictor and platelet aggregating factor. However in endothelium the endoperoxides are converted not to thromboxane A_2 but to prostacyclin (prostaglandin I_2), a powerful vasodilator and platelet anti-aggregatory factor. Thus aspirin inhibition of the conversion of arachidonate to endoperoxides will lead to essentially opposite effects in platelets (where there is loss of a vasoconstricting and pro-aggregatory potential) and in endothelium (where there is loss of a vasodilating and anti-aggregatory effect). Thus the potential benefit and disadvantage from the aspirin would appear to cancel each other out, and there would seem to be little net effect from using aspirin in the whole animal unless there were quantitative differences between the effects of the drug on platelets and on endothelium.

The inhibition of cyclo-oxygenase by aspirin (achieved by acetylating serine residues on the enzyme) appears to be irreversible. Therefore the effect of a single dose of aspirin will last until new enzyme is synthesized. Platelets, being non-nucleated cells, cannot form new enzyme, while endothelium, being nucleated, can. Therefore the effects of aspirin inhibition of platelet cyclo-oxygenase last for the life of the platelet (some 7 to 10 days), whereas the consequences of aspirin inhibition of endothelial cyclo-oxygenase begin to fade after some hours, as new cyclo-oxygenase forms. Thus, at least in theory, it is possible to obtain a differential

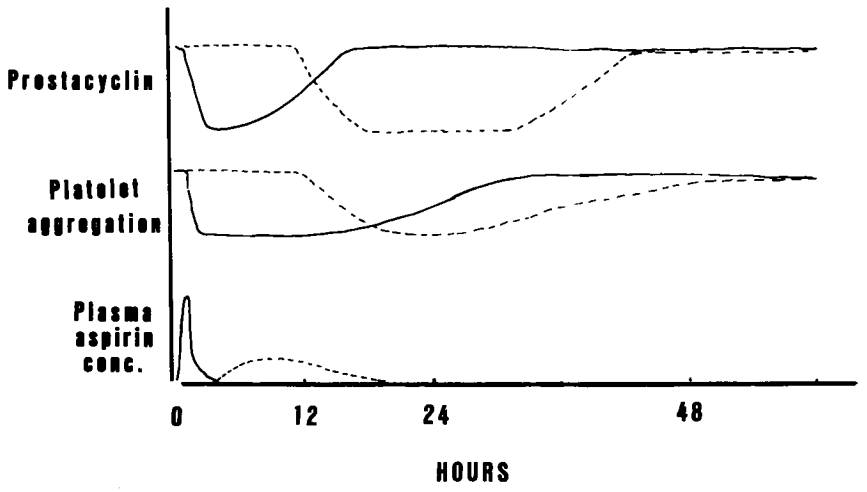

Figure 1. Predicted time courses of inhibition of endothelial prostacyclin formation and of platelet aggregation related to the time courses of plasma aspirin concentrations produced by giving oral aspirin in a brief pulse (solid line) and in a slow release form (dashed line).

platelet anti-aggregatory effect by using pulsed doses of aspirin given at as long an interval as possible. Such a differential effect would not be attained if aspirin were present continuously (Figure 1). Further, there have been reports that low doses of aspirin inhibit platelet cyclo-oxygenase more efficiently than they inhibit the endothelial enzyme.[1,2] However, findings to the contrary have also been published.[3]

The above considerations suggest that to obtain a relatively selective platelet anti-aggregatory effect with minimal impairment of endothelial prostacyclin function, *it would be best to give the minimum effective quantity of aspirin in a pulsed fashion, with the longest practicable interval between doses*. The rapid elimination of aspirin (half life 12–20 minutes) makes it very suitable for pulsed dosage. The aspirin should be absorbed as rapidly as possible from the preparation used because this will shorten the duration of the aspirin pulse and because it produces the highest aspirin concentrations relative to concentrations of salicylate formed from the aspirin. The latter consideration is relevant because salicylate competitively interferes with the action of aspirin on platelet cyclo-oxygenase.[4–6] Therefore low salicylate concentrations relative to aspirin concentrations early in the aspirin pulse are desirable.

The Role of Platelets in Stroke

The above theoretical arguments may define the most effective way of using aspirin to obtain a platelet anti-aggregatory effect, but of what value would this be in the various types of stroke?

It seems clear that the majority of carotid territory transient ischaemic attacks are due to platelet emboli arising from sites of internal carotid ulceration in the cervical portions of the arteries. Aspirin would appear to have potential in treating this situation. However, such transient ischaemic attacks themselves are completely reversible, and their effects are brief, though distressing. Their greater importance lies in their role in heralding more major embolism or thrombosis, affecting the cranial, coronary or other arterial circulations. What is the role of platelets in these latter situations? There would be some who would argue that initial platelet adhesion to areas of endothelium damaged by haemodynamic stresses or by atheroma is the precursor of much local mural thrombosis. If this is so, aspirin could play a preventive anti-thrombotic role. However, there may well be other mechanisms for instigating local thrombosis, just as there are other types of emboli apart from platelet aggregates which cause transient cerebral ischaemic attacks (including atheromatous debris, fibrin and cellular clot). Of course, aspirin would appear to have no immediate role in treating already established stroke.

It would be unrealistic to expect aspirin to prove universally efficacious in the prevention of stroke when some strokes may be due to mechanisms not involving platelets and when, as yet, there has been little experimental study of the biochemical basis for the use of aspirin in the platelets and endothelium of those who are prone to stroke.

The Use of Aspirin – Evidence of Clinical Efficacy

Even though there is insufficient background information to determine the most appropriate way to use aspirin in the prevention of stroke, clinical studies have been carried out to assess whether aspirin is useful in this role in practice.

Transient Ischaemic Attacks

There are oral reports, and occasional literature descriptions, of aspirin terminating series of transient ischaemic attacks.[7] Such accounts provide evidence of the platelet anti-aggregatory effectiveness of aspirin, but they do not provide evidence that aspirin will prevent stroke or other major arterial catastrophe.

Major Arterial Thrombo-embolism

Several major studies have been published which attempt to assess the efficacy of prophylactic aspirin in persons who have experienced transient cerebral ischaemic episodes (see review in ref. 8). Various criteria of success have been used including reduction in stroke rate, reduction in rate of other arterial vascular (commonly coronary) disasters and reduction in death rate. Although the largest of these studies, the Canadian Cooperative Study,[9] appeared to show at a statistically significant level of confidence a degree of protection against subsequent stroke in males, it is probably fair to say that the consensus from the published studies is that aspirin may be of some use but that this has not been demonstrated unequivocally, despite a great deal of effort.

The various studies have been criticized rather heavily as to several aspects of the experimental methods employed. They are also vulnerable to censure in that more recent knowledge (as discussed above) makes it likely that too high an aspirin dose was used in every study (perhaps a 5- to 10-fold excess of the drug). This, by inhibiting the formation of endothelial prostacyclin, may have denied aspirin the most favourable circumstances in which to show its capacities. Further, only a subgroup of the subjects studied may have had an arterial disease whose pathogenesis made it susceptible to a platelet anti-aggregatory effect. This subgroup would be difficult to define, though a start might be made by considering only those patients whose transient ischaemic attacks were due to platelet emboli (rather than other forms of emboli) or to haemodynamic factors.

Aspirin – Appropriate Use

Contemporary Use

Although there is little convincing evidence that aspirin can help to prevent stroke, the drug is being widely prescribed for this purpose in persons who have

already had strokes, and even in persons who have experienced almost any kind of episode which might suggest that they are at heightened risk of stroke. Aspirin is also beginning to be used by the asymptomatic but health-conscious as they approach the age when arterial disease starts to appear. The dose of aspirin used varies, although it is becoming lower as the medical profession becomes more aware of the theoretical basis for the use of aspirin in stroke prevention.

This widespread, even indiscriminate, use of an unproven therapy seems to have developed because doctors are very familiar with aspirin and regard it as relatively innocuous. In a situation where there is often little else to offer, the prescription of aspirin in (to the patient) an unexpectedly low dose is seen as providing some therapeutic action, little risk of harm, and some possibility of benefit at very little financial cost.

When Should Aspirin be Used?

Clearly the use of aspirin is justified in cerebral transient ischaemic attacks due to platelet emboli. Aspirin probably has no place in the therapy of ischaemic attacks of haemodynamic origin, or when attacks are due to embolism of atheromatous debris. Because platelet adhesion and aggregation may be the precursor of local intra-arterial thrombosis, a reasonable case can be made for aspirin prophylaxis in transient ischaemic attacks due to clot. When aspirin is used for transient ischaemic attacks the prescriber should realise that prevention of further episodes is not necessarily a guarantee of protection against subsequent major stroke or coronary thrombosis.

In many other types of cerebral arterial disease the use of aspirin can be seen only as a reasonably based act of faith, unlikely to be harmful but of dubious benefit. In some conditions, such as cardiogenic emboli, the use of aspirin is probably pointless and perhaps even contraindicated.

Appropriate Aspirin Dosage

The bioavailability of aspirin may differ between the various marketed preparations of the drug intended for oral use. Certainly there are very clear differences between the time courses of plasma aspirin concentrations after single doses of the drug given in soluble and in enteric-coated or sustained-release forms (Figure 2). Because of possible differences in bioavailability it would be useful to determine the threshold plasma aspirin concentration required to inhibit platelet aggregation, and to work back from this to the doses of different aspirin preparations. However, different plasma aspirin concentrations are required to inhibit platelet aggregation, depending on whether the drug enters the circulation in a single pulse or in a sustained mode. These differences arise because of the irreversible nature of the inhibition of platelet cyclo-oxygenase by aspirin. Because the inhibition of the enzyme will be cumulative, aspirin that keeps entering the circulation for some hours need not achieve as high a concentration in plasma to inhibit platelet aggregation as aspirin which enters the circulation in a brief aspirin pulse

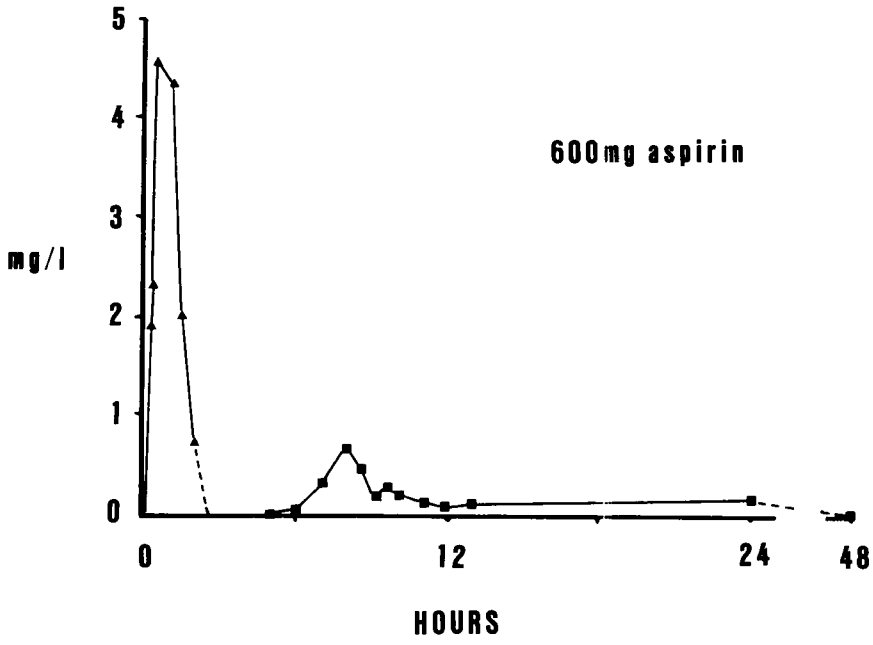

Figure 2. Time courses of plasma aspirin concentrations in the same subject given by mouth on separate occasions. Solid triangles represent administration of 600 mg of soluble aspirin; solid squares represent 600 mg of enteric-coated aspirin.

that is present only for an hour or so. However, as pointed out earlier, the brief pulse, if it attains a sufficient concentration just to inhibit platelet aggregation, minimizes the risk of endothelial cyclo-oxygenase inhibition and also shortens the duration of any inhibition that occurs. Therefore a pulsed threshold aspirin dose, with as long a dosage interval as feasible, appears to offer the best prospect for a selective antiplatelet effect. The threshold plasma aspirin concentration required to inhibit platelet aggregation varies depending on the method used to initiate the aggregation. The threshold is lower for arachidonate-induced aggregation than for adrenaline-, ADP- or collagen-induced aggregation. Arguing that a combination of aggregants (arachidonate, collagen and ADP) may be a more realistic model than any single aggregant for the situation in the floor of an atheromatous ulcer, we have found that the threshold peak plasma aspirin concentration required to inhibit platelet aggregation is around 1.2 mg per litre, if the aspirin is given in pulsed mode. An 80 to 100 mg dose of the soluble aspirin preparations used in the studies would suffice to produce such a plasma drug concentration. This dosage is similar to the range of aspirin doses (40–100 mg) found by others who have studied the effects of the drug on platelet aggregation without giving much attention to the associated plasma aspirin concentrations.

It should be plainly recognized that the above data apply only for platelet aggregation studied *ex vivo* after a single pulsed intake of aspirin in healthy

volunteers. The requisite plasma aspirin concentrations, doses and dosage intervals for optimal chronic aspirin therapy in stroke prevention have still to be worked out, first for normal subjects, and then for persons at heightened risk of arterial disease. The effects of these aspirin concentrations and dosage regimens on the production of endothelial prostacyclin have still to be determined, and to do that would raise some rather formidable technical and analytical problems.

Even when all that is done, one will only know the theoretically optimal aspirin regimen. This must then be tested in practice, and that will require a major therapeutic trial in a large group of carefully evaluated subjects. There is a long distance to go before we will really know when, and how, aspirin should be used in the prevention of stroke.

Summary

Many strokes are thought to develop as a consequence of platelet aggregation on areas of arterial endothelial damage, with subsequent embolism or thrombus formation. Aspirin prevents platelet adhesion and aggregation by inhibiting the formation of thromboxane A_2 by platelets. This suggests that aspirin could be used to prevent stroke. However aspirin also inhibits endothelial formation of the anti-aggregatory substance prostacyclin, though probably only in a slightly higher dose than that just capable of inhibiting platelet aggregation. Consequently, too high an aspirin dose may defeat its purpose. The effect of aspirin on platelets lasts for as long as they survive, whereas the effects of aspirin on endothelium are shorter.

Theoretical considerations suggest that aspirin, given in brief pulses just to reach platelet inhibitory concentrations in plasma, and administered at the maximum interval that will maintain inhibition of platelet aggregation, should offer the most favourable balance between altered platelet and altered endothelial function from the viewpoint of stroke prevention. Data are presented showing that rapid rather than slow or delayed release aspirin preparations are necessary to achieve suitable plasma aspirin concentration-time profiles in humans, and that a peak plasma aspirin concentration of around 1.2 mg/L is necessary *in vivo* to inhibit aggregability of previously untreated platelets.

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Cerebral Infarction due to Presumed Haemodynamic Factors in Ambulant Hypertensive Patients

G.D. McLaren and G. Danta†*

The role of haemodynamic factors in the pathogenesis of cerebral infarction is contentious. A recent review of stroke pathophysiology suggests that systemic haemodynamic factors rarely lead to cerebral infarction.[1] Pathological studies have provided evidence that most non-haemorrhagic strokes are caused by atheromatous thromboembolic disease,[1-3] and yet a meticulous clinical study, which employed extensive angiography, failed to explain the mechanism in 11% of cortical infarcts in the carotid territories.[4]

Meyer, Leiderman and Denny-Brown proposed in 1956 that systemic hypotension could produce focal neurological deficits in patients with cerebrovascular disease.[5] Using a tilt-table to induce postural hypotension, they produced EEG changes consistent with cerebral ischaemia in 21 of 23 patients with carotid insufficiency. Only 2 of the 23 patients developed cerebral symptoms when their mean systolic blood pressures were lowered by 25%. Later authors cast doubt on these findings and the haemodynamic theory fell into disrepute. Kendall and Marshall, in 1963, induced hypotension in 37 patients with cerebrovascular disease, lowering the mean systolic blood pressure by 58%.[6] The majority of their patients developed symptoms of global cerebral ischaemia before focal neurological deficits occurred. They concluded that hypotension was not a common cause of transient cerebral ischaemia. Yet over one-third of their patients who had previously suffered a major ischaemic episode developed global cerebral ischaemia when their systolic blood pressure was higher than 100 mmHg. Three of 14 patients in this group developed focal deficits when their systolic pressure was above 100 mmHg.

Watershed cerebral infarction, occurring in the border zone between 2 arterial perfusion beds, is invariably caused by haemodynamic factors. This situation can be

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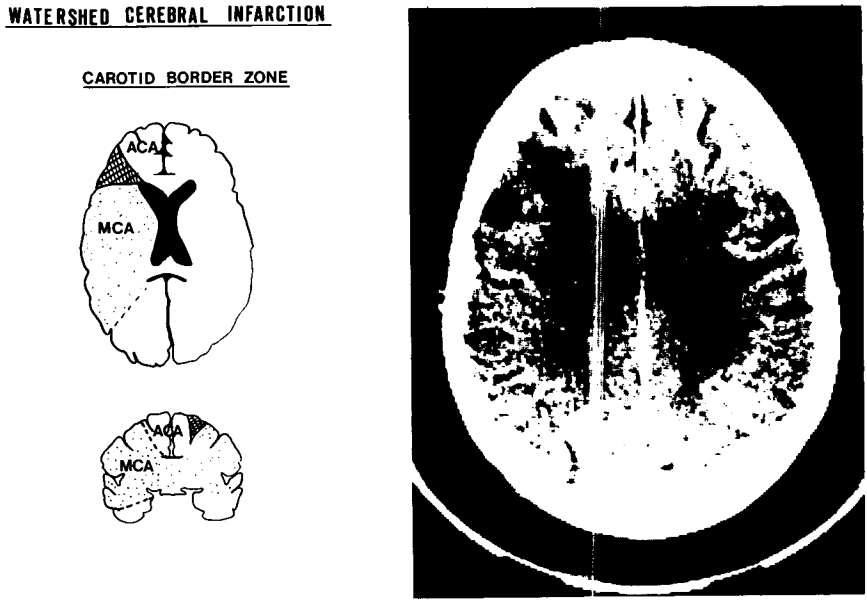

Figure 1. Diagram and CT scan of infarct in the watershed between the anterior and the middle cerebral arteries.

likened to the decrease in flow at the end of a long irrigation pipe when perfusion pressure falls. Distal field infarction, which occurs in the terminal zone of end-arteries, can also result from haemodynamic factors.

Watershed cerebral infarction is most commonly found in elderly patients after failure of cerebral perfusion. In pathological studies it is found after myocardial infarction, congestive heart failure, general surgery, blood loss or episodes of systemic hypotension.[7] In rare cases watershed infarction may be due to cholesterol or tumour microemboli which, because of their small size, pass to the distal parts of an arterial tree.[8] Platelet-fibrin emboli, by contrast, tend to cause infarction within the distribution of one major cerebral artery.[9,10] Internal carotid artery occlusion may produce watershed cerebral infarction, presumably by haemodynamic mechanisms.[11]

At autopsy 10% of all supratentorial cortical infarcts are located in watershed zones.[12] Common anatomical sites include the following:

(i) the middle frontal gyrus posteriorly, which is the carotid border zone of Romanul and is the watershed between the anterior and middle cerebral arteries (Figure 1),[13]

(ii) the parieto-occipital convexity, which is the border zone between the anterior, middle and posterior cerebral arteries (Figure 2),[14]

(iii) the cerebellum between the territories of the superior and the anterior and posterior inferior cerebellar arteries (Figure 3), and

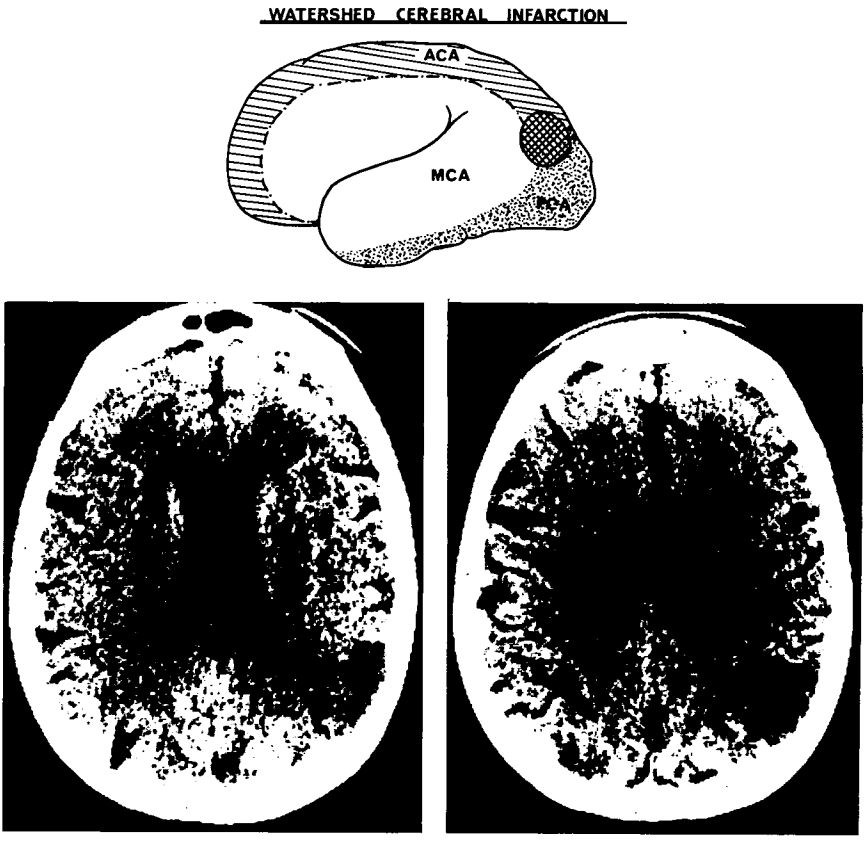

Figure 2. Diagram and CT scan of infarct in the border zone of the anterior, the middle, and the posterior cerebral arteries.

(iv) the head of the caudate nucleus, which is the watershed between the lenticulostriate and the pial branches of the middle cerebral artery.[15,16]

With the advent of CT scanning, watershed cerebral infarction can be diagnosed in stroke survivors.[17–20] Two cases of bilateral watershed infarction were reported following cardiac bypass surgery.[17] The authors concluded that traditionally accepted perfusion pressures during cardiopulmonary bypass did not always ensure adequate regional cerebral blood flow. There is no published study of watershed cerebral infarction occurring in ambulant hypertensive patients.

Patients and Methods

During the past 2 years we have seen 14 cases where systemic haemodynamic factors contributed to the pathogenesis of cerebral infarction in ambulant, treated

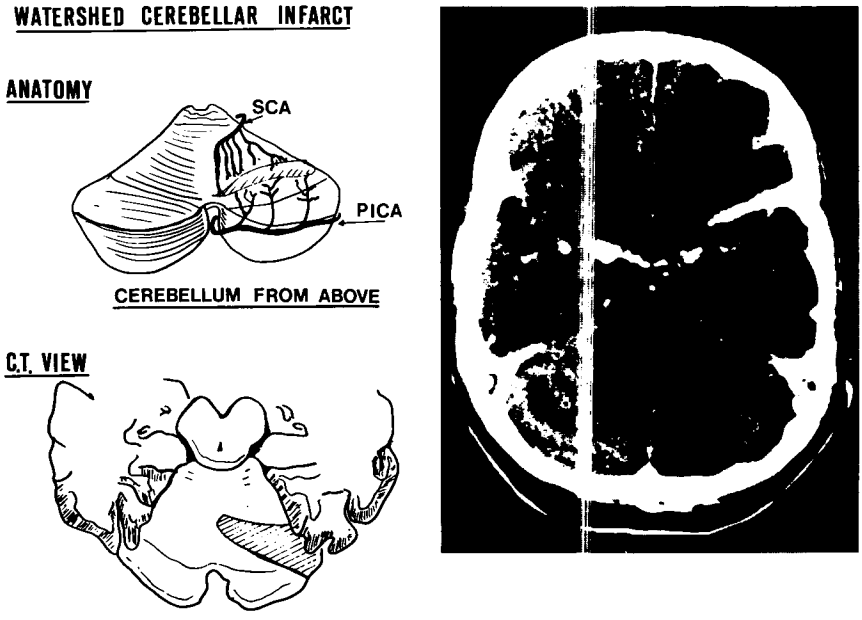

Figure 3. Diagram and CT scan of infarct in the watershed between the superior and anterior and posterior cerebellar arteries (bilateral in scan).

hypertensive patients. These patients comprise 10% of new stroke referrals to a regional rehabilitation unit during this period. Their ages ranged from 44 to 83 years, with a mean age of 68 years. Four patients were under 60 years of age. Twelve patients were women, and of these 9 were over 69 years of age. Six of these elderly women had a long history of labile hypertension.

All cases were selected on the basis of the clinical history. Posture-related or exercise-induced transient ischaemic attacks (TIAs) occurred in all patients before and in some cases after their stroke. In 8 patients these TIAs began when vasodilator medication was commenced or increased. In all cases posture-related TIAs ceased when vasodilator medication was discontinued. All patients described postural dizziness or syncopal attacks before their stroke. Few patients volunteered the postural nature of these symptoms. The majority attributed their symptoms to high blood pressure since the symptoms had commenced soon after hypertension was diagnosed and treatment started. Four patients suffered ischaemic neurological symptoms on bending forward, for example, while gardening. Many patients had difficulty walking back to bed from the toilet in the middle of the night.

Postural hypotension was noted on admission in all patients (Table 1). Postural falls in systolic blood pressure ranged from 15 mmHg to 100 mmHg with a mean of 29 mmHg. Four patients were able to walk short distances around the room on admission. Standing post-exercise blood pressures were between 30 mmHg and

Table 1. Basic patient data, blood pressures and medications on admission

Case no.	Sex	Age (years)	Duration of hypertension (years)	Blood pressures (mmHg)				Medication			
				Supine before stroke	Supine on admission	Postural systolic drop*	Postural systolic drop after exercise*†	Prazosin	Diuretic	Beta blocker	Other
Carotid territory infarcts											
1	F	44	2	130/80	110/80	15	–†	+	+	+	Antihistamine
2	F	58	1	130/70	140/90	30	–	+	+	+	
3	F	45	1	120/80	155/110	20	100	+	+	–	
4	F	79	10	150/90	150/90	15	–	–	+	+‡	
5	F	83	10	150/80	150/105	30	–	+	+	–	Methyldopa Nitrates
6	F	75	10	150/90	180/80	30	–	–	+	+‡	Phenytoin Quinidine
7	F	79	10	160/80	180/90	30	–	+	+	–	Nifedipine Nitrates
8	M	65	10	150/90	140/80	20	–	+	+	+	
Vertebrobasilar territory infarcts											
9	M	59	2	160/90	170/90	15	35	+	–	–	Digoxin
10	F	75	10	130/90	210/110	20	–	+	–	+‡	
11	F	72	10	160/90	160/90	35	55	+	+	+	
12	F	69	10	180/80	230/100	15	30	+	–	–	
13	F	71	10	170/90	240/120	40	–	+	+	–	
14	F	76	?	160/90	170/90	100	–	–	+	–	Imipramine
	Mean	68 years			Mean	29	Totals	11	11	7	

* On admission to Rehabilitation Unit. † Only 4 patients were able to walk short distances on admission to Rehabilitation Unit. ‡ Pindolol which acts as a vasodilator with chronic use.

Table 2. Sites of infarction

Watershed infarcts	
Anterior/middle cerebral arteries ('carotid border zone')	11
Anterior/middle/posterior cerebral arteries ('triple border zone')	0
Cerebellar watersheds	5
Deep hemispheric	1
Distal field infarcts	
Posterior inferior cerebellar artery	1
Posterior cerebral artery	4
Total	22

100 mmHg below supine systolic pressure. Supine systolic blood pressure was 110 mmHg or higher on admission in all patients.

Thirteen patients were taking vasodilator agents at the time of their stroke (Table 1). Eleven were receiving prazosin in daily doses ranging from 1 mg to 5 mg. Ten patients were taking vasodilator agents and a diuretic. Four were taking a combination of prazosin, diuretic and a beta blocker. Pindolol, in contrast to other beta blockers, acts as a vasodilator owing to its sympathomimetic action.[21] Postural hypotension was not related to the first dose effect of prazosin.

Following admission, vasodilator agents were ceased in all patients and other hypotensive drug doses were reduced. All patients improved significantly after cessation of medication and there were no immediate complications of drug withdrawal. Following rehabilitation, all patients except one were discharged to their own homes. One 83 year old woman with dyspraxia, right hemiparesis and macular degeneration required hostel placement.

Cerebral CT scans showed watershed or distal field infarction in 10 cases. The commonest site of infarction was the carotid border zone between the anterior and middle cerebral arteries (Table 2). One patient had a lateral medullary syndrome preceded by multiple episodes of posture-related vertebrobasilar TIAs. Three patients had clinical evidence of carotid border zone infarction but CT scans performed within the first 4 days were normal.

All cases were followed up at intervals of 3 to 27 months (mean 15 months). No patient had recurrence of posture-related or exercise-induced TIAs following cessation of vasodilator medication. Eight patients were in excellent health and had good neurological recovery. The 4 younger patients had returned to their previous occupations. Four elderly women remained disabled as a result of their strokes but continued to be in good health and to live at home. One 83 year old woman had developed resistant left ventricular failure and required nursing home placement because of visual impairment and dyspraxia. One 72 year old woman had sustained a further contralateral watershed cerebral infarct while taking diuretic and beta blocker therapy.

The following case history is representative.

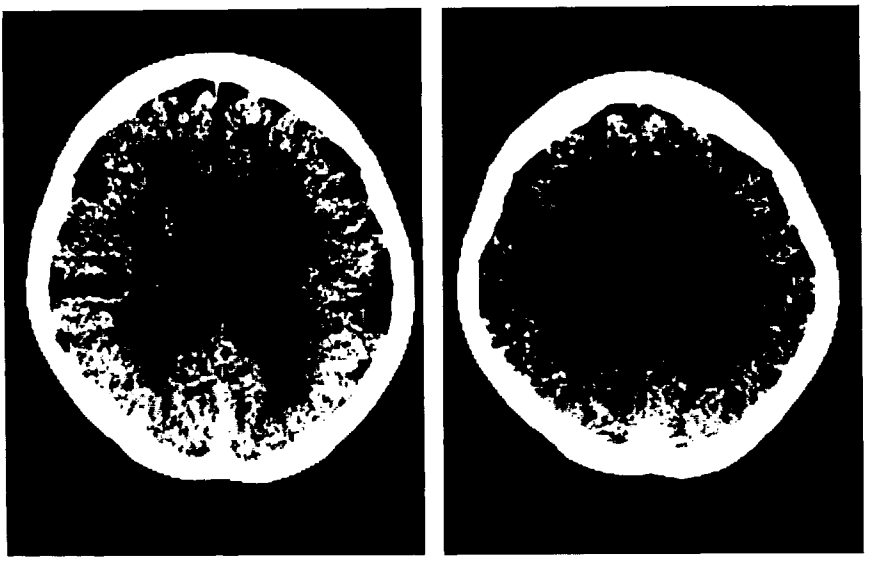

Figure 4. Normal CT scan 6 weeks before admission.

Case Report

A 75 year old woman presented with a stuttering right hemiparesis and dysphasia. Three months before admission she had experienced transient repetitive, stereotyped episodes of dysphasia associated with right hand weakness. These episodes always occurred while she was standing or sitting and were relieved by lying flat. A cerebral CT scan 6 weeks before admission showed no abnormalities (Figure 4). She was unable to care for herself and was admitted to the rehabilitation unit for nursing home placement.

Her hypertension had been treated for over 10 years. Three years before admission she had suffered an extensive anteroseptal myocardial infarct. Subsequent echocardiography revealed no evidence of left ventricular aneurysm.

At admission, while sitting, she was drowsy to the point of falling asleep. When laid supine she became more lucid. There was a right hemiparesis with non-fluent dysphasia. She was unable to stand unsupported. While she was sitting both plantar responses were extensor. However, when lying supine with her head tilted below the horizontal, the left plantar response became flexor. This change in the plantar response was reproducible. Her blood pressure was 180/80 supine and 150/70 standing. The apex beat was displaced and dyskinetic in type. There was no evidence of cardiac failure. Left carotid and right femoral bruits were heard. Her fundi showed grade II hypertensive changes. Her ECG was unchanged from previous readings which showed ST elevation in the anteroseptal leads. Her cardiac enzymes were normal and the serum creatinine level was 0.16 mmol/L (normal range 0.04–0.09 mmol/L).

Her daily medications on admission were: frusemide 60 mg, pindolol 2.5 mg, digoxin 0.125 mg, quinidine bisulphate 750 mg, phenytoin 300 mg, potassium chloride 3.6 g and glyceryl trinitrate. Pindolol, frusemide, phenytoin and quinidine were ceased on admission. Within 2 days there was dramatic clinical improvement. She became mentally alert and was able to walk with assistance. On day 21 she was discharged to live in the community. Her blood pressure on discharge while taking digoxin and aspirin was 180/95 with no postural drop.

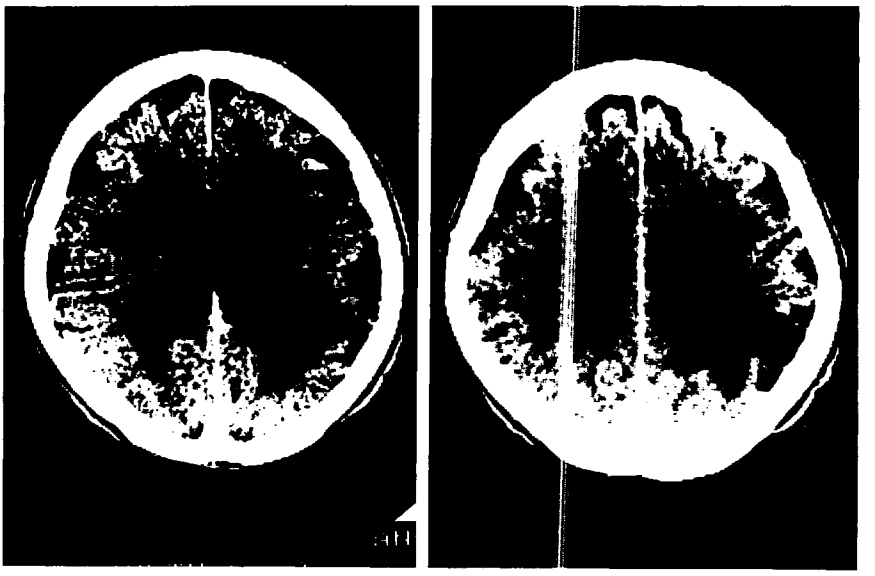

Figure 5. CT scan showing distal field infarction.

A repeat CT scan showed infarction in the distal field of the left middle cerebral artery (Figure 5). Fourteen months later intravenous digital subtraction angiography demonstrated minor narrowing at the right carotid bifurcation but the left carotid and both vertebrobasilar arteries were normal (Figure 6). Nineteen months later she remained in good health and lived on her own. She was independent in self-care and mobility but had residual right hand inco-ordination and difficulty in finding words. Her blood pressure was 160/80 mmHg and she was taking no hypotensive medication.

The clinical history in this case implicates haemodynamic factors in the pathogenesis of cerebral ischaemia and ultimately of cerebral infarction. Multiple posture-related, stereotyped TIAs preceded a distal field cerebral infarct. Subsequent angiography revealed no significant carotid disease. Before her stroke she was taking a combination of diuretic, beta blocker and quinidine. Phenytoin treatment had also been commenced one month before admission, after her EEG showed a left hemispheric slow wave abnormality. Following cessation of medication there was rapid clinical neurological recovery.

Discussion

There are few clinical reports of watershed cerebral infarction in stroke survivors and most of these cases followed cardiac surgery.[17,18] Hijdra and Meerwaldt described one case of bilateral parietoccipital watershed infarction which was presumably due to systemic hypotension at the onset of atrial fibrillation.[19] Wodarz performed a detailed CT and angiographic study of 55 patients with carotid occlusion or stenosis. Watershed or distal field infarction was demonstrated in over 40% of these patients.[20] He emphasized that CT changes were often very subtle

Figure 6. Selected views of digital subtraction angiogram. Arrow indicates lesion at origin of right internal carotid artery.

and could be overlooked if the vertex sections were ignored. An association between watershed cerebral infarction and vasodilator medication has not previously been described.

Elderly patients with generalized atherosclerosis have impaired cerebral autoregulation. Wollner *et al.* studied cerebral blood flow in elderly patients with symptomatic postural hypotension.[22] They found that global cerebral blood flow fell by up to 67% when mean arterial blood pressure was reduced by less than 33 mmHg. Postural hypotension has been noted in over 35% of patients above 65 years of age who are living at home.[23]

Strandgaard (1983) demonstrated that in chronic hypertension the cerebral autoregulation curve is shifted to the right.[24] Thus, cerebral perfusion falls at pressures that would otherwise be considered normal. In elderly hypertensive patients this dysautoregulation is usually due to irreversible structural changes in the arteriolar wall.[25] Ruff *et al.* noted that hypertensive patients with carotid stenosis often develop TIAs when mean arterial blood pressure is lowered by 20 mmHg.[26]

To our knowledge, the effect of prazosin on regional cerebral blood flow in patients with focal cerebral ischaemia has not been studied. Other vasodilator agents may produce intracerebral steal in the presence of focal cerebral ischaemia.[27] Prazosin is a selective post-synaptic alpha blocker that decreases peripheral resistance. It differs in action from other vasodilators like hydralazine because it does not produce tachycardia. It is also a potent venodilator and thus decreases both cardiac preload and afterload. Prazosin increases cardiac output when left ventricular end diastolic pressure is high but may cause postural decreases in cardiac output in normal hearts. When volume depletion is present, for example with chronic diuretic therapy,[28] the orthostatic effect of prazosin may be augmented.[29] Combinations of beta adrenergic blockers and diuretics with prazosin would be expected to produce large falls in post-exercise blood pressure when cardiac reserve is limited. When total peripheral resistance falls and heart rate is controlled, blood pressure is maintained only by increases in stroke volume.

Topol *et al.* recently used echocardiography to define a subset of elderly hypertensive women with poor ventricular compliance and reduced diastolic filling.[30] When these patients were given vasodilator medication, half of them developed severe hypotension and one died. Limited left ventricular compliance may be an early response to hypertension.

Conclusions

Haemodynamic factors may contribute to the pathogenesis of cerebral infarction more commonly than is currently believed.

Inappropriate use of potent antihypertensive medications may produce cerebral ischaemia or infarction in patients with impaired cerebral vascular reactivity. These infarcts are often located in watershed zones.

Vasodilator therapy in these patients should be monitored clinically, with special reference to resting and post-exercise postural blood pressure readings.

Combinations of vasodilator, diuretic and negative chronotropic agents should be used with caution for elderly patients and for those with chronic hypertension.

Summary

The role of haemodynamic factors in the pathogenesis of cerebral infarction is unclear. Watershed or distal field infarction is most often caused by haemodynamic mechanisms. Watershed cerebral infarcts can now be identified in stroke survivors using CT scanning.

The clinical findings are presented of 14 patients with cerebral infarction in whom haemodynamic factors contributed to the stroke. Evidence for this diagnosis includes (i) a history of posture-related or exercise-induced syncopal attacks or neurological deficits before and in some cases after the stroke, (ii) the demonstration of watershed or distal field infarction on CT scan, (iii) commencement of symptoms after increase in antihypertensive medications, and (iv) improvement following reduction of treatment.

Regional cerebral hypoperfusion may be a more common cause of cerebral infarction than is generally thought. Particular care should be exercised when potent antihypertensive medication is prescribed for elderly hypertensive patients.

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Subcortical Arteriosclerotic Encephalopathy: Binswanger's Disease

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Binswanger,[1] in his 1894 dissertation on the differential diagnosis of general paresis of the insane, described 8 cases of slowly progressive dementia with focal neurological signs, associated at post-mortem examination with macroscopic loss of white matter and ventricular enlargement. Olszewski[2] first used the term 'subcortical arteriosclerotic encephalopathy' in a clinicopathological review of the literature in 1962 in which he emphasized the marked hyalinization and narrowing of the small arterioles perforating the white matter and the deep grey structures. In recent years interest was rekindled when CT head scanning showed extensive white matter low densities. The purpose of this study was to define the clinical spectrum of patients with these CT appearances seen in the Heidelberg Repatriation Hospital.

Methods

We reviewed 22 cases, presenting over 12 months, in which a radiological diagnosis of Binswanger's disease had been made by a single radiologist on the basis of extensive patchy or confluent white matter hypodensity, involving more than the frontal zones. Lacunar disease, ventricular enlargement and cortical infarcts were considered acceptable additional abnormalities.

There were 18 men and 4 women, aged between 61 and 92 years, in the series (male veterans predominate in our hospital population). These patients were then assessed for clinical evidence of dementia and neurological deficits. We looked also for co-existing systemic vascular disease, hypertension or diabetes, and sought a

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history of acute stroke events and of cigarette and alcohol abuse. Syphilis serology was negative in all cases. Where possible, neuropsychological, EEG, carotid doppler and angiographic data were studied.

Results

Most of the patients had the 'classical' picture described in the literature,[3] showing a combination of dementia, corticobulbar dysfunction and gait dyspraxia (Table 1). In some, one symptom was markedly predominant. Six had only minimal evidence of dementia, and 4 of these showed very mild neurological deficits. However the degree of clinical abnormality did not always correlate well with the extent of the CT changes.

Psychiatric features have been described previously,[4] and 2 of our patients first presented through the psychiatric unit, one with hypomania and the other depressed and having taken an overdose (Table 2). Sixty per cent of the study group had a history of acute stroke events, and focal cortical or lacunar infarcts were a frequent CT finding. Over 75% were hypertensive and 50% had evidence of other vascular disease. None of the patients was diabetic. Cigarette and alcohol

Table 1. Clinical features

Dementia-minimal	6
-significant	15
Gait disturbance	17
Corticobulbar dysfunction	14

Table 2. Presenting symptoms

Acute stroke/transient ischaemic attack	6
Gait disturbance	5
Dementia/debility	5
Dysarthria/dysphagia/aspiration	3
Psychiatric/hypomania (1)	2
/depression (1)	
Other (seizure)	1
Total =	22

Table 3. Associated features

Hypertension	75%
Other vascular disease	50%
History of acute stroke/transient ischaemic attack	60%
Diabetes	0%
Smoking	36%
Alcohol	23%

abuse did not seem particular risk factors but levels of consumption were difficult to corroborate (Table 3).

In 2 patients with focal neurological deficits at presentation, recent anoxic or hypoglycaemic insult could not be excluded as the cause of the CT abnormalities. Post-mortem examination in one of these cases revealed arteriolosclerosis and lacunar infarcts, but not the typical white matter changes of Binswanger's disease.[6]

Discussion

The characteristic CT appearances were encountered relatively frequently in our population of war veterans, and appeared strongly associated with hypertension and other forms of vascular disease. While the exact pathogenesis is in doubt, the cause of Binswanger's disease is probably chronic or acute-on-chronic ischaemia of the white matter and basal ganglia secondary to arteriolosclerosis of penetrating vessels. If the cortical blood supply is also impaired then the white matter may be a potential watershed zone.[5] This understanding leads us to propose that it is the pattern of vessel involvement, large and small, which predicts the type of 'vascular dementia' developing in any one patient, and that Binswanger's disease is part of a continuum which encompasses multi-infarct dementia. Clinically the disorders can be differentiated by their time course; patients with Binswanger's disease show a more subacute course.

Prolonged follow-up of such patients is necessary to document the natural history of the disease and ultimately to obtain pathological correlates for the clinical and CT appearances.

Summary

Binswanger, in his 1894 dissertation on the differential diagnosis of general paresis of the insane, described a slowly progressive dementia associated with macroscopic loss of white matter. In recent years interest in Binswanger's disease was rekindled with CT demonstration of extensive white matter low densities in some patients. To define the clinical spectrum, we reviewed 22 consecutive cases in which the CT appearances suggested a diagnosis of Binswanger's disease.

Two patients had focal neurological deficits at presentation, but recent anoxic or hypoglycaemic insults could not be excluded as the cause of the CT abnormalities. The 20 remaining patients were demented and showed variable combinations of corticobulbar dysfunction and gait dyspraxia. The duration of symptoms ranged from a few months to several years. Sixty per cent of this group gave a history of discrete stroke events and focal cortical and/or lacunar infarcts were a frequent CT finding.

Binswanger's disease is probably due to chronic or acute-on-chronic white matter ischaemia. The association with lacunar and cortical infarctions suggests that a combination of large and small vessel disease produces diffuse ischaemia maximal in white matter watershed zones. Binswanger's disease is clinically differentiated from multi-infarct dementia by its time course.

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Cranial CT Scan Appearances that Correlate with Patient Outcome in Acute Stroke

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The major roles of computerized tomography (CT) in acute stroke are to eliminate alternative diagnoses and to detect intracerebral haemorrhage if anticoagulation therapy or surgery is being considered.[1] Recognizing that certain clinical features have prognostic significance for stroke recovery, it was considered that a CT scan might also be used to predict recovery following stroke.

A prospective study was undertaken to determine whether certain characteristics of lesions seen on CT scan correlated with recovery from acute stroke.

Methods

A total of 178 acute stroke patients admitted to Royal Perth Hospital between 10 September 1984 and 11 March 1985 were assessed by 4 neurologists in a prospective study. For each patient 83 data items were entered into a computer.

One hundred and fifty patients (84%) underwent cranial CT scan and these scans were reviewed by an independent radiologist; 45 radiological data items were added to the programme and computerized for subsequent analysis.

Information from CT scan appearances, including lesion number, site, artery of distribution, size, mass effect and pathology, was cross-tabulated against parameters of patient outcome including time in hospital, mortality, and residence, activities of daily living status, mental state and continence at discharge.

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Results

Of the 150 cranial CT scans performed 78% were abnormal and 22% normal. The vast majority (81%) were non-contrast scans, in accordance with our hospital's policy of avoiding the use of intravenous contrast in acute stroke patients: 2% of abnormalities showed contrast enhancement. Of the abnormal CT scans, 62% were characterized by only one lesion but other incidental lesions were seen in the remaining 38%. Of patients with multiple incidental lesions on CT scan, 57% were discharged home compared with 78% of those with a single lesion.

The common sites of pathology were the basal ganglia and internal capsule (in 35% of abnormal scans), the cortex and deep white matter (in 25%), the deep white matter alone (in 20%), the cortex alone (in 11%) and posterior fossa structures (in 9%). Only 50% of the 24 patients with deep white matter lesions were discharged home, compared with 77% of patients with lesions in other sites. The difference between these figures was statistically significant ($p < 0.025$). Of the patients with deep white matter lesions, 17% died while 35% had an altered mental state at the time of discharge compared with only 13% of patients with lesions in other sites. The difference between these figures was statistically significant ($p < 0.025$).

Seventy-nine per cent of lesions were in the distribution of the anterior circulation and 21% in the posterior circulation. Of the 15 patients with lesions in the distribution of the posterior cerebral artery, 36% had an altered mental state at the time of discharge compared with 15% of patients with lesions in other arterial territories.

Three-quarters of the lesions were smaller than 50 cm^3 in volume and 32% were smaller than 5 cm^3 in volume. The range of lesion size extended up to 550 cm^3. Twenty-three per cent of patients with lesions larger than 50 cm^3 in volume died compared with 5% of those with lesions smaller than 50 cm^3. The different between these latter figures was statistically significant ($p < 0.005$).

A mass effect was present in 55 abnormal CT scans (47%). A mild mass effect was defined as effacement of the cortical sulci. A moderate mass effect was diagnosed when there was effacement of cortical sulci and also compression of underlying structures such as the ventricles. A severe mass effect was defined as mid-line shift. There were 8 cases with a severe mass effect, of whom only 3 (37%) were discharged home ($p < 0.05$). Two were institutionalized and 3 died. Of patients with a mass effect on CT scan 35% had an altered mental state at discharge compared with only 2% of those without a mass effect. The difference between these figures was statistically significant ($p < 0.005$).

An attempt was made to diagnose the nature of the lesion seen on the CT scan according to the criteria used in the Harvard Co-operative Stroke Registry (1978). Bland infarction without a haemorrhagic component and not confined to the territory of a single surface artery was diagnosed as large artery thrombosis. Small deep infarctions in the territory of a penetrating vessel were diagnosed as lacunar infarcts. Infarction in the form of low density lesions involving the superficial cerebral artery territories were diagnosed as embolism. A focal mass of high density without the use of contrast enhancement was diagnosed as haemorrhage.

Cerebral embolism was diagnosed clinically in 26% of cases, and by CT scan in 14% of cases; 85% had evidence of cardiac disease.

Ten of the 20 patients with cerebral haemorrhage either died or were discharged to a hostel, nursing home or other hospital. The mortality rate for haemorrhage was 25%. This was significantly greater statistically than the 9% mortality from other disease ($p < 0.05$). Forty-four per cent of patients with cerebral haemorrhage had an altered mental state at the time of discharge compared with 11% of patients with other abnormalities.

Discussion

The results indicate that the cranial CT scan may be useful as a predictor of patient outcome following acute stroke. The presence of multiple incidental lesions, in addition to the relevant lesion, was associated with a higher rate of institutionalization and dependent status in the activities of daily life. Lesions situated in the deep white matter were associated with a higher mortality and higher dependency in the activities of daily life, and correlated significantly with an altered mental state at the time of discharge and a reduced chance of being discharged home. Lesions in the distribution of the posterior cerebral artery were associated with a higher rate of altered mental states. Larger lesions correlated significantly with a higher mortality and were associated with a higher rate of dependency in the activities of daily life. The presence of a mass effect correlated significantly with an altered mental state and was also associated with a higher rate of mortality and dependency in the activities of daily life. Intercerebral haemorrhage correlated significantly with greater mortality and was associated with a higher rate of institutionalization, dependency in the activities of daily life and altered mental state at discharge.

CT scans were considered normal if there was no evidence of infarction or haemorrhage. Cortical atrophy was present in 13% and subcortical periventricular hypodensity in 10% of all CT scans; the latter feature was associated with hypertension in 100% of cases. The presence of a normal CT scan was not found to be of prognostic significance for patient outcome. This may, however, be a reflection of the small sample size or sample contamination with false negative scans. Of the normal scans, 34% were performed in the first week after the stroke, at which time an infarcted area may not have had time to change radiolucency. Unfortunately follow-up scans were not performed.

Miller and Miyamoto studied the CT scans and functional outcome of 40 stroke patients.[2] They suggested that lesion site and size are both important in predicting functional outcome. A good prognosis was associated with small, superficial lesions and a normal CT scan, while deep lesions in the basal ganglia, internal capsule and thalamus were poor prognostic features. However Henley *et al.* performed CT scans on 59 patients 2 weeks after their stroke and found that pathology, side, region, size and the presence or absence of contrast enhancement did not correlate significantly with patient outcome.[3]

Clinical and CT assessment did not always agree when diagnosing cerebral

embolism. It is possible that embolism was over-diagnosed clinically whenever a potential embolic basis, such as atrial fibrillation or a cardiac murmur, was detected. The CT scan may have under-diagnosed cerebral embolism and, if so, possible reasons are that at the time of CT an infarcted area may not have had time to change its radiolucency or, alternatively, that a haemorrhagic component may not have time to develop.

Although the results of this study suggest a possible role for CT scan in predicting patient outcome in acute stroke, it must be stressed that such information should be used only as an adjunct to complete clinical assessment in the evaluation of patients' prognosis for stroke rehabilitation.

Summary

Certain clinical features are known to correlate with patient outcome in acute stroke, but the potential of cranial CT scan as an aid to predicting recovery after stroke remains unclear.

In a prospective study, 178 acute stroke patients admitted to Royal Perth Hospital were assessed by 4 neurologists; 150 cranial CT scans were performed and these were reviewed by an independent radiologist. CT lesion characteristics were cross-tabulated against clinical indices of patient outcome.

Lesions greater than 50 cm^3 in volume were associated with a 23% mortality compared to a 5% mortality for lesions smaller than 50 cm^3. The mortality rate from intracerebral haemorrhage was 25% compared to 9% for other disease. Of patients whose CT scan showed a mass effect, 35% had an altered mental state at discharge compared to only 2% of those without a mass effect. Of the patients with deep white matter lesions, 35% had an altered mental state at discharge compared to only 13% of patients with lesions in other sites, and only 50% were discharged home compared to 77% of patients with lesions in other sites.

CT scan features that correlated significantly with a poor outcome following acute stroke were large lesion size, intracerebral haemorrhage, mass effect and deep white matter lesions.

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Clinically Unsuspected Cardiac Disease in Patients with Cerebral Ischaemia

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It is well established that cardiac disease is the single most common cause of death in patients with transient ischaemic attacks (TIAs) or minor strokes.[1,2] In recent years it has been suggested that patients should be thoroughly investigated and, if indicated, undergo coronary artery bypass surgery when they present with minor cerebral ischaemia.[3]

It could be argued, however, that patients with symptomatic cardiac disease are in fact receiving optimum modern therapy and that vigorous investigation of the cardiac status in patients with cerebral ischaemia would be justified only if a significant number of patients do not develop symptoms of heart disease before death due to cardiac disease. In an analysis[4] of the highly selected group of patients in the International Extracranial-Intracranial Anastomosis trial, although 37% of the deaths due to ischaemic heart disease or sudden death (considered cardiac in origin)[5] had not had symptoms of cardiac disease before the fatal event, the risk of death due to myocardial infarction or sudden death in patients without prior symptoms of ischaemic heart disease at entry was only 1% per year.

This study was undertaken to evaluate the frequency of cardiac abnormalities in patients presenting with cerebral ischaemia. Although cardiac disease in patients with stroke has been studied in the past, a more recent evaluation appeared justified because of the availability of computerized tomography (CT) scanning (which can differentiate stroke due to ischaemia from that due to haemorrhage) and because of the known change in the natural histories of both cerebral vascular[6] and ischaemic heart disease.

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Methods

A 6 month prospective study was undertaken at St Vincent's (February–July) and Prince Henry's (January–June) Hospitals during the first half of 1985. Only patients with definite TIAs or ischaemic strokes were included in the study. Stroke due to intracerebral, subdural or subarachnoid haemorrhage was excluded. All patients were seen within 24–48 hours of admission.

A prior history of cardiac disease and the examination findings were those recorded by the intern and registrar (3 or more years after graduation) of the admitting unit. Where these differed, the findings of the registrar were used. A CT scan was used to differentiate stroke due to intracerebral haemorrhage from that due to infarction and was carried out in 221 cases (95.3%). The following electrocardiographic (ECG) abnormalities constituted evidence of cardiac disease: pathological Q waves in leads 11,111 and AVF (old inferior myocardial infarction) or in 1, AVL, and V1–V4 (old anterior myocardial infarction); elevation of the ST segment in either the anterior or inferior leads indicated recent myocardial infarction only when confirmed by elevation of the cardiac enzymes in plasma. Left ventricular hypertrophy was indicated by an R wave in AVL greater in amplitude than 13 mm and V1 plus V5 or V6 greater than 35 mm. Minor degrees of ST elevation or depression, because of their non-specificity, were not taken as evidence of cardiac disease. Cardiomegaly seen on chest x-ray examination was defined as a cardiothoracic ratio of greater than 0.5. Where the chest x-ray and clinical findings did not agree, the x-rays were read 'blind' by a radiologist (A.H. or M.P.) who measured the cardiothoracic ratio.

Results

During this 6 month study, 232 patients were ultimately diagnosed as suffering from TIA or cerebral infarction (all grades of severity). Sixteen patients with suspected cerebral ischaemia who had intracerebral haemorrhage on CT scan were excluded. Two patients died within 12 hours of onset of the stroke and are excluded because no investigations were performed. The most likely diagnosis in these 2 patients was intracerebral haemorrhage, particularly as one was taking warfarin at the time of the stroke.

Of the 232 patients, 132 were men and 100 women with ages ranging from 28 to 92 years. The average age was 67 years. Fifty-five patients presented with a cerebral (carotid or vertebro-basilar) TIA, 11 with unilateral amaurosis fugax, 6 with retinal infarction and 160 with cerebral infarction (all grades of severity). One hundred and one (50%) had a stroke severity scale of 4 or less, which is a transient ischaemic attack or minor stroke with minor functional impairment but where the patient remains independent of external assistance. Previous episodes of cerebral ischaemia, either TIA or stroke, were present in 43% of the patients. Hypertension, diabetes and peripheral vascular disease were present in 55.2%, 10.3%, and 11.6%, respectively.

A prior history of heart disease was obtained in 100 (43%) patients. Ischaemic

heart disease was present in 55, of whom 25 had prior myocardial infarction only, 18 prior angina and 12 both angina and myocardial infarction. A history of atrial fibrillation was obtained in 25, in 7 of whom it had been a transient phenomenon. Valvular heart disease was present in 13 and a history of cardiac failure in 24. A number of patients had a past history of more than 1 cardiac disorder. A similar incidence (43%) of prior cardiac disease was present in the 101 patients with TIA or minor stroke. In the 131 patients presenting with their initial episode of cerebral ischaemia, however, prior cardiac disease was present in only 27%. In 30 patients with a previous history of cardiac disease no cardiac abnormality was detected on subsequent investigation. The previous cardiac diagnoses in these patients were: angina pectoris 12, myocardial infarction with or without angina 7 and heart failure 11.

The unexpected abnormalities detected by examination, routine ECG and chest x-ray examination are shown in Table 1. Twenty-three patients were thought on examination to be in atrial fibrillation (AF). Among the 25 patients with a previous history of AF, 6 were no longer felt to be in AF, although ECG subsequently showed that 1 patient was in AF. Four of the patients in AF had a prior history of cardiac disease but not of AF and 1 patient had no prior history of cardiac disease. Fifty patients had an enlarged heart on examination: of these 31 had cardiomegaly on chest x-ray examination and/or left ventricular hypertrophy on ECG. A further 4 with suspected cardiomegaly had ECG evidence of myocardial infarction and 2 had AF on ECG but none had ECG or x-ray evidence of cardiomegaly. Nineteen patients thought to have an enlarged heart did not have cardiac disease confirmed on subsequent investigation. Eleven of the patients with clinical evidence of cardiomegaly (subsequently confirmed by investigation) did not have a prior history of cardiac disease.

Table 1. Cardiac abnormalities found by clinical examination, ECG and chest x-ray examination. Figures in parentheses represent the number of unexpected findings.

		Prior cardiac disease	No prior cardiac disease
Examination	AF	22 (4)	1
	Cardiomegaly	31 (20)*	19 (11)*
Electrocardiogram			
	AF	25 (2)	6 (5)
	LVH	11 (1)	13 (10)
	LBBB	–	1 (1)
	Old MI	3	7 (7)
	Recent MI	3 (3)	2 (2)
Chest x-ray examination			
	Cardiomegaly	40 (21/12)†	27 (17/10)†

* These figures are the number subsequently confirmed by ECG and/or chest x-ray examination.
† The first figure in parentheses is the number without cardiomegaly clinically; the second number represents those without cardiomegaly clinically and no LVH on ECG. AF = atrial fibrillation, LVH = left ventricular hypertrophy; LBBB = left bundle branch block, MI = myocardial infarction.

Electrocardiograms and chest x-rays were obtained for all but 8 and 4 patients, respectively. In patients with pre-existing cardiac disease the ECG disclosed 7 unexpected findings. Two further patients with unsuspected AF were detected and 1 had left ventricular hypertrophy that had not been detected clinically. Three patients were found to have recent myocardial infarction. In patients without pre-existing cardiac disease, as assessed by both history and examination, left ventricular hypertrophy, AF, left bundle branch block, and old and recent myocardial infarction were present in 10, 5, 1, 7 and 2 patients, respectively.

The chest x-ray examination detected a total of 67 patients with an enlarged heart, of whom 40 had a previous history of cardiac disease. Amongst these 40 patients, 21 did not have cardiomegaly detected by examination. In these 21 patients the pre-existing cardiac disease was ischaemic heart disease in 14, AF in 6 and cardiac failure in 1. A total of 27 patients without a previous history of cardiac disease had radiological evidence of cardiomegaly: of these 15 did not have an enlarged heart detected clinically. In 8 patients cardiomegaly on chest x-ray examination was the only indication of cardiac disease.

Discussion

This study was undertaken following an analysis of the EC/IC Anastomosis Trial in which it was found that 37% of patients who died of either documented myocardial infarction or sudden death had no prior evidence of ischaemic heart disease. The patients in that study were a highly selected group with, in general, severe atherosclerotic vascular disease in the neck, and in whom cardiomegaly (because of its influence on prognosis) was an exclusion criterion in order not to dilute the important study endpoints of stroke and stroke death.[7]

The present study has shown a high frequency of previously asymptomatic or clinically unsuspected cardiac abnormalities in patients with cerebral ischaemia. Direct comparison with other studies is difficult because of the different patient populations. In the study of 390 patients with TIA by Heyman *et al.*[8] prior myocardial infarction and angina were present in 26% and 29% respectively (it is unclear how much overlap occurred between the two categories) and there was ECG evidence of left ventricular hypertrophy in approximately 14%. Although their patients were slightly younger on average (61 7 years), significantly fewer suffered from hypertension (23%), whilst diabetes (18.7%) and peripheral vascular disease (20%) were more frequent than in our study. In the study by Heyman *et al.*[8] diabetes mellitus, prior myocardial infarction or angina, ECG evidence of left ventricular hypertrophy and ECG abnormalities (type unspecified) and peripheral vascular disease were predictive of subsequent myocardial infarction or sudden death. However it is unclear how many of the patients who succumbed to myocardial infarction or sudden death had no prior symptoms of cardiac disease.

In another study of 117 patients in a retirement village,[9] a diagnosis of coronary artery disease before the stroke was present in 41.9%, AF in 19.7%, and left ventricular hypertrophy on ECG and cardiomegaly on chest x-ray in 7.7% and 26.5%, respectively. The mean age of the patients was 72 years, higher than in the present study.

In a recent study[10] of 250 consecutive patients with TIA (mean age 63 years), 6 patients with previously unsuspected AF were detected by routine ECG, 3 of whom had no history of heart disease. Thirteen (5.2%) patients without prior heart disease had ECG evidence of myocardial infarction (criteria not stated), a figure almost identical to that in the present study. A further 10 patients without prior evidence of cardiac disease had a potential cardiac embolic source identified by 2D echocardiography, but it is unclear whether 2D echocardiography was the only indicator of cardiac disease. Echocardiography was not employed in our study because its value in patients over the age of 50 is doubtful and because it is not readily available to more isolated physicians. Many studies performed in the large teaching hospitals employ expensive technology that is not generally available and the results of such studies cannot readily be applied outside these major centres. By employing tests that are freely available we hoped to avoid this problem.

The present study is a prelude to a longitudinal follow up of patients with TIA and minor stroke which will investigate how many patients die with the first symptom of cardiac disease and the risk of such an event in patients without heart disease. The findings of this study would suggest that the number of deaths may be small because of the frequency of previously unsuspected cardiac abnormalities detected by careful evaluation including ECG and chest x-ray examination.

Summary

In a 6 month prospective study of 232 patients with cerebral ischaemia, 100 (43%) had a prior history of heart disease. In 22 of the patients with prior heart disease an unsuspected cardiac disorder was subsequently detected (6 atrial fibrillation, 13 cardiomegaly or left ventricular hypertrophy and 3 ischaemic heart disease). In patients without prior heart disease, 47 (20%) were found to have cardiac disease: 6 atrial fibrillation, 31 cardiomegaly or left ventricular hypertrophy 9 ischaemic heart disease and 1 left bundle branch block. Previously unsuspected or asymptomatic cardiac disease is common in patients with cerebral ischaemia.

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Electrically Evoked Skin Vasodilatation: A Quantitative Test of Nociceptor Function in Man

R.A. Westerman, A. Low,* A. Pratt,* J.S. Hutchinson.* J. Szolcsanyi,† W. Magerl,‡ H.O. Handwerker‡ and W.M. Kozak***

Traditional tests of nociceptor function in humans, such as measurement of thresholds for pain sensation evoked by noxious heat,[1] electrical stimulation,[2] or mechanical pressure,[3] provide useful but limited information about the function of nociceptors in the areas of skin tested. However, a quantitative test is needed for the study of cutaneous nociceptor activity in such diseases as diabetic or other polyneuropathy both to detect abnormalities and to enable more accurate monitoring of the course of the disease.

This paper summarizes the technique we have developed for recording local cutaneous vasodilatation in response to noxious percutaneous electrical stimulation. Microvascular dilator responses to electrical stimulation of skin were described in Lewis' classic studies[4,5] but, to our knowledge, have not been applied in neurological disease or for the quantitative study of neurogenic vasodilatation.

Materials and Methods

The local nociceptor-induced vasodilatation (that is, the axon reflex part of Lewis' triple response) was recorded from the hairy skin of the anterior forearm or the dorsum of the foot in most subjects (consenting volunteers) but was also recorded from other hairy and glabrous skin sites on the upper and lower extremities. A Periflux Pf 1 laser doppler flowmeter (Perimed, Sweden) was used to

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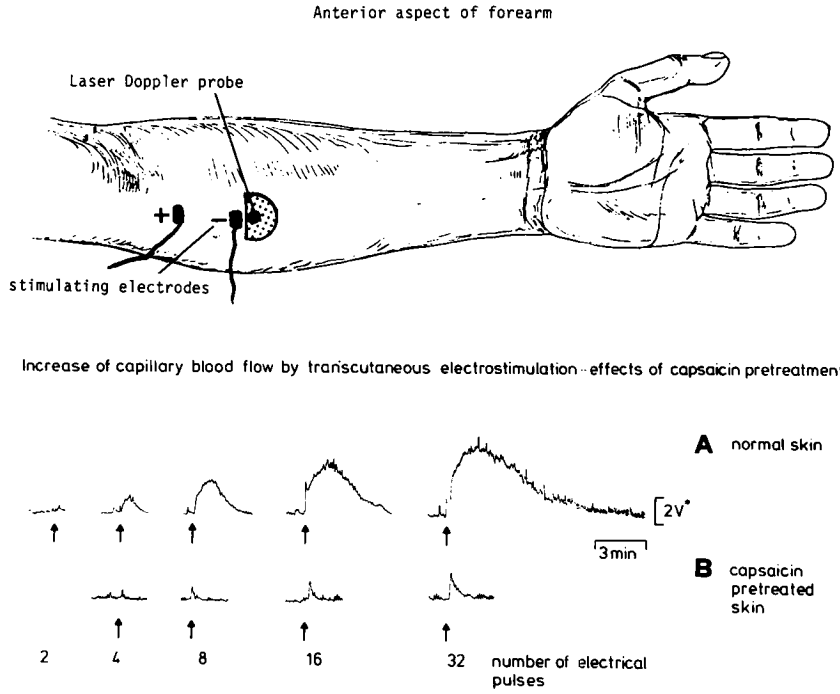

Figure 1. Upper diagram shows typical arrangement of stimulating electrodes and laser probe on forearm: panels A and B show increase of microvascular blood flux by transcutaneous electrical stimulation of normal skin and capsaicin-pretreated skin, respectively. The number of stimulus pulses required to evoke each dilator response are shown below. The time and laser signal voltage calibrations bars apply to both A and B.

record the changes in skin blood flux. The laser doppler probe holder was fixed to the skin by a double-sided adhesive disc. An indifferent anodal electrode was applied 5 cm proximal to the test site, where the cathode was a 30 mm^2 gold-plated disc electrode taped onto the skin 1 cm from the laser probe (Figure 1). Although a range of stimulus parameters were explored in the preliminary tests (Westerman RA, Szolcsanyi J, Magerl WM, Handwerker HO, unpublished observations) it was found that the minimum stimulation giving reproducible responses in normal skin was a series of pulses each of 150 volts, 0.5–1.0 ms in duration, at a frequency of 2 Hz. The total number of pulses delivered in each brief train ranged from 1 to 32. All healthy subjects reported that this stimulus produced pain at the cathode, and several did not consent to receive the train of 32 stimuli.

An area of forearm skin was then desensitized with capsaicin in 6 volunteers. A 1% ethanol solution of capsaicin[6] was applied 3 or 4 times daily for 3 or 4 days until its application no longer evoked redness and pain. The capsaicin-treated skin area was tested on the following day.

The area of each vasodilator response was measured as the voltage–time

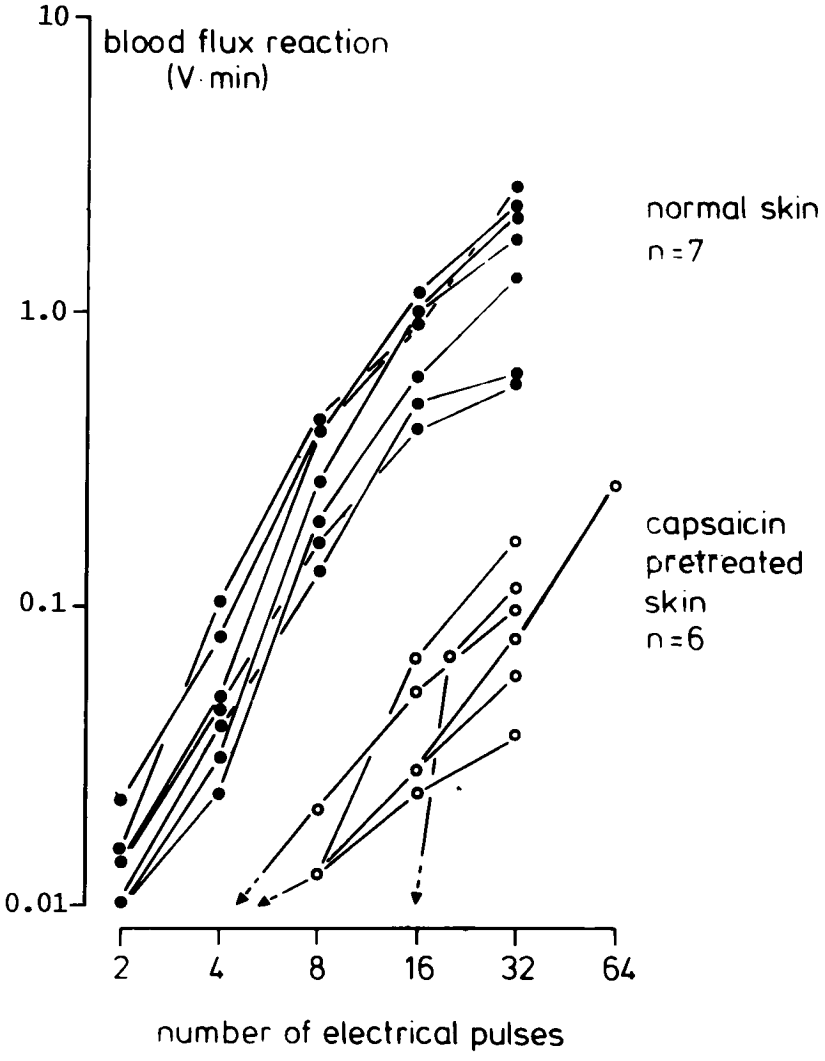

Figure 2. The increase of microvascular blood flow after transcutaneous electrical stimulation with 0.5 ms pulses at 2 Hz, and total numbers of stimuli 2, 4, 8, 16, 32, and 64 (in one case). The data shown are for normal and capsaicin-treated skin of the same subjects. The transient vasodilatations (like those shown in Figure 1) are plotted logarithmically as areas (volt min) on the ordinate and the number of pulses on the abscissa, to give a typical dose-response plot.

integral using a Zeiss MOP image analysis computer with a magnetic tablet and stylus attached. The logarithms of responses and stimuli were then plotted (Figures 2 and 4). The means, standard errors of the means, and 95% confidence limits were calculated for all normal subjects and are shown in Figure 4.

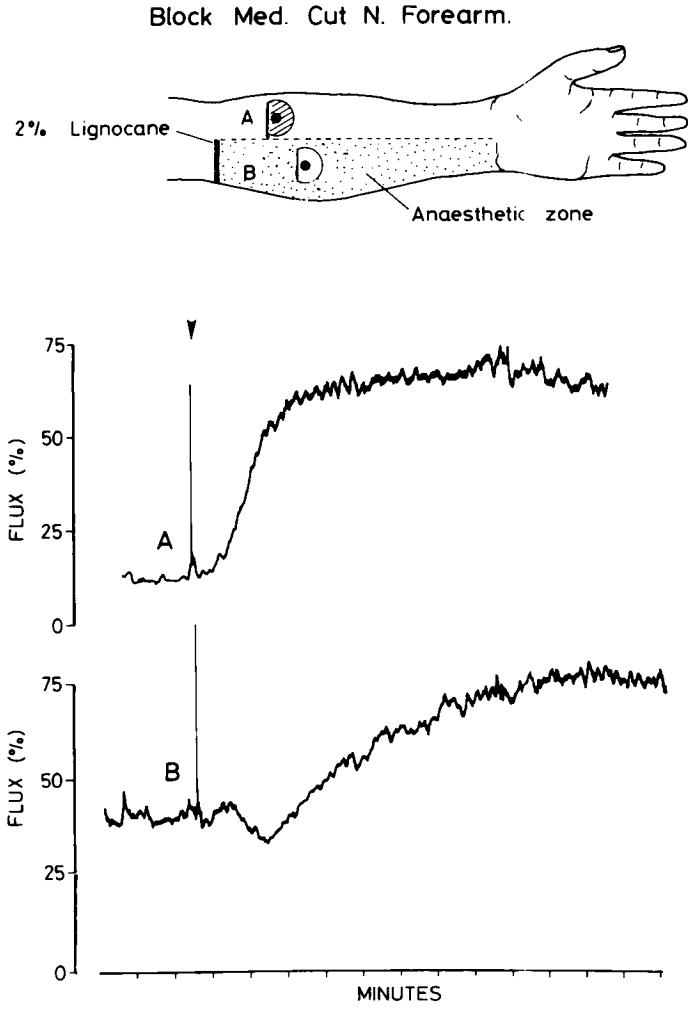

Figure 3. Flux changes are shown for normal and locally anaesthetized skin after increased stimulation compared to Figures 1 and 2 (total 64 pulses). The arrow indicates the stimulus artefact. The medial cutaneous nerve was blocked 6 minutes before record B. Note that the resting skin blood flux (37%) after local anaesthetic is elevated compared to that in unanaesthetized skin A (12%).

Results

In 27 experiments a reproducible increase of skin blood flux was recorded by the laser probe in response to transcutaneous electrical stimulation with the parameters described. These stimuli were perceived as painful and must be

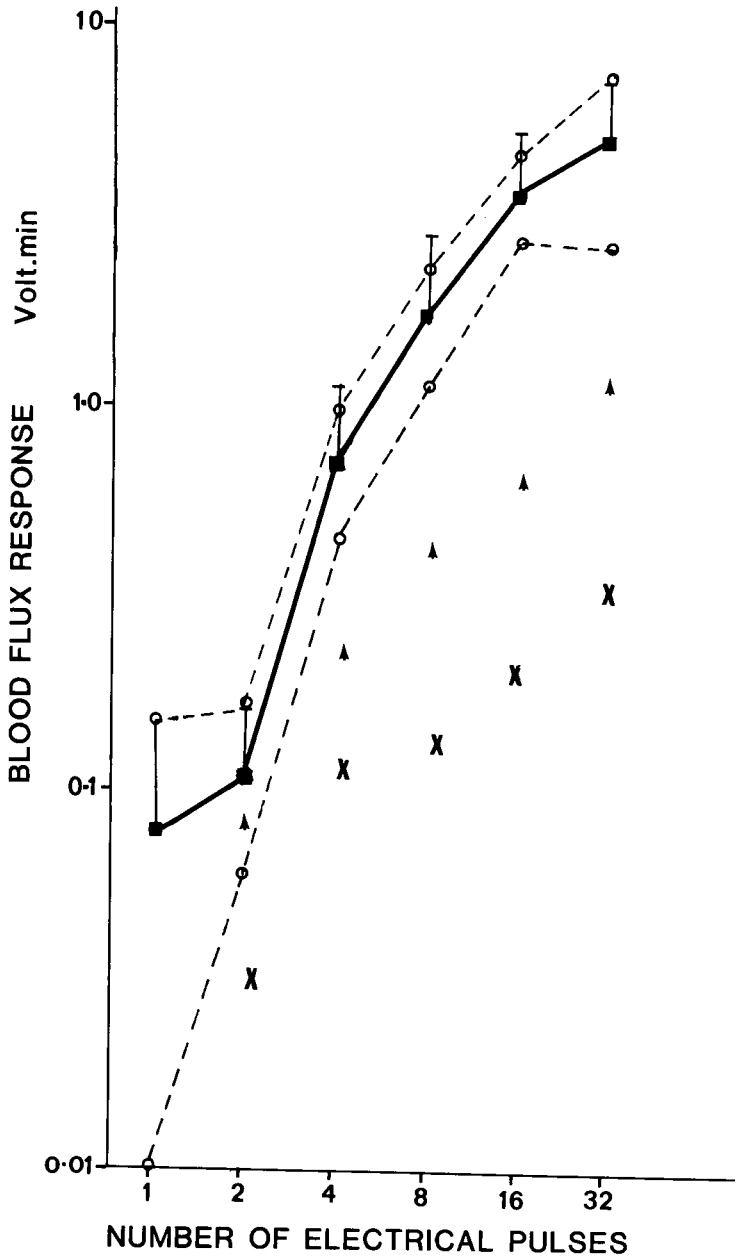

Figure 4. A logarithmic plot of responses to the electrical stimulus pulse series for 15 healthy volunteers similar to those shown in Figure 2. Means (squares) and standard errors (vertical bars) are shown, as well as the 95% confidence limits for the population data (broken line). Also depicted are results for electrical percutaneous stimulation of one subject with polyneuropathy (X) and one with sympathetic neuropathy (▲) associated with posterior root damage.

presumed to activate nociceptors and other C-fibres. The geometry of the recording probe and stimulating electrodes is shown in Figure 1 together with a series of vasodilator responses to the stimulus trains of 2, 4, 8, 16 and 32 pulses before and after capsaicin treatment. The amplitude of the microvascular blood flux increase and its duration are seen to depend on the 'dose' of electrical stimulation expressed as the total number of electrical pulses. In the normal skin at higher stimulus doses the vasodilatation was often preceded by a transient vasoconstriction, and this can just be seen in the response to 32 pulses at the arrow. The capsaicin-desensitized skin gave very markedly reduced responses to the same series of electrical stimulus pulses, applied in the same manner. The perceived pain from the electrical stimulation of capsaicin-treated skin was much reduced, and in two of the subjects the noxious heat threshold was found to be elevated by 2.3°C and 3.1°C, respectively. The other capsaicin-treated subjects were not tested in this manner, but elevated noxious heat thresholds have been reported in previous studies using capsaicin.[6]

The polygraph skin blood flux records were measured for the total area of each blood flux response, and the results are depicted graphically in Figure 2. The responses before and after capsaicin treatment indicate that, although vasodilator response and pain perception are both markedly reduced, some vasodilatation remains, evoked by larger total numbers of electrical stimulus pulses.

Figure 3 shows 2 responses to the same total stimulus (64 pulses) in the same subject, in whom approximately half of the anterior surface of the forearm was anaesthetized by 2% lignocaine block of the medial cutaneous nerve of the forearm. The large and prolonged vasodilator response seen in A was evoked by 64 pulses at 2 Hz applied near the laser probe at site A on the lateral (unanaesthetized) side of the forearm. In B, the resting skin blood flux is seen to be already elevated to 37% 6 minutes after the nerve block, compared with the resting flux of about 12% before the stimulus train was applied to the non-anaesthetized skin of the lateral side. Note that in B the stimuli did not evoke a perception of pain, but a brief vasoconstriction during the first 2 minutes was followed by considerable vasodilatation with increase in microvascular flux to reach an almost identical figure to that produced at the unanaesthetized site, A.

In Figure 4 the mean flare responses, standard errors of the means and the 95% confidence limits of the normal subjects' responses to the standard noxious electrical stimulation are shown. The reduced blood flux responses from a patient with dorsal root damage neuropathy (▲) and another with chronic polyneuropathy (×) show the degree to which this nociceptor-mediated response is reduced in both patients.

Discussion

The inflammatory response to necrosis or deep infection in the feet of patients with long standing diabetes mellitus is often accompanied by only slight superficial redness of the skin. This suggests a possible impairment of the neurogenic vasodilatation, that is, the axon reflex portion of the inflammatory triple response.[4,7]

This suggestion is supported by the findings of Hutchison *et al.*[8] that the histamine flare response, as measured by the rise in skin temperature in response to intradermally administered histamine, is reduced in diabetics.

Our technique was developed as a non-invasive quantitative test of how nociceptor function contributes to the axon reflex flare evoked by percutaneous electrical stimulation. The responses resemble closely in form and duration the 'local' vasodilatation obtained by Blumberg and Wallin[9] from intraneural microstimulation in microneurography. The responses are not reflexes requiring CNS participation since they persist after local anaesthetic block of the medial cutaneous nerve of the forearm (Figure 3). The same painful electrical stimuli applied at skin sites remote from the laser probe failed to evoke vasodilatation, as did non-painful levels of stimulation (less than 60–80 V) near the laser probe. The presence of an early vasoconstrictor response, seen as transient falls in skin blood flux with higher stimulation parameters, suggests that sympathetic vasoconstrictor fibres are excited by these levels of electrical stimulation which evoke an axon reflex flare (as in Lewis' triple response). Capsaicin pretreatment is known to reduce the substance P levels in epidermal primary afferents and their small cell bodies in the dorsal root ganglia.[10] Capsaicin treatment might therefore be predicted to shift the electrical stimulation dose-response plot in a similar manner to neuropathic states and result in impaired nociceptor function. A comparison of the data in Figures 2 and 4 supports this view.

After capsaicin pretreatment (Figure 2) the presence of some residual vasodilatation evoked by a larger total number of pulses suggests either that capsaicin desensitization of the nociceptor was incomplete or that other mechanisms may be involved in the vasodilation.

Other small nerve fibres in the skin which can be activated at the stimulus levels used include sudomotor (sympathetic postganglionic cholinergic fibres) and/or active sympathetic vasodilator fibres, whose transmitter is not known.[11] Of these, the cholinergic sudomotor fibres are not likely to participate in the response because atropine does not affect the local flare response[9] or our percutaneous vasodilatation (Westerman RA, Szolcsanyi J, Magerl WM, Handwerker HO, unpublished observations). We cannot exclude possible involvement of active vasodilator fibres.[11]

The sensitivity of the skin flare response, albeit transient, to very few stimulus pulses tempts us to consider a possible physiological role for this mechanism in local microvascular blood flow regulation. Further evidence of the sensitivity of the response of cutaneous nociceptors is found in the skin redness evoked by 'prickly' fabrics.[12] These sensations of 'prickle', and often small amplitude local vasodilatation, can be evoked by very small currents (10^{-7} A) applied so as to stimulate only the most superficial epidermal nerve fibres (Kenins P, Garnsworthy R, Gully R, Westerman R, Walker A, unpublished observations) which are shown by immunofluorescence to include substance P containing unmyelinated primary afferent fibres. The stimulus parameters and protocol shown in the present paper to be effective in evoking a neurogenic vasodilatation are proposed as a quantitative test of cutaneous nociceptor function contributing to axon reflex flare. This proposal is now being tested in diabetic patients with neuropathy.

Summary

Direct stimulation of intact forearm skin affects adjacent microvascular blood flux. Pulses of current, known to activate C-fibres effectively, were applied over a period of 1–16 seconds at 2 Hz using transcutaneous stimulation. An increase of up to 50% was observed in skin microvascular blood flux. Increased blood flux correlated well with increasingly painful sensations. Some subjects responded to one or two pulses at 2 Hz, 0.5 ms in duration and 150 volts. A response onset latency of 4–15 s, lasting up to 5 minutes, was recorded. At higher frequencies (4–8 Hz) and more pulses (16–32) vasoconstriction was frequently observed before the usual flux increase. After administration of local anaesthesia (2% ligocaine) the resting skin blood flux increased, but electrical stimulation still produced vasodilatation. The local cutaneous flare response to electrical stimulation was abolished or greatly reduced by capsaicin pretreatment. Excitation of small intracutanous forearm nerve C-fibres produces increased microvascular blood flux which is dependent on local release of vasodilator substances. Thus the neurogenic flare (axon reflex) may have a physiological role in regulating skin blood flow, and nociceptor function may be measured by applying the aforementioned transcutaneous electrical stimulation.

Note Added in Proof: A reduction in the neurogenic vasodilator response to electrical stimulation has now been observed in 25 diabetics with clinical symptoms of early sensory neuropathy.

Acknowledgements

We thank Mr C. Hogan for technical assistance, Mr V. Jones (Hadland Photonic, Mt Waverley) for lending us the Periflux laser doppler blood flux meter, and all the volunteer subjects who participated. The financial support of the Australian Research Grants Scheme and Monash Special Research Grants (to R.A.W.) and of the Lions International Diabetes Institute (to W.M.K.) is also gratefully acknowledged.

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Neurogenic Flare Responses in Chronic Rheumatic Pain Syndromes

*R.D. Helme, G.O. Littlejohn and C. Weinstein**

Chronic rheumatic pain syndromes are poorly understood clinical conditions of unknown cause. The sufferer complains of chronic pain and aching but there is no obvious underlying abnormality. Conditions included in this group include the fibrositis syndrome, 'whiplash', low back pain syndrome, and regional pain syndrome.[1]

The presence of tender points in predictable anatomical locations is essential to the diagnosis of a chronic rheumatic pain syndrome.[2] Exaggerated dermatographia is also commonly observed.[3] This sign is elicted by firm mechanical stimulation over an area of tenderness, especially in the back. The origin of the pain is unclear although it has been suggested to be largely the result of effects within the central nervous system rather than in the primary afferent pathway concerned with the transfer of nociceptive information to the central nervous system.[4]

The presence of dermatographia, however, suggests that activity in the primary afferent pathway may be important in this group of patients. This phenomenon is thought to be due to a local axon reflex mediated by nociceptors of unmyelinated primary afferent nerves [5,6] It has been suggested that polymodal nociceptors are responsible for this neurogenic inflammatory response. We therefore examined the flare response to mechanical stimulation and to topical capsaicin, a chemical method of stimulating local axon reflexes.[7]

Methods

Twelve patients with a chronic rheumatic pain syndrome and 10 controls were examined. Seven patients had the fibrositis syndrome with more than 10 Smythe tender points[1,3] and 5 had the regional pain syndrome with more than 5 regional-

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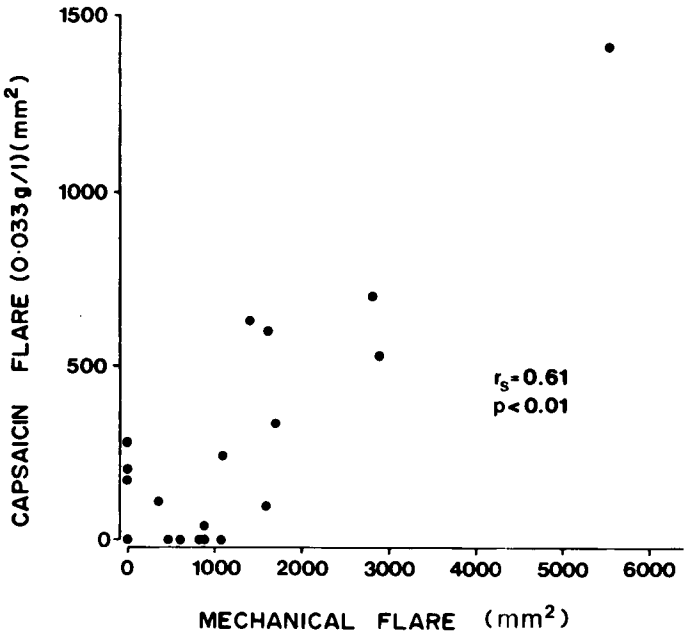

Figure 1. Scatter diagram of flare size (in mm^2) for mechanical stimulation (vertical axis) against chemical stimulation (horizontal axis) for 22 subjects. (Correlation coefficient, $r_s = 0.61$: $p < 0.01$)

ized tender points. All patients had had symptoms for over 3 months and none had abnormal radiology or biochemistry or evidence of inflammation. No controls had symptoms of aching or pain or tender points on examination. No subjects were atopic or were being treated with steroids, anti-histamines or topical medication. Mechanical dermatographia was elicited by the application of a standard firm linear pressure from a wooden swab stick across the mid-dorsal back for a distance of 15 cm. The flare response was outlined and traced at 3 and 10 minutes.

Capsaicin (Sigma) was applied by dispensing pipette as aliquots of 20 μL (in concentrations between 0.005 g/L and 0.2 g/L in 70% alcohol) to 1 cm^2 pieces of blotting paper applied at sites across the shoulders and neck. Seventy per cent alcohol was used as a control. The blotting paper was covered by paper tape for 30 minutes and the flare was then outlined and traced. The area of flare was measured using a digitizing tablet. Flare sizes were compared using the Mann–Whitney U-test. Spearman's rank correlation was used to evaluate the relationship between chemically and mechanically induced flare sizes.

Results and Discussion

The relationship between the area of flare induced by mechanical stimulation and that induced by chemical stimulation is shown in Figure 1. The positive

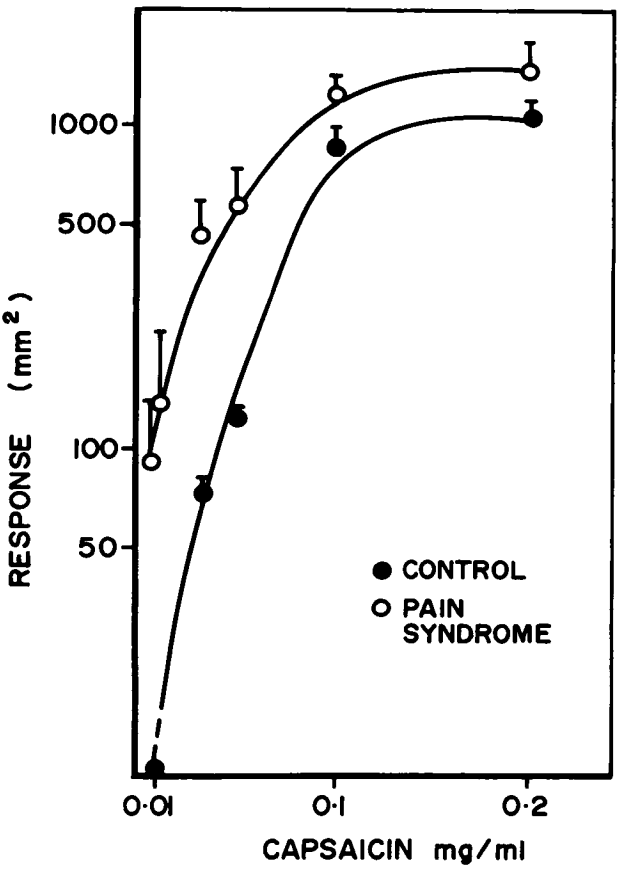

Figure 2. Flare size with different concentrations of capsaicin applied across the trapezoid ridge and neck. Points represented as means ± SE. Differences significant at capsaicin concentrations of 0.02 mg/mL ($p < 0.05$) and 0.033 mg/mL ($p < 0.05$).

correlation suggests that there may be a common underlying mechanism for the responses. We suggest that the polymodal nociceptor is initiating the local axon reflex response to both stimuli.

The response to capsaicin in patients and controls is shown in Figure 2. The patients with a chronic rheumatic pain syndrome had a lower threshold for capsaicin-induced flare. They also had larger flares at concentrations of capsaicin just above threshold. These results demonstrate that peripheral axon reflexes are more active in patients with chronic rheumatic pain syndromes than in normal controls. If polymodal nociceptors are more active in inducing axon reflexes it is possible that they may be more active in initiating transfer of nociceptive information to the central nervous system.

A positive relationship between pain and flare size has been documented

previously for topical capsaicin[7] and thermal stimulation[8] in normal subjects. Our study suggests that increased polymodal nociceptor activity may contribute to the pain experienced by patients with chronic rheumatic pain syndromes. The mechanisms for this activation remain to be elucidated.

Summary

Chronic rheumatic pain syndromes such as the fibrositis syndrome, 'whiplash' syndrome, low back pain syndrome and regional pain syndrome are common clinical disorders of unknown cause. The presence of tender points in predictable anatomical locations is essential to their diagnosis. Exaggerated dermatographia or flare response to mechanical stimulation is also a commonly observed physical finding. Dermatographia is thought to be a local axon reflex mediated phenomenon, and, as such, is a component of the neurogenic inflammatory response. Because neurogenic inflammation may be mediated by polymodal nociceptors we examined the flare response to topical capsaicin, a chemical method of stimulating local axon reflexes, in 12 patients with chronic rheumatic pain syndromes and in 10 controls.

There was a significant correlation ($r_s = 0.61$; $p < 0.01$) between the area of flare induced by mechanical stimulation and the area of flare induced by chemical stimulation for all subjects. Patients with chronic rheumatic pain syndromes had a lower threshold for capsaicin-induced flare responses compared with controls. They also had larger flares at capsaicin concentrations of 0.02 and 0.033 mg/mL ($p < 0.05$) applied as 20 μL aliquots over 30 minutes.

It is concluded that neurogenic flare responses are increased in patients with chronic rheumatic pain syndromes.

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Neurogenic Plasma Extravasation in Response to Mechanical, Chemical and Thermal Stimuli

*P.V. Andrews and R.D. Helme**

The term 'neurogenic inflammation' refers to the vasodilation[1] and plasma extravasation[2] which follows electrical stimulation of peripheral nerves. This response is believed to be mediated by small-diameter primary afferent nerves[3] that contain substance P.[4] Further evidence for the role of substance P has come from the use of the neurotoxin capsaicin that selectively destroys small-diameter primary afferent nerves[2] and subsequently inhibits the inflammatory reaction.

Electrical stimulation has been widely used to induce neurogenic inflammatory responses[5] and to measure the release of substance P from primary afferent nerves.[6–8] More recent studies have attempted to show neurogenic inflammation with physiological stimuli including heat[9,10] and parenteral administration of chemicals,[11] and in 1 study neurogenic inflammation to a mechanical stimulus in the trachea has been demonstrated.[12] Plasma extravasation in these studies was measured as accumulated Evans Blue, a protein-binding dye.

The aim of the present study was to develop a model of the inflammatory response that would allow investigation of mechanical, chemical and thermal stimuli in the one system. The model we describe here is a modification of a blister model of inflammation in the skin.[13]

Methods

Male outbred Sprague–Dawley rats (200–250 g) were used in all experiments. Some animals had been treated with capsaicin (Sigma) (50 mg/kg, administered subcutaneously) on day 2 of life.[15] The effectiveness of denervation was assessed

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by measurement of the substance P content of the skin using a sensitive radioimmunoassay.[14] Animals were anaesthetized with pentobarbitone sodium (50 mg/kg, intraperitoneal) and a femoral vein catheter was inserted. The animals were volume loaded with normal saline (1 mL/50 g) and anaesthesia was maintained with pentobarbitone sodium administered intravenously as required. Animals were maintained at approximately 37 °C with a warming lamp. Blisters were induced on the hind footpad by placing the footpad against a metal suction device maintained at 40 °C by an attached heating element. A negative pressure of 40 kPa produced blister formation in approximately 30 minutes. After a blister had been produced the blister epithelium was removed and a perspex perfusion chamber was placed over the exposed blister base. Perfusion of Ringers' solution over the blister base was maintained using a peristaltic pump (LKB, Sweden) at a perfusion rate of 4 mL/h. The temperature of the perfusate was maintained by feedback from a thermocouple on the blister base.

For mechanical stimulation experiments a perspex rod was inserted through two 'O' rings in the perfusion chamber roof. Wool fabric was used as a mechanical stimulus and this was fixed to the lower end of the rod. The upper end was attached to a micromotor (type 1212, Minimotor SA, Switzerland) that turned the rod at 4 rpm *via* a reduction gearhead (type 12/3 1190: 1, Minimotor SA, Switzerland) and a variable voltage supply. The perfusate was maintained at 42.5 °C at the inlet port by means of a fixed resistor. Experiments were performed for 2 30-minute periods, an initial control period and then a stimulation period. For chemical stimulation the perfusate was maintained at 40 °C. Experiments were performed for 2 30-minute periods, an initial control period and a stimulation period where the blister base was perfused with bradykinin (10^{-4} M) for 10 minutes. For thermal stimulation experiments the perfusion chamber had a heating element attached to the roof. The perfusate was maintained at 40 °C. Experiments were performed for 2 30-minute periods, an initial control period and a stimulation period where the perfusate was heated to 48 °C for 5 minutes.

Perfusate from each period was collected into an equal volume of 2 M acetic acid on ice. Each perfusate sample had its protein content determined by the method of Bradford.[16] The assay had an interassay variation of ± 6% and an intra-assay variation of ± 3%.

Control and stimulation period groups were compared using Student's *t*-test for paired samples. Differences between normal and capsaicin-pretreated animals were compared using analysis of variance.

Results

Capsaicin pretreatment caused a 69% depletion of substance P (0.630 ± 0.121 fmol/mg to 0.195 ± 0.023 fmol/mg) in the skin of the back, as measured by radioimmunoassay. There was no difference in plasma protein concentration between normal and capsaicin-pretreated animals after fluid loading (27.22 ± 0.85 mg/mL to 28.87 ± 1.37 mg/mL).

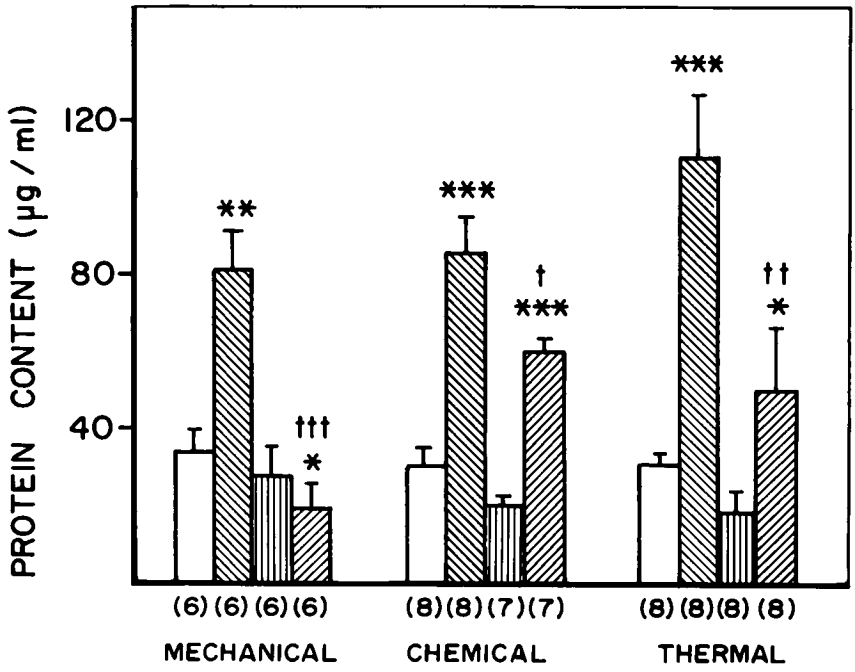

Figure 1. Protein content of perfusate following physiological stimulation. Bars represent means ± SEM. Number of animals per group in brackets. ☐ control period; normal animals ▨ stimulation period; normal animals ▥ control period; capsaicin-pretreated animals ▨ stimulation period; capsaicin pretreated animals. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$. Student's *t*-test for paired data between control and stimulation periods. † $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$. Analysis of variance between stimulation periods of normal and capsaicin-pretreated animals.

Figure 1 shows the effect of a mechanical stimulus on plasma extravasation. There was a significant increase in the protein content of the stimulation period perfusate compared with the control period. In animals that had been pretreated as neonates with capsaicin the mechanical stimulus had no effect on plasma extravasation. When there was no wool attached to the perspex rod during the stimulation period there was no change in plasma extravasation (data not shown).

Chemical stimulation with bradykinin resulted in a significantly increased plasma extravasation into the perfusate. In capsaicin-pretreated animals, chemical stimulation significantly increased plasma extravasation but this increase was significantly less than that in normal animals.

A perfusate temperature of 48 °C for 5 minutes caused a significant increase in plasma extravasation. There was also a significant increase in plasma extravasation in capsaicin-pretreated animals but this increase was significantly less than that in normal animals.

Discussion

In this model the inflammatory reaction, measured as plasma extravasation, has been demonstrated for the first time following physiological mechanical, chemical and thermal stimuli to the peripheral nociceptor in the 1 system. That this plasma extravasation is neurogenically mediated is indicated by the absence or significant reduction of plasma extravasation in capsaicin-pretreated animals following the same physiological stimuli. In this study mechanical stimulation experiments were limited to the use of wool fabric. It is not implied that wool is exceptional amongst textile fibres in inducing the response.

Neurogenic inflammation initially appeared to be a non-physiological curiosity that occurred following electrical nerve stimulation but not after physiological stimulation or during any pathological conditions. Recently, however, it has been proposed that neurogenic mechanisms may modulate the pathological response in rats subjected to a cigarette smoke stimulus,[17,18] noxious thermal stimulation[9] and adjuvant-induced arthritis.[19] All these inflammatory conditions are reduced in adult animals pretreated as neonates with capsaicin. With the possibility that neurogenic inflammation may have some relevance to human pathology it would be useful to have a model where the inflammatory response could be studied in detail. This has not been possible with previously described models.

Advantages of the blister model of inflammation also include the possibility of studying the dynamics of the inflammatory reaction. Collection of perfusate for shorter periods will allow a more detailed examination of the phases of inflammation. Although some aspects of the response are well known,[20] it should be possible to determine how the nervous system is able to modulate the response. Perfusion also allows local application of drugs to the inflammatory reaction rather than having to interpret non-specific effects of systemic administration. Sensitization and desensitization are common observations with nociceptors. The mechanisms of these important effects of nociceptor stimulation are not understood. It may be possible to elucidate some of these mechanisms in the blister model.

Summary

Nociceptors at distal terminals of unmyelinated primary afferent nerve fibres mediate neurogenic inflammation. Most studies have examined only the neurogenic inflammatory response to non-physiological antidromic electrical nerve stimulation. It has not been possible to determine whether polymodal nociceptors mediate the response to physiological stimulation with mechanical, chemical and thermal stimuli. In this study we have induced plasma protein extravasation to stimulation with wool fabric ($81 \pm 9\,\mu g/mL$), bradykinin ($86 \pm 8\,\mu g/mL$) and heat ($111 \pm 16\,\mu g/mL$) in perfused vacuum-induced blisters on the rat hind footpad. These values represent significant increases over the protein concentration of $30\,\mu g/mL$ ($p < 0.005$; $p < 0.001$; $p < 0.001$, respectively; $n = 6$ to 8 for each group). Plasma extravasation was significantly reduced for each stimulus modality

($p < 0.001$; $p < 0.05$; $p < 0.01$, respectively) in animals pretreated as neonates with capsaicin, demonstrating that part of the response is neurogenically mediated. It is concluded that neurogenic inflammation to polymodal physiological stimuli occurs in the rat through capsaicin-sensitive primary afferent nerve fibres.

Acknowledgements

The technical assistance of Miss K. Thomas is gratefully acknowledged. This work was supported by a grant from the Wool Research Trust Fund on the recommendation of the Australian Wool Corporation.

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Magnetoencephalography: Locating the Source of P300 *via* Magnetic Field Recording

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Background

Neuromagnetic Measurements

Every electric current produces a magnetic field in accordance with well established laws of magnetic induction. Thus all of the commonly measured manifestations of the body's electrical activity, such as the electrocardiogram, the electroencephalogram and evoked potentials, have magnetic counterparts – the magnetocardiogram, the magnetoencephalogram and magnetic evoked fields. Magnetic fields and electric potentials arising from the same generating source tend to have similar waveforms, and since the present generation of biomagnetic technology is somewhat inconvenient to use, and its results are relatively noisy, there might appear to be little justification for departing from the more familiar and proven electrical potential measurements. However, magnetic fields differ markedly from electric potentials in their distribution over the surface of the body. This difference is crucial because there is reason to believe that magnetic field measurements, unlike their electrical counterparts, in most cases provide a reliable means of determining the position within the body of the generating source.

Figure 1 illustrates the flow of current and magnetic field lines associated with a localized current dipole source, a useful model for many types of neural activity. The current circuit is completed by the return flow of volume currents in the tissue

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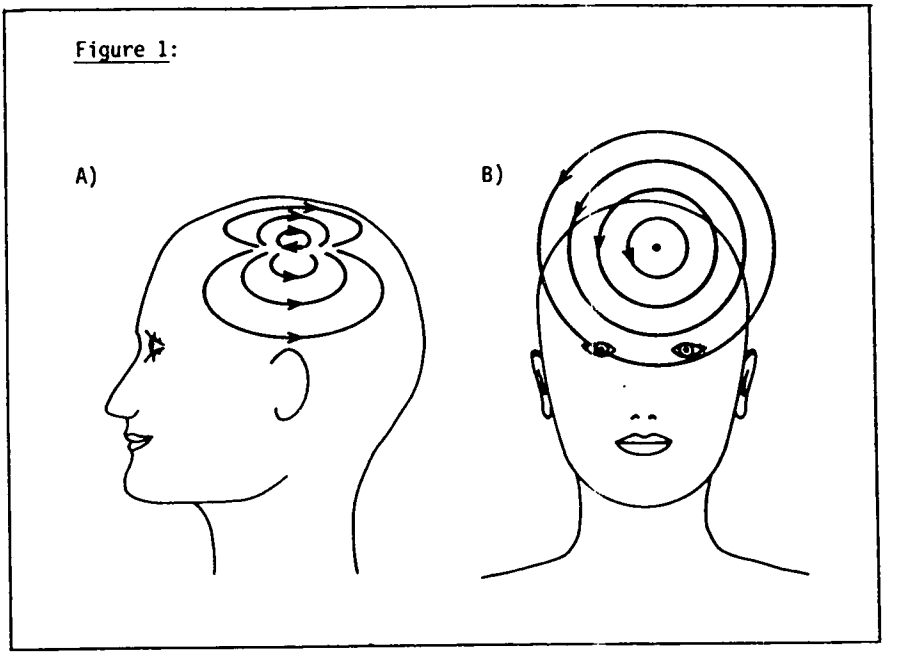

Figure 1. Cortical current dipole showing (A) volume currents produced by a current dipole, and (B) its magnetic field distribution.

surrounding the source. Part of the volume current flows in the subcutaneous layer and gives rise to the potential differences which are measured on the scalp using electrodes. Since the distribution of volume currents is in general a complicated function of the geometry and conductivities of the various tissues through which they flow, it is very difficult to determine the position of the dipolar source from potential measurements with any accuracy. The magnetic field due to the current dipole, on the other hand, has a simple circular pattern which emerges from the head as shown, and is essentially undistorted by the magnetically transparent biological tissue. The position, orientation and strength of the source may be determined unambiguously from measurements of its own field outside the head.

Certain qualifications of this optimistic picture must be mentioned. The first concerns the effects of volume currents, which themselves produce magnetic fields which may be expected to modify the simple circular pattern shown in Figure 1. These effects may be minimized by measuring the magnetic field in a direction normal to the surface of the head. It has been shown theoretically and confirmed in electrolytic tank models that, for several simple surface shapes and conductivity distributions, the normal component of the magnetic field of the volume currents is small or zero.[1,2] While direct application of these conclusions to a complex

anatomical structure like the head is difficult, provided measurements are made perpendicular to the scalp, it does seem likely that the field measured will be predominantly that of the source, with only a secondary contribution from the field due to volume currents. This contrasts with the situation with electrical potential measurements, which are produced entirely by volume currents.

A second qualification derives from the theoretical work of Grynszpan and Geselowitz,[3] who showed that certain dipole sources produce no magnetic field outside the head, and hence are magnetically invisible. Broadly, these are sources which are oriented radially within the head. For the general case of an obliquely oriented source, only its tangential component will be detected magnetically. Estimates of the proportion of brain sources whose orientations are unfavourable for magnetoencephalography vary. Since radial sources usually produce good electrical signals, joint measurement of potentials and fields, as practised in this study, should ensure that no important sources are missed.

Thirdly, it cannot be assumed that the localized current dipole is an adequate representation of neural activity in every case since spatially extended sources or multiple sources may be present in certain cases. The current dipole produces a characteristic field map. It consists of 2 regions of maximum field intensity, one entering and one leaving the head, separated by a distance which is directly related to the depth below the surface of the dipole. A surprisingly good first estimate of the position of the source is obtained by assuming it to be located below a point midway between the maxima, lying perpendicular to the line joining them, and at a depth equal to the length of that line divided by 1.41. Field maps differing significantly from those described above may arise from noisy or sparse data, but may also be indicative of the presence of sources other than a single dipole, or possibly some other failure of the modelling assumptions, such as volume current effects.

Finally, an important conceptual and operational difference between magnetic field and electric potential measurements should be mentioned. The magnetic measurement is made at a single point, in contrast to the electrical measurement which is always a measure of the potential difference between 2 points. Of course multiple measurements must be made if one wishes to build up a map of the distribution of fields over the surface of the head, and this is equally true of electrical measurements. However, in neuromagnetic measurements there is no analogue of the reference electrode in electrical measurements, and it is possible to speak unambiguously of the magnetic field at any one location. In this study the magnetic field measurements were undertaken on a spherical co-ordinate system based on the 10–20 system of electrode placement (Figure 2). The top half of the head approximates a sphere. The equator of this sphere was taken to be a line running around the head through points which were 10% of the distance from the nasion to the inion, up from the nasion and the inion and the electrode points T3 and T4 of the 10–20 system. The origin then lay in the centre of the head. The spherical co-ordinate system is the most convenient for marking points on the surface of a sphere and this was defined in the usual way, *i.e.* theta (θ) was the angle between the x axis and the projection of the position vector P in the XY plane, and phi (ϕ) was the angle between the z axis and the position vector P.

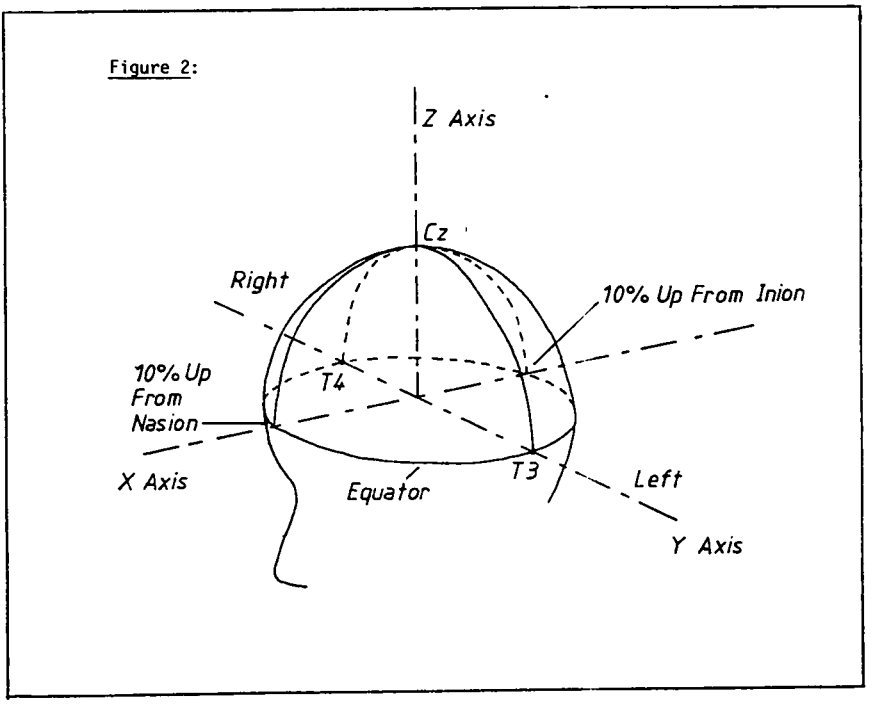

Figure 2. The spherical co-ordinate system used to undertake the magnetic field measurements.

SQUID Gradiometer

Neuromagnetic fields are very weak, generally less than one picotesla (1 pT or 10^{-12} tesla). The earth's magnetic field, for comparison, is about 50 microtesla, or more than 7 orders of magnitude larger. Such small fields can only be measured using a SQUID, or superconducting quantum interference device, a magnetic flux sensor of very low intrinsic noise and high sensitivity. SQUIDs were developed in the mid-1960s and were first used to detect magnetic fields from the heart[4] and the brain[5] in the early 1970s.

In a hospital environment the level of ambient magnetic noise may exceed by several orders of magnitude that of the neuromagnetic signals under investigation. Such noise arises by magnetic induction from currents in the wiring of the building and in computers and other nearby electrical equipment, as well as from movement of nearby steel objects such as lifts, motor vehicles, trolleys and watches. The earth's constant field is usually not a problem as most commonly studied phenomena may be high-pass filtered without loss of information and the constant effects thereby eliminated. However small vibrations of the magneto-

meter in the earth's field may produce interfering noise components at the vibration frequency. Also the earth has an alternating current magnetic field which may amount to several picotesla in low frequency measurements.

To minimize the effects of such ambient noise sources the SQUID is equipped with a set of input coils wound in such a way as to make the instrument a gradiometer, that is, a detector of spatial gradients in a magnetic field. These coils are carefully balanced to reject optimally fields from remote sources (whose gradient tends to be small even when the field itself is strong) and to detect those from sources a few centimetres away, whose gradient is relatively large. The coils are superconducting and are mounted, with the SQUID, in a Dewar flask of liquid helium at a temperature of 4.2 K (about −269 °C), with the lowest coil only a few millimetres from the Dewar nose so that it can be positioned within about a centimetre of the head. The gradiometer used at Westmead Hospital is a third order type manufactured by CTF Systems Inc. designed for operation in harsh magnetic noise environments. It is mounted in a simple gantry permitting vertical movement and one axis of tilt. The SQUID gradiometer and its associated electronics produce an electrical output which may be processed by filtering, digitizing and averaging in the same way as amplified electrophysiological signals.

The P300 Event-Related Potential Component

The P300 component has been widely investigated as a physiological indicator of cognitive processing. It occurs approximately 300 ms post-stimulus in response to novel (rare) and task-relevant stimuli to which the individual pays attention. Its latency reflects the time taken to make a task-related decision, and its amplitude is thought to reflect factors which include the subjective probability of stimulus occurrence and decision certainty. P300 increases in amplitude with the rarity of the eliciting stimulus; it may even be recorded when an expected stimulus is not presented, a feature indicative of its endogenous character.

The latency of the P300 component is being investigated as an objective means of distinguishing persons with dementia from normals and from those with psychiatric disorders, particularly depression, with which dementia may be confused in its early stages. Since P300 is thought to reflect aspects of cognitive processing, an abnormal delay in its latency might be regarded as evidence of cognitive slowing, which is one of the hallmarks of dementia. A number of studies have found that the latency of this component is abnormally delayed in most cases of dementia,[6–10,23] but not in depression[6,10,23] or schizophrenia.[6] Other studies, using different paradigms to elicit P300, have found less consistent results.[1,12]

In research of psychiatric disorders, a diminished amplitude of the P300 component has consistently been found in schizophrenia.[13–19] The amount of reduction may also be related to the severity of psychopathology.[20] There is also some evidence that reduced P300 amplitudes are present in children who may be at high risk genetically for developing schizophrenia: P300 amplitude may thus be a premorbid indicator of this condition.[21,22] However it is not certain how specific these findings are to schizophrenia. One study, for example, has found that P300 is

also reduced in depression, although the amount of reduction appears to be less than in schizophrenia.[22]

Knowledge of the generator site(s) of P300 may help elucidate which areas of the brain are perhaps dysfunctional in the above disorders. Magnetic field recordings were undertaken in the present study to determine the source of the P300 component.

Methodology

The Auditory Paradigm used to Invoke the Electrical and Magnetic P300

Twenty-five simultaneous magnetic and electrical recordings were undertaken in 2 normal subjects, one man and one woman, both 28 years old. Two hundred binaural tone bursts (50 ms duration, 5 ms rise–fall time) at 80 dbSPL were presented through air conduction headphones at a rate of 1 per second. Eighty-five per cent of the tones were of 1500 Hz (the frequent tones) and the remaining 15% were of 2000 Hz (the rare tones). The rare and frequent tones were randomly intermixed. The subjects were instructed to ignore the frequent tones and to keep a count of the number of rare tones heard. This number was reported (correctly in each case) during rest periods of one minute.

EEG Recording

For each recording a tin electrode was affixed to the scalp at C_z of the 10–20 system and referenced to linked ear lobes. The ground electrode was positioned in the middle of the forehead. The EEG was amplified to 50 000 times with a bandpass of 1–100 Hz, and averaged for 600 ms altogether (100 ms pre-stimulus and 500 ms post-stimulus) for rare and frequent tones separately. The P300 component was defined as the most positive point (after 250 ms) of the average waveform to the rare tones. The amplitude of P300 was measured from baseline to peak. This baseline was defined for each subject as the average voltage of the 100 ms epoch before the onset of each stimulus. Multi-electrode recordings (from 14 sites) were also carried out over two recording runs.

Magnetic Field Recording

Magnetic field recordings in both subjects were undertaken over the right hemisphere. The signal was passed through a 50 Hz mains rejection filter, then through a bandpass filter of 1–20 Hz with 40 dB gain and then to the analogue-to-digital converter. The magnetic signal was then digitally processed and averaged in the same manner as the electrical event-related potential. The biogradiometer was moved systematically to 28 sites over each subject's right hemisphere and magnetic field recordings were made from each site.

Figure 3:

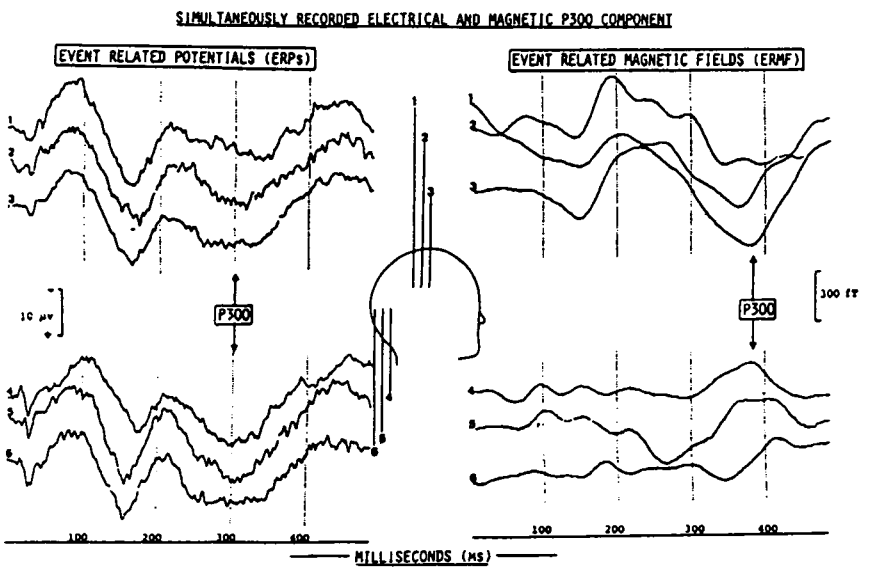

Figure 3. Simultaneously recorded electrical and magnetic field measurements from 6 sites (female subject). Note reversal of the polarity of P300 magnetic field recordings, indicating the areas of entry and exit of the magnetic fields from the head. The magnetic P300 is delayed by 50 ms compared with the electrical P300 because the magnetic signals were passed through an additional bandpass filter.

Results

Raw tracings of the simultaneously recorded electrical and magnetic P300 component are illustrated in Figure 3. The image of the electrical P300 shows a centroparietal maximum and a wide distribution of this component (Figure 4A). The image of the magnetic P300 component shows a relatively localized dipolar field (Figure 4B). After collection of all the magnetic field data, a computer program determined the location of the current dipole which had produced the magnetic fields recorded on the surface of the head. This was not determined directly, but by a process where the dipole was placed at a likely starting point and the theoretical dipole distribution was calculated; the dipole position was then adjusted iteratively until the best agreement between the model and real measurements was obtained. The computed source location in the right hemisphere was 2.7 cm deep and 2 mm posterior to T_4 in the female subject. The orientation of the dipole was 7 degrees (clockwise) from the vertical axis. Similar results were obtained in the male subject.

Figure 4

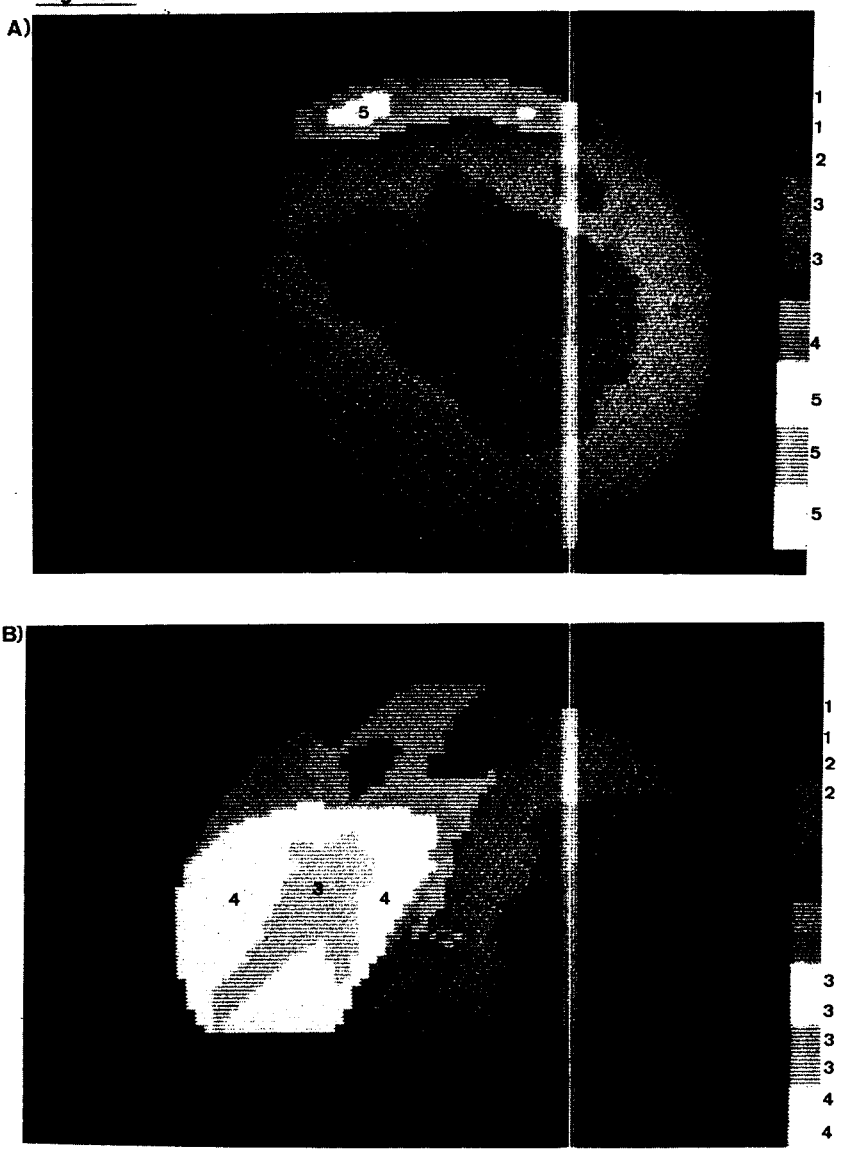

Figure 4. (A) An image of the topographical distribution of the electrical P300 amplitude as recorded from 14 sites. The picture looks down upon the head with the nose protruding. Although the highest amplitude (1, 2) is around the central C_z region, P300 has a wide distribution all over the scalp (3–5). In (B) an image of the P300 magnetic distribution in the right hemisphere is shown in the same subject. The magnetic dipole is located at D, midway between the points at which the magnetic field emerges from the head (1, 2) and enters the head (3, 4).

Discussion

The above results, obtained by simultaneous electrical and magnetic recording, indicate that at least a significant portion of the electrical P300 obtained in response to novel auditory stimuli originates in the temporal lobe. The distribution of the magnetic fields indicates that these sources are not widespread, but are relatively restricted in extent compared with the electrical P300. These results provide preliminary evidence of a localized source of the endogenous auditory P300 component elicited by aspects of cognitive processing. The neural generator of any other event-related potential component can also be determined using similar procedures. Importantly, since event-related potential components earlier than P300 may be recorded with less concentration and voluntary attention on the part of the subject, a large number of trials may be recorded within each average. More reliable magnetic field maps might perhaps be obtained of earlier rather than later event-related potential components, particularly with a single channel bioradiometer such as was used in this study.

Conclusion

This is the first neuromagnetic recording undertaken in Australia. The results show that magnetic field recordings are capable of providing information about the generator sites of evoked potentials. Such information cannot be obtained accurately from electrical recordings from the scalp.

If magnetoencephalography fulfils its promise of allowing us to locate with a high degree of accuracy the generators of event-related potential components and EEG rhythms, it may also provide us with information concerning the specific sites within the brain of those electrophysiological abnormalities which have been found in neurological and psychiatric disorders.

Summary

A description is given of the theory and instrumentation involved in measuring magnetic fields of the brain. The magnetic counterpart of event-related potentials are capable of locating more accurately the generators of these electrical signals. Preliminary results of the first application of magnetoencephalography in Australia are presented. These localize the generator of the auditory P300 event-related potential component to the temporal cortex.

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Gliomas Presenting Outside the Central Nervous System

*B.J. Brew and R. Garrick**

Extracranial metastasis as the presenting feature of a glioma is recorded only rarely. This paper outlines the clinical features of 2 patients whose initial presentations were related to extracranial metastases from an astrocytoma and considers possible mechanisms of pathogenesis.

Case Reports

Case 1

A 56 year old man presented with right facial swelling and pain that had developed over the preceding 3 months. Right-sided deafness and facial numbness had developed 2 months before admission and focal olfactory seizures were noted after admission to hospital.

Physical examination revealed swelling in the region of the right maxilla and anterior cervical fullness on the right. Sensation was diminished in the maxillary division of the right trigeminal nerve. A partial peripheral right facial nerve palsy and conductive deafness were also observed. Palatal sensation and movement were reduced on the right and the soft palate was swollen on that side.

Computerized tomography (CT) revealed a mass in the right maxilla with extension into the pharynx, and also a cystic right parietal lesion (Figures 1 and 2).

An initial biopsy of the swollen soft palate showed features of an astrocytoma with positive staining for glial fibrillary acidic protein (Figures 3 and 4). At subsequent craniotomy a tumour was found in the right parietal lobe; there was no breach of the dura and no surface vascular disturbance. Histology revealed a high grade astrocytoma with positive staining for glial fibrillary acidic protein.

The patient was treated with radiotherapy and survived for 2 years before progressive neurological deterioration. An autopsy was not peformed.

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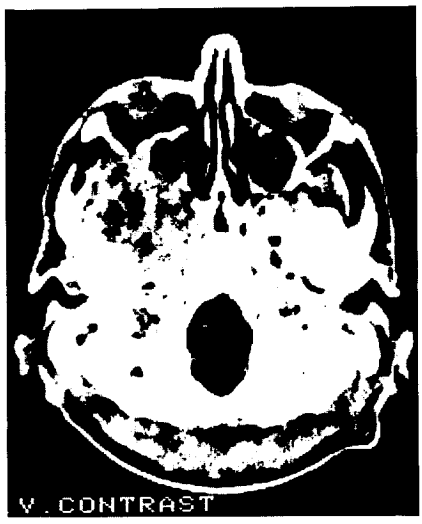

Figure 1. (Case 1) CT scan showing large soft tissue mass in the deep right maxillary and pharyngeal spaces.

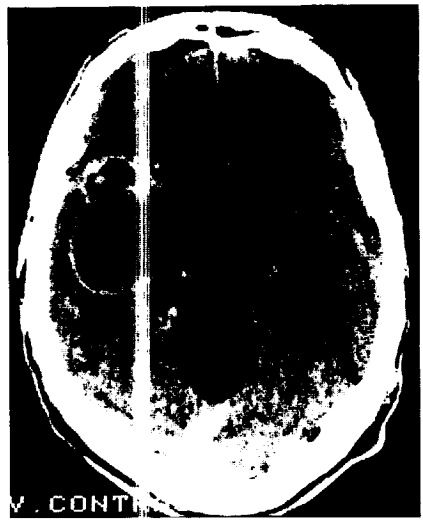

Figure 2. (Case 1) CT scan without contrast showing large cystic deep right temporal lobe mass lesion.

Figure 3. (Case 1) Glial fibrillary acidic protein stain. High power view of nasopharyngeal tumour confirming its neural origin.

Figure 4. (Case 1) Haematoxylin and eosin stained high power section of nasopharyngeal tumour showing both astrocytoma and normal skeletal muscle elements.

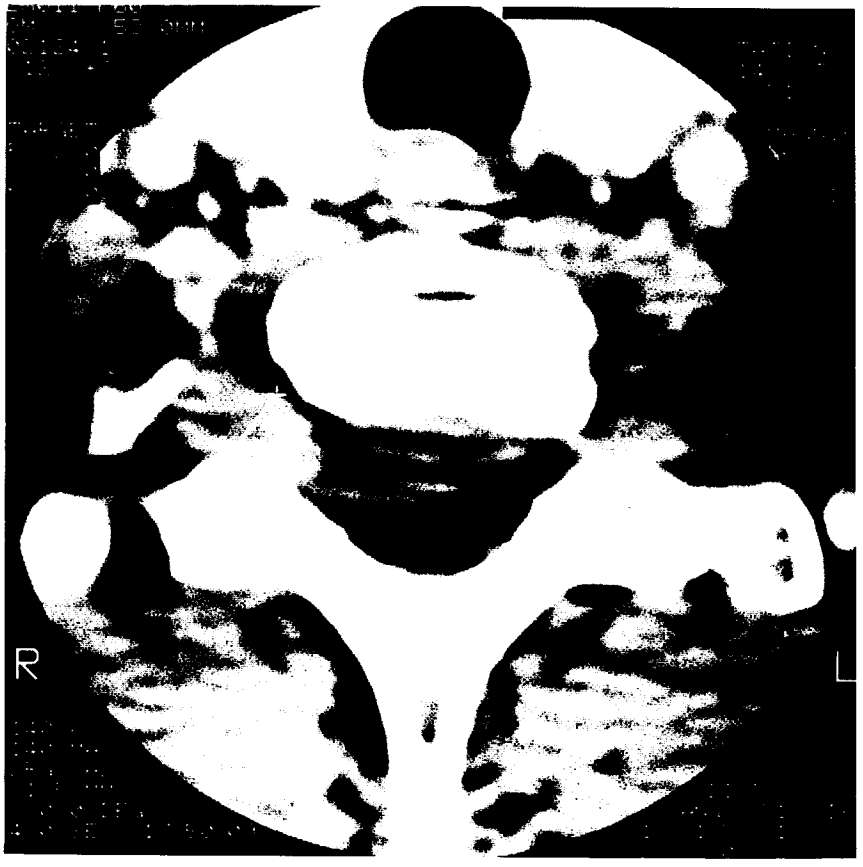

Figure 5. (Case 2) CT scan without contrast of C7 level of cervical spine showing bilateral masses in neural foramina.

Case 2

A 60 year old woman presented with a 2 month history of painful paraesthesiae involving the right fourth and fifth fingers, the medial aspect of the forearm and the arm. Electromyography showed evidence of mild denervation of the abductor digiti minimi. CT scan of the cervical spine showed soft tissue masses in the intervertebral foramina at C7–T1 level (Figure 5). Two weeks before reassessment, she noted numbness of the lateral aspect of the left leg and tingling in the saddle area.

Weakness of the intrinsic muscles of the right hand and diminished sensation in the right C8 dermatome were observed. Vibration sense was impaired at the ankles bilaterally; other modalities of sensation were normal.

Full spine myelography showed only minor spondylotic changes. Cerebrospinal fluid protein was elevated at 1937 mg/L. The IgG/albumin ratio was elevated at 28% (the normal range being less than 14%); no oligoclonal bands were observed. Five lymphocytes cm^{-3} and 10 mononuclear cells cm^{-3} were detected but no malignant cells were seen on cytospin. CT of the brain revealed 2

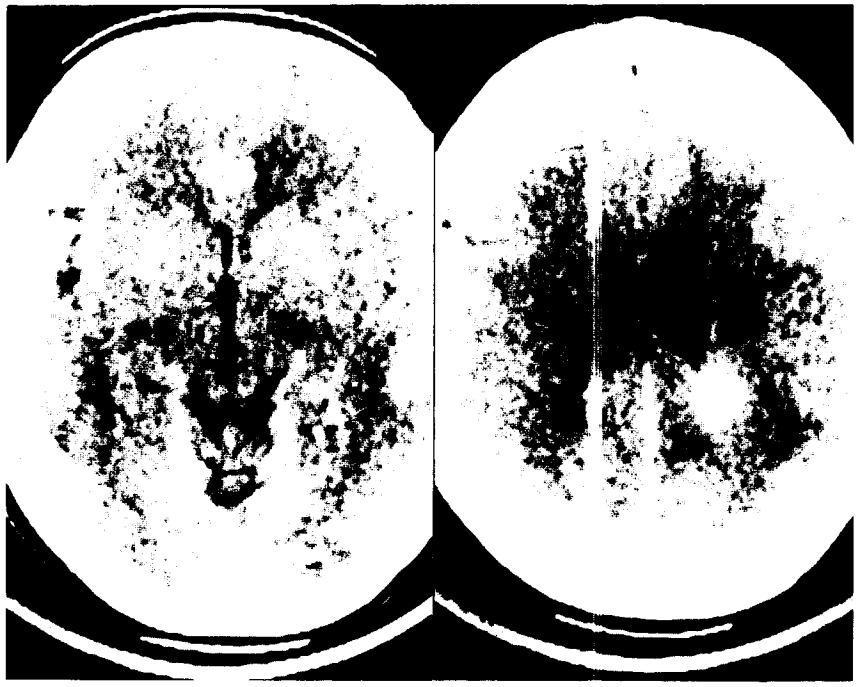

Figure 6. (Case 2) CT scan of head with contrast showing contrast dense lesions at anterior end of falx cerebri and posterior tip of left lateral ventricle.

small lesions, one at the anterior end of the falx and the other at the posterior tip of the left lateral ventricle (Figure 6).

At cervical laminectomy a tumour was found involving the C8 dorsal root ganglion on the right side, 3 mm beyond the dura and not in continuity with it. A high grade astrocytoma was identified on histological examination (Figure 7). The specimen was positive for glial fibrillary acidic protein (Figure 8).

Over the subsequent weeks, obstructive hydrocephalus developed which required the insertion of a ventriculo-peritoneal shunt. Treatment with radiotherapy and chemotherapy (CCNU) was instituted. However, the patient died of overwhelming sepsis 4 months after presentation. An autopsy was not performed.

Discussion

In 1955 Weiss[1] set out 4 criteria that he felt should be fulfilled before a diagnosis of metastasing central nervous system tumour could be accepted. These were that (i) the presence of a single histologically characteristic tumour of the central nervous system must have been proved, (ii) the clinical history must indicate that the initial symptoms were due to this tumour, (iii) a complete

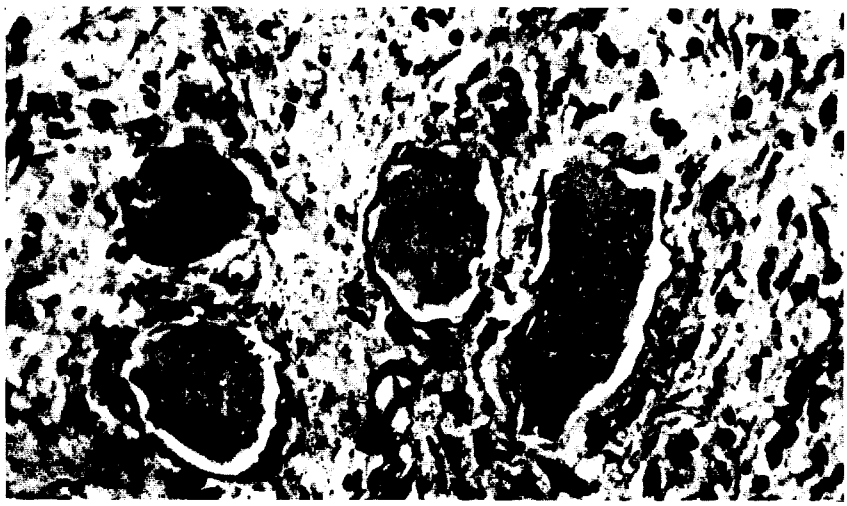

Figure 7. (Case 2) Haematoxylin and eosin stained high power section of C8 nerve root showing high grade astrocytoma and normal dorsal root ganglion elements.

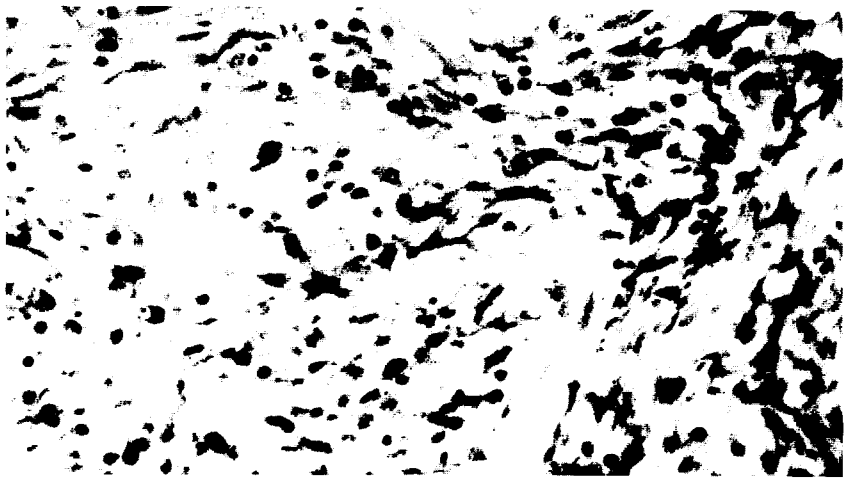

Figure 8. (Case 2) Glial fibrillary acidic protein stained high power section of C8 nerve root lesion confirming the features of a high grade astrocytoma.

necropsy must have been performed and reported in sufficient detail to exclude the possibility of any other primary tumour site and (iv) the morphological appearance of the tumour of the central nervous system and the distant metastases must have been identical after due allowance for differences in degree of anaplasia. Though neither of our 2 cases fulfils all of these criteria, it is nonetheless felt that they should be accepted as examples of glioma metastases as there was positive staining of both specimens for glial fibrillary acidic protein. In addition, the histology was independently reviewed in each case. There is also the possibility that these cases represent extracranial ectopic gliomatous tissue. This seems unlikely since the only reported cases of such a condition involved children and have not been associated with glioma in the brain.[2]

To date, 8 cases of extracranial spread of glioma in the absence of surgery have been described.[3–10] Several hypotheses have been advanced to explain the rarity of extracranial gliomatous metastases. Ley *et al.*[11] discussed 5 relevant factors, as follows: (i) the absence of true lymphatics in the central nervous system, (ii) the dense dural coats of venous sinuses retarding neoplastic invasion, (iii) the thin walled small cerebral veins which may collapse before advancing tumour, (iv) the failure of neoplastic neurological cells to survive in foreign territories, and (v) the rapid evolution of cerebral tumours to cause death before metastases have time to develop. Our two cases and those previously described in the literature would seem to render it unlikely that neoplastic glial cells fail to survive outside the central nervous system or that rapid progression of intracranial neoplasia causes death before metastases have time to occur. The exact reasons for extracranial glioma spread remain unknown; perhaps immunological factors play a role.[12]

The route by which intracranial gliomas metastasize in the absence of surgery has been considered to be haematogenous[3] through venous sinus invasion, or *via* lymphatics.[6] Case 2 and perhaps Case 1 raise the possibility of neural spread of malignant cells. The presumed primary tumour in Case 2 was periventricular in location. It is likely that malignant cells could have seeded the cerebrospinal fluid and then infiltrated nerve roots.

These 2 cases indicate that metastases from intracranial gliomas may occur in the absence of surgery and may be the presenting feature of the illness. It is possible that a neural pathway of spread may operate in some cases.

Summary

Tumours outside the central nervous system rarely prove to be intracranial glioma metastases. The mechanism of glioma metastasis has been thought to be related to dissemination of tumour cells either at the time of surgery or later through the surgical defect. However, 8 cases have been recorded to date in which metastases have occurred in the absence of surgery. This report details the clinical findings in 2 such patients. One presented with a pharyngeal mass that was found to be a metastasis from an anatomically remote parietal lobe astrocytoma. The other patient presented with a C8 nerve root tumour which was external to the dura. Biopsy revealed an astrocytoma that had metastasized from the roof of the lateral

ventricle. Possible mechanisms of pathogenesis are discussed, including that of neural spread.

Acknowledgements

We are grateful for the generous assistance of Dr H. Okazaki who reviewed the histology in both cases.

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Neoplastic Angioendotheliosis

B.J. Brew, D.J. O'Sullivan,* P. Darveniza,* G. Selby,† J. Fryer‡ and W. Evans***

Neoplastic angioendotheliosis is an unusual malignant disease of blood vessels, often with neurological complications. We report 3 patients who had widespread and variable neurological involvement. The correct diagnosis was not made during life in any case, but was established at autopsy. We hope that the presentation of the symptoms and signs of these cases will make earlier diagnosis during life easier so that any available treatment can be instituted.

Case Reports

Case 1

A man, aged 67, presented to St Vincent's Hospital in October 1982 with difficulty in walking and paraesthesiae of the soles of his feet. He had normal power, preserved knee jerks, absent ankle jerks, flexor plantar responses and loss of pin prick and light touch from S1 to S5 bilaterally. General medical examination showed no abnormalities and nor did routine haematological and immunological studies. CSF analysis was normal and a myelogram showed only minor L4-5 spondylotic disease. No definite diagnosis was made. Five months later he was readmitted because of sudden weakness of his legs and urine retention. The weakness improved within an hour and bladder function recovered over several days. Repeat myelogram showed no change and the CSF protein level was 0.76 g/L. A CT scan after the myelogram demonstrated canal stenosis and eventually a lumbar decompression laminectomy was carried out, but no improvement was achieved. Because of the fluctuation in his symptoms, angioma of the lower cord was considered a possibility but full spine myelography failed to reveal any disease. His clinical condition deteriorated with the development of a spastic paraparesis, bilateral extensor plantar responses and retention of urine. Sensory examination remained unchanged; there was no improvement with steroid therapy. A CT scan of the brain showed mild atrophic changes and detailed neurophysiological studies were

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normal, apart from a conduction delay in the thoracic spinal cord in sensory evoked potentials. He was transferred to the Royal North Shore Hospital Spinal Unit for management of paraplegia. While he was there he was very confused mentally and it was thought that he was dementing. The EEG showed diffuse bilateral slow activity but no focal abnormalities. At the end of 1983 he had a complete spastic paraplegia but otherwise remained reasonably stable until February 1984. He then deteriorated fairly rapidly with mental confusion, diplopia and divergent squint and had some seizures. Examination then showed a spastic paraplegia with a sensory level at T4. There was also a left hemianopia, conjugate gaze palsy to the left, a mild paresis of the left arm and a right-sided neglect. A CT brain scan showed moderate cortical atrophy with a non-enhancing low density area in the right temporal lobe. The CSF protein had by then risen to 1.0 g/L but the fluid contained no cells and no malignant cells. Culture of the CSF was negative. Within 2 weeks he improved spontaneously and all his cerebral symptoms resolved. He was left only with a mild weakness of the left side of the face. The spastic paraparesis persisted and the sensory level dropped to T6. He was discharged to his home early in April 1984, but his improvement was short lived. He deteriorated rapidly, became semiconscious and eventually lapsed into coma. He died on 6 June 1984. Post-mortem examination established a diagnosis of neoplastic angioendotheliosis (see below).

Case 2

A man, aged 65, with a past history of migraine and hypertension presented in September 1983 with an attack of severe headache, drowsiness, speech disturbance and impaired memory. Migraine was diagnosed but it was 5 weeks before he improved. No investigations were performed and according to the family he never fully recovered. Further episodes occurred which were associated with clumsiness of his right hand. Following each attack his memory became worse. He was admitted to St Vincent's Hospital in January 1985 because of further deterioration. Examination revealed impairment of memory, slow mentation, dysphasia and mild right hemiparesis. General medical examination was normal. Computerized tomography (CT) of the brain (Figure 1) demonstrated non-enhancing low density areas in the left fronto-temporal, left occipital and right occipital regions; full investigations for a primary malignancy including chest x-ray, abdominal CT scan and bone marrow examination were negative. Cerebrospinal fluid analysis revealed 20 lymphocytes per mm^3, a protein level of 2.0 g/L, a negative Gram stain and no growth on culture; cryptococcal antigen testing was negative. Cerebral angiography showed slight elevation of right middle cerebral artery, but was otherwise normal. Detailed immunological studies were normal and progress CT scans showed enlargement of the low density areas. A trial of corticosteroids and acyclovir produced no improvement and his clinical condition deteriorated rapidly. He died 2 weeks after admission. Neoplastic angioendotheliosis was diagnosed at post-mortem examination.

Case 3

A man, aged 69, presented with a history of recurrent falls and confusion over the preceding few months. He had a background of stable angina and a previous infarct in the right basal ganglia. Whilst in hospital a variable quadriparesis developed with a fluctuating sensory level, urinary retention, confusion and fever. Myelography was normal, but the CSF contained 16 lymphocytes per mm^3 and a protein level of 1.056 g/L. CT scan of the brain showed an area of infarction in the right basal ganglia. Over subsequent weeks his condition deteriorated and he died of a cardiac arrest. A complete autopsy was performed and the histological changes of neoplastic angioendotheliosis were found. No other malignancy was found.

Pathology of Case 1

General post-mortem examination showed severe generalized atherosclerosis with ischaemic myocardial fibrosis and an abdominal aortic aneurysm. No macroscopic tumour was found and there were no enlarged lymph nodes.

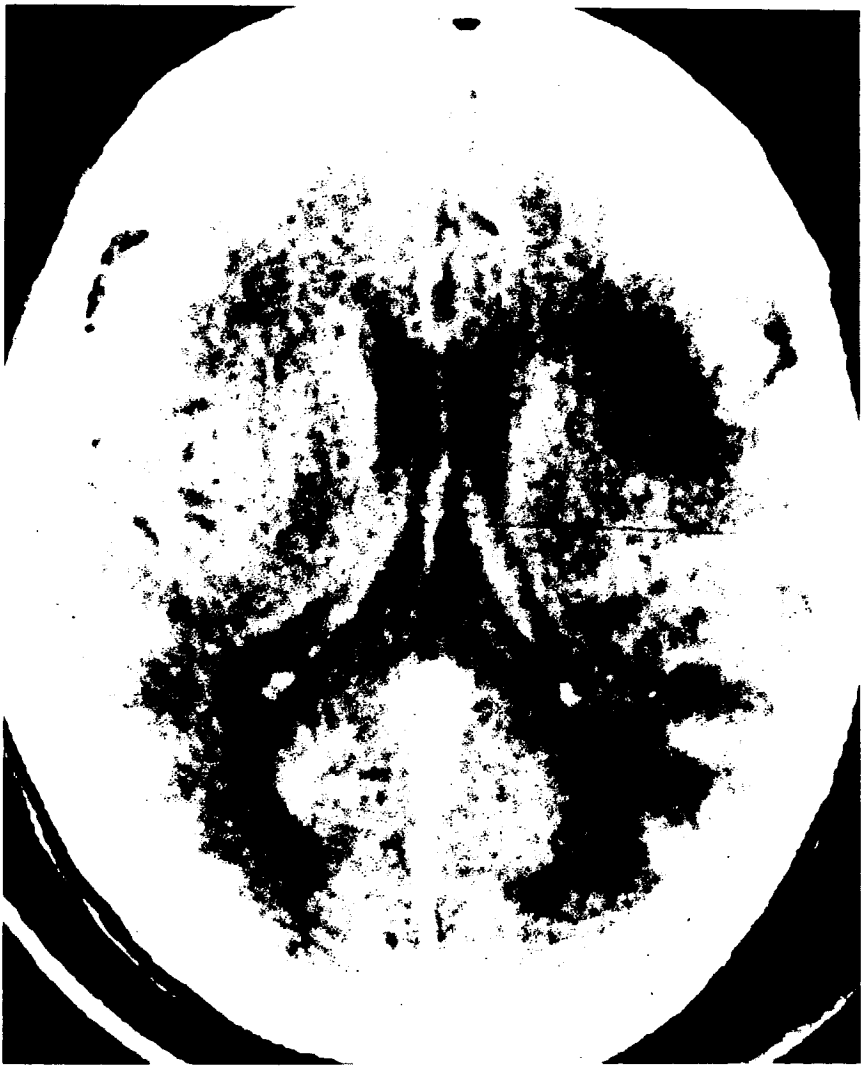

Figure 1. CT scan showing non-enhancing areas in left frontotemporal, left occipital and right occipital areas.

The brain weighed 1430 g and no external abnormalities were evident. The vessels of the circle of Willis contained moderate atheroma but were patent. Sectioning of the brain after fixation revealed multiple areas of softening in both cerebral hemispheres and cerebellum; the largest infarct, in the right frontal lobe, measured 3.5 × 2.0 cm.

In the spinal cord there was marked softening in the third and fourth thoracic segments and, distal to this, the cord was shrunken and firm with thickening and adhesions of the leptomeninges.

Veins around the nerve roots of the cauda equina were distended but no vascular malformation or tumour was present.

Microscopy revealed malignant tumour cells within small blood vessels in the tongue, thyroid, mediastinum, heart, kidneys and prostate. The proliferating cells in all viscera were confined to the vascular lumina.

In the central nervous system there was similar extensive intravascular neoplastic proliferation associated with the infarcts observed macroscopically in the brain and spinal cord. Tumour involved small leptomeningeal and intracerebral vessels and capillaries within cranial nerves also contained malignant cells. The anterior spinal artery was occluded by tumour in the lower cervical segments and showed focal occlusion in the thoracic cord. There was extension of tumour into septal branches and small intramedullary vessels. In the lumbo-sacral segments there was intimal fibrosis and evidence of recanalization in the anterior spinal artery. Posterior vessels were also involved by tumour, particularly in the thoracic and lumbo-sacral regions, and there was recanalization in posterior spinal arteries in the third thoracic and third lumbar segments.

The cerebral infarcts contained foamy macrophages and were surrounded by varying degrees of myelin rarefaction, astrocytic hyperplasia and vascular proliferation. Microscopic foci of softening were present in the brain stem. Extensive recent necrosis was present in the posterior half of the spinal cord in the third and fourth thoracic spinal cord segments, with some anterior sparing (Figure 2). Discrete microscopic foci of necrosis were scattered in the distal thoracic and lumbar cord. The sacral cord showed almost complete demyelination associated with marked loss of anterior horn cells, considerable gliosis, and proliferation of small capillary vessels throughout the grey matter. Marked secondary demyelination was present in the long tracts in the intervening cord.

A high nuclear/cytoplasmic ratio was seen in the neoplastic cells. The nuclei were irregular and often folded with coarsely clumped chromatin and numerous mitoses. The cells appeared as clumps in the vascular lumen (Figure 3) or were seen in continuity with the endothelial lining cells. In the anterior spinal artery tumour cells were also observed in a subendothelial location. Small mature lymphocytes were present in perivascular areas but no extravascular tumour cells were found.

At electron microscopy, typical endothelial lining cells were identified adjacent to hyperplastic endothelial cells, the nuclei of which contained prominent nucleoli. Occasional malignant cells appeared to line the vessel walls in continuity with hyperplastic endothelial cells, suggesting a possible transition from more typical endothelium (Figure 4). However, the cytoplasm was poorly preserved and there were no distinguishing ultrastructural features. In particular, no Weibel–Palade bodies were identified.

Immunoperoxidase staining for factor VIII antigen showed some focal positivity within the neoplastic cells. More convincing staining, however, was obtained for common leucocyte antigen. Staining for epithelial cell markers was negative.

Discussion

The first description of this disease was in 1959 when Pfleger and Tappeiner[1] reported a woman whose skin biopsy showed vessels with intraluminal tumour cells. Her only clinical problems were a relapsing fever and an erythematous rash. There was no obvious primary malignancy and with steroid treatment the patient's condition subsequently improved. The neurological features of the disease, however, were not described until 1965 when Stroud *et al.*[2] reported 2 patients with bizarre neurological symptoms and signs culminating in dementia and death. Autopsies on these patients showed the features of neoplastic angioendotheliosis.

The neurological involvement in our 3 cases typifies the findings which have commonly been described in the literature. The most frequent abnormality is a dementia of fluctuating severity which gradually worsens.[3] Less commonly, there may be spinal cord involvement with variable severity and fluctuation.[3] Transient

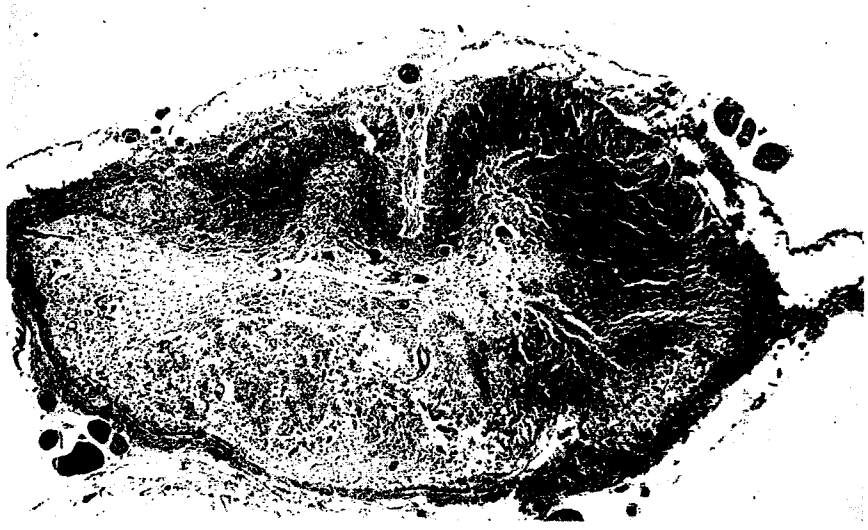

Figure 2. Lower power photomicrograph of spinal cord in Case 1 (×12). Extensive recent infarction in the third thoracic segment with some anterior sparing.

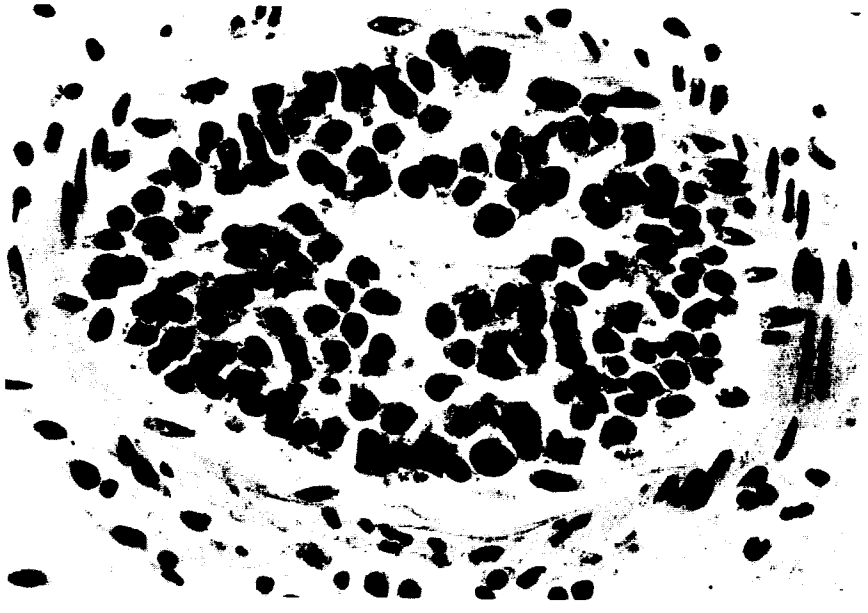

Figure 3. Occlusion of small vessel in midbrain in Case 1. Intravascular malignant cells with large irregular hyperchromatic nuclei and numerous mitoses (×540).

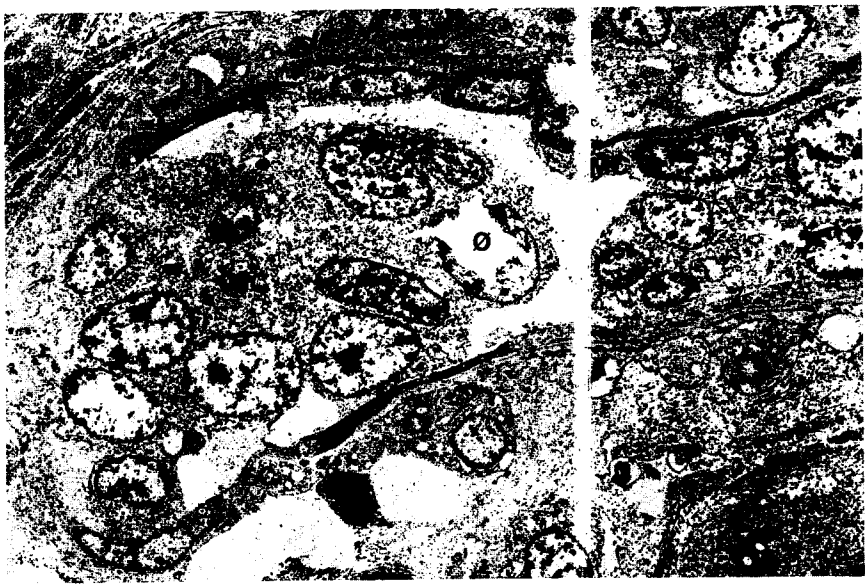

Figure 4. Electron microscopic appearance of intravascular tumour in the spinal cord of Case 1 suggests a transition from normal endothelial cells to malignant intraluminal cells. 'EC' endothelial cells, 'Tr' altered endothelial cells, 'MC' malignant cells (×3000).

episodes of weakness, numbness or aphasia may occur, suggesting transient ischaemic attacks[2,4–6] or multiple sclerosis.[7] In accordance with other reports, hemiparesis and seizures were preterminal events, as illustrated in Case 1,[3] and the average survival time is approximately 6 months, with a range of one to 24 months.[7]

Investigations are non-specific. The erythrocyte sedimentation rate is often raised. CSF parameters are normal except for the raised protein which helps to distinguish the disorder from progressive multifocal leucoencephalopathy, in which the CSF protein is normal.[8] CT scan may show multiple non-enhancing lucencies mainly in the white matter,[3] and it has been suggested that the diagnosis may be made by meningeal biopsy. Reinglass[6] proposed that the dementia produced by the disease may be treatable with steroids, but any benefit has been shown to be temporary.[3,7] Such is not the case, however, if the disease is restricted to the skin, when some patients remained in remission with steroid therapy.[1,9]

Histologically the disease is characterized by widespread intravascular proliferation of malignant cells. Tumour tissue is typically confined to the vascular lumina but has also been observed as microscopic perivascular extensions. In some cases tumorous masses have been described, particularly in the adrenal glands.[2,3,5,10] Bilateral extravascular tumour masses were present in the brain of one of the patients reported by Beal and Fisher,[3] but the gross cerebral lesions were usually infarcts secondary to vascular occlusion by neoplastic cells.

The origin of the tumour cells in neoplastic angioendotheliosis remains controversial. Is there a widespread proliferation of endothelial cells in small blood vessels throughout the body or do the vascular lumina provide a favourable environment for the proliferation of metastatic cells from another primary site? The previously popular theory of malignant change *in situ* in endothelial cells has been supported, but not proven, by light microscopy which showed an apparent transition from non-neoplastic endothelium to intravascular malignant tumour.[5,11] In only 2 cases have ultrastructural studies revealed the rod-shaped microtubulated (Weibel–Palade) bodies characteristic of endothelial cells.[5,12] Immunoperoxidase staining for factor VIII antigen, a marker for endothelial cells, has been variously reported as positive, equivocal or negative.

Exclusion of a primary malignancy outside the central nervous system is of the utmost importance and requires careful post-mortem examination. Dolman[13] reported changes identical to those of neoplastic angioendotheliosis in 2 patients who were found to have occult carcinomas in the thyroid gland and pancreas, respectively.

Based on the finding of a 0.8 cm nest of tumour cells in a para-aortic lymph node, Yamamura *et al.*[10] considered malignant lymphoma as the origin of the diffuse intravascular tumour in their case report. Sheibani *et al.*[14] in a recent report established the lymphoid nature of the tumour cells in their 3 cases by immunological studies on fresh tissue and suggested 'angiotropic large-cell lymphoma' as a more appropriate name for this disease. The finding, in our Case 1, of positive immunoperoxidase staining for common leucocyte antigen, is in keeping with this concept.

We hope that early biopsy diagnosis and characterization of the tumour cells by immunohistological techniques will result in a more rational approach to therapy.

Summary

Neoplastic angioendotheliosis is a rare disease in which malignant cells are found within numerous blood vessels throughout the body in the absence of any detectable extravascular primary malignancy. The disorder has a propensity for clinical neurological involvement despite pathological evidence of systemic spread. To date 23 patients with neurological involvement have been described. This report adds a further 3 cases. There was no definite evidence to support the theory that the malignancy arises in endothelial cells; no primary extravascular tumour was found. At present a definite conclusion about the cause of the disease cannot be made.

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Cryptococcal Infections of the Central Nervous System: A Ten Year Experience

*J.A. Waterston and B.S. Gilligan**

Cryptococcal meningitis is the most serious complication of systemic cryptococcal infection and is a relatively common cause of CNS infection. The organism, *Cryptococcus neoformans*, is an encapsulated yeast-like fungus and is abundant in soil and organic debris, particularly in pigeon droppings. Without treatment the disease is invariably fatal and, before the introduction of amphotericin B, mortality approached 100%.

Subjects and Methods

A retrospective analysis was conducted of the records of 20 consecutive cases of cryptococcal meningitis admitted to the Alfred and Fairfield Infectious Diseases Hospitals during the period 1975–1985. All patients were newly diagnosed.

Results

Epidemiology

The age range of patients at presentation was 19–69 years with a mean of 45 years. The maximum incidence was seen in the third and seventh decades (5 patients in each group) and there was no sex preponderance. In 40% of the patients there was serious underlying illness and a further 15% had possible risk factors (Table 1).

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Table 1. Predisposing conditions in patients presenting with cryptococcal meningitis

Definite risk factors (40%)
Leukaemia (3): acute lymphatic, chronic lymphatic, chronic myeloid.
Renal transplantation (2)
Chronic corticosteroid therapy (2)
Non-Hodgkin's lymphoma (1)
Possible risk factors (15%)
Pregnancy (1)
Previous splenectomy (1)
Intravenous drug abuse (1)

Clinical Manifestations

The more frequent clinical features are listed in Table 2 and their previously documented incidence in 97 patients[1] is listed for comparison. Headache was an almost universal presenting feature. Fever and meningeal signs were not. Only one patient had documented neck stiffness. A further 2 had photophobia. The headache was usually bifrontal and non-specific, but occasionally there were features to suggest raised intra-cranial pressure.

Three patients presented with seizures. One of these patients had multiple mass lesions on CT brain scanning, which had been biopsied on suspicion that they were metastatic deposits. Visual disturbances were relatively uncommon at presentation; however 1 patient had a monocular field defect and papilloedema initially and then developed bilateral visual blurring and obscurations from persistently raised intracranial pressure. Another patient developed chronic papilloedema and progressive visual impairment later in the course of her illness.

Table 2. Clinical manifestations and their frequency in patients presenting with cryptococcal meningitis

		Other series[1]
Headache	95%	87%
Altered mental state	55%	52%
Nausea and vomiting	45%	53%
Fever	35%	60%
Ataxia	20%	26%
Papilloedema	15%	28%
Seizures	15%	15%
Pyramidal signs	15%	—
Meningeal signs	15%	50%
Cranial nerve palsies	10%	32%
Visual disturbances	10%	33%

Table 3. CSF abnormalities

	Percentage	Actual no.
Elevated protein	95%	(18/19)
Positive culture	95%	(19/20)
Positive latex agglutination	93%	(14/15)
Elevated white cell count	90%	(18/20)
Elevated opening pressure	90%	(9/10)
Positive Indian ink smears	60%	(12/20)
Low glucose level	58%	(11/19)

Pyramidal signs were seen in 3 patients and in 1 unilateral choreoathetotic movements were also present. Impairment of conscious state was a common finding and varied from mild memory disturbance to unconsciousness. Palsies of the sixth and eighth cranial nerves were seen in 2 patients.

The mean time interval from onset of symptoms to diagnosis was 10 weeks, with a range of several days to 18 months.

Laboratory Studies

(i) *Cerebrospinal Fluid Examination*

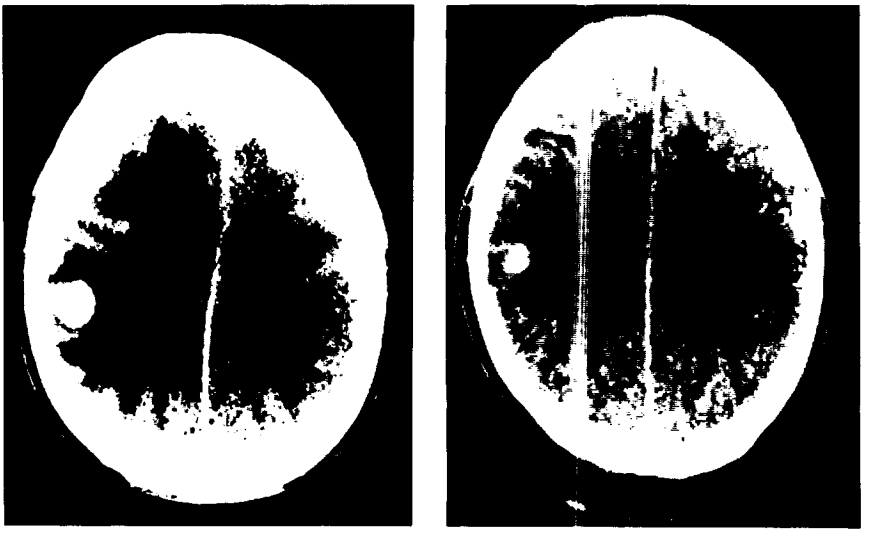
All patients underwent CSF examination. The major abnormalities are listed in Table 3. Protein elevation ranged from mild to moderate (0.46–5.2 g/L) and was greater than 1.6 g/L in those patients with hydrocephalus. CSF pressure, when measured, was also elevated in most patients. Of importance was the low diagnostic sensitivity of Indian ink smears. Culture was particularly sensitive; however, several days of incubation were often needed for detection of the organism. Measurement of cryptococcal antigen by latex agglutination was helpful because of its high sensitivity. One patient had a positive latex agglutination test with negative Indian ink stains and culture, even after prolonged incubation. The only patient with a negative latex test had a positive culture (the latex test was positive on a second specimen). Low CSF glucose concentration was not a universal finding, usually being observed in the more severely ill patients.

(ii) *CT Brain Scanning*

Abnormalities on CT brain scans were detected in 5 of 17 patients (29%). Two patients had mass lesions (Figures 1A, 1B, 2), 3 had hydrocephalus and 2 had multiple cystic paraventricular lesions (Figure 3).

(iii) *Other Investigations*

Mild lymphopaenia (less than 1500/mL) was a common feature, being present in 70% of patients. All patients underwent chest x-ray examination and 45% of



(A) (B)

Figure 1. (A) Multiple cerebral mass lesions with surrounding oedema. (B) The same patient after 30 months of medical treatment.

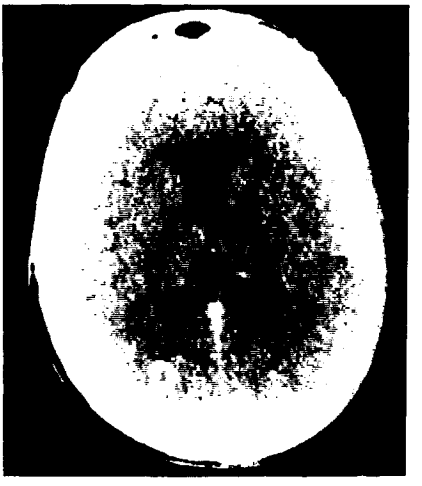


Figure 2. Solitary cerebral mass lesion.

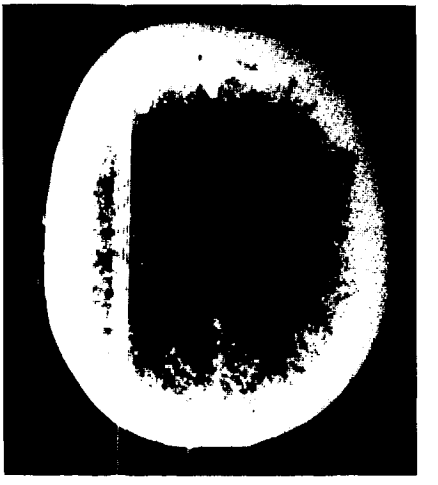


Figure 3. Hydrocephalus and cystic paraventricular lesions.

Figure 4. Pulmonary cryptococcoma in left lower lobe.

these showed evidence of pulmonary cryptococcal infection, varying from a miliary infiltrate to single mass lesions (Figure 4). Three patients had cryptococcaemia and a further 70% had detectable serum cryptococcal antigen by the latex agglutination method. Hyponatraemia was seen in 2 patients and was attributed to inappropriate secretion of anti-diuretic hormone.

Treatment

Upon diagnosis patients were routinely treated with a combination of intravenous amphotericin B (AMB) and oral 5-fluorocytosine (5FC). The dose of AMB was increased slowly to 0.8–1 mg/kg, which was given on alternate days, and treatment with 5FC was commenced at a daily dose of 150 mg/kg in patients with normal renal function. Full blood counts, electrolytes and 5FC blood levels were monitored regularly. Side effects from treatment were common, particularly with AMB, and included phlebitis, renal impairment, rigors and hypokalaemia. Rigors were managed with intravenous corticosteroids and antihistamines at the time of the infusion and occasionally by lowering the AMB dose. Renal impairment was mild and transient and improved with dose adjustment. Difficulties with intravenous access were encountered because of the prolonged periods of treatment and, as a result, the insertion of Hickmann's catheters or construction of arterio-venous fistulae was occasionally required. The use of 5FC was associated with a mild depression of haemoglobin levels and very occasionally with a depressed lymphocyte count. These effects were also reversed by temporary cessation of the drug or reduction in its dose.

AMB was given to a total dose of at least 1.5 g and until there was sustained improvement in clinical and CSF parameters (chiefly sterile cultures and falling CSF lymphocyte counts). Treatment was then continued with oral 5FC, often with the addition of ketoconazole. After the first course of treatment with this regimen remission was obtained in 70% of patients. Three of these 14 patients (21%) required second courses of treatment because of subsequent relapse. The average total dose of AMB required for cure was 3.6 g, with a range of 1.1–10 g. The two patients with cryptococcomas required higher cumulative doses for resolution of the mass lesions. In patients without mass lesions, an average of 3.0 g of AMB was required.

Corticosteroids were given to 6 patients, chiefly for control of cerebral oedema. In no case was there any deterioration in clinical state when corticosteroids were introduced and most patients improved. The condition of one of these patients, who presented with hydrocephalus and bilateral enhancing isodense lesions, improved with corticosteroid therapy before the diagnosis of cryptococcal meningitis was made. Another patient with multiple cerebral mass lesions was given steroids when clinical progress was slow because of persistent cerebral oedema related to the lesions (Figure 1A). This therapy resulted in dramatic improvement and further resolution in the size of the lesions with continued antifungal therapy (Figure 1B). Another patient became dependent on steroids and repeated lumbar punctures for control of raised intra-cranial pressure. Eighteen months after initial treatment with a prolonged course of AMB, followed by 5FC and ketoconazole, he continued to experience headache, impaired visual acuity and obscurations of vision each time a reduction in his steroid dose was attempted. Eventually a lumbo-peritoneal shunt was performed and this resulted in relief of the headache with improvement in visual acuity and fundal appearances.

Another 2 cases had chronically raised intra-cranial pressure. One patient's problem was managed with regular lumbar punctures and resolved spontaneously.

The other patient underwent optic nerve decompression because of deteriorating visual acuity: this resulted in improvement.

One other patient required ventriculo-peritoneal shunting for non-communicating hydrocephalus and later developed an isolated fourth ventricle which required further shunting. A patient who had been shunted for hydrocephalus presented later with symptoms and had multiple shunt revisions performed because of malfunction. The diagnosis of cryptococcal meningitis was not made until his last admission when external drainage was required to manage CSF obstruction. He developed extensive intraventricular haemorrhage whilst receiving anti-fungal therapy and died.

Intrathecal therapy was reserved for acutely ill patients who had responded poorly to the above modes of treatment. It was used in 3 patients. Of 2 patients who received AMB by this route, one who was having his treatment through a Rickham reservoir developed *Staphylococcus aureus* meningitis and died. Treatment was ceased in the other patient because of confusion. The third patient received intrathecal miconazole, but this was ceased because of the development of severe headache and galactorrhoea. Two patients in relapse received courses of transfer factor, which appeared to result in improvement.

Thoracotomy for resection of pulmonary cryptococcoma gave satisfactory results in 3 patients.

In this study there was 1 patient who was 26 weeks pregnant at the time of presentation. She had a history of 1 month of persistent headache and vomiting, and on chest x-ray examination there was a left-sided apical mass lesion. She underwent treatment with AMB (total 1200 mg) and 5FC. At 31 weeks' gestation, thoracotomy, with resection of the cryptococcoma, was performed. All treatment was ceased 1 month later. The pregnancy then proceeded uneventfully and she gave birth to a healthy baby. Two weeks post-partum she presented with headache and was found to have relapsed. A second course of treatment with AMB (total 2000 mg) and 5FC was commenced: further therapy with ketoconazole and transfer factor resulted in cure, with no evidence of relapse over 3 years of subsequent observation.

Prognosis and Outcome

The overall mortality from cryptococcal infection was 30%. Three patients died directly from uncontrolled cryptococcal infection. Another patient, previously mentioned, developed *Staphylococcus aureus* meningitis and died despite appropriate antibiotic therapy, and another 2 patients died from intraventricular haemorrhage and aspiration, respectively. Most patients without serious underlying disease who were successfully treated made an excellent recovery with few residual deficits. One patient developed focal epilepsy which has been satisfactorily controlled with anticonvulsants.

The mean follow up of all cases in remission was 2.5 years (range 6 months to 10 years). Two patients have since died from other causes and 2 patients, both with mass lesions, are still taking oral therapy.

Discussion

The age incidence corresponded well with other series.[2] No sex preponderance was observed in our series, in contrast to other studies where 70% of affected patients were male.[3,4] A high incidence of underlying serious disease has been noted previously.[3,5,6] Infection and dissemination run a similar course to *Mycobacterium tuberculosis* infection. The organism gains entry into the lungs through inhalation and in most patients is contained by host defences. Many pulmonary nodules are asymptomatic. It is presumed that exposure to the organism is common, given its widespread occurrence in the environment, and dissemination rarely occurs in the immunologically normal host, but nearly always in the immunosuppressed host. Meningeal involvement usually follows haematogenous dissemination, and local factors such as the absence of fungistatic anti-cryptococcal factors and the presence of vital growth factors in CSF[7] may be important pathogenetic mechanisms.

Patients with cerebral mass lesions generally are not immunosuppressed, as in this series, and this probably reflects the ability of these patients to localize the infection.[8] Forty-five per cent of the series had abnormalities on chest x-ray examination. The numbers in other series vary widely from 6% to 63%[2,9] but tend to be lower in North American series. This did not seem to affect ultimate prognosis, although 3 patients required resection of thoracic lesions. Sputum culture was positive in only 2 of 7 patients tested.

Diagnosis is suggested by the presence of a persistent, often severe, headache[2] which is frequently associated with altered mental state, nausea and vomiting. Fever and meningeal signs were less frequent and should therefore not be relied upon to exclude the diagnosis of a chronic infective meningitis. Patients were more likely to have an altered mental state if there was an underlying immunodeficiency.

Both patients with cerebral mass lesions had no focal symptoms or signs, a finding which has often been observed in other series.[8] Therefore, all patients with cryptococcal meningitis should undergo CT brain scans to exclude asymptomatic mass lesions. Cryptococcal granulomata often have peripheral enhancement with central hypodensity and there may be considerable surrounding oedema.[10,11] The differential diagnosis includes metastatic tumour deposits, which was thought initially to be the diagnosis in 1 of our patients.

Other CT abnormalities have been recognized recently, such as cystic non-enhancing lesions.[12,13] These have been found on post-mortem examination to be due to multiloculated gelatinous lesions which contain cryptococcal organisms.[12,14] They are found chiefly in grey matter including the thalamus and basal ganglia and have been termed 'gelatinous pseudocysts'.[12] It has been claimed that these gelatinous pseudocysts precede the formation of granulomata.[15] However the reverse would seem to be true in our patient with cystic paraventricular lesions in whom these lesions were initially isodense with contrast enhancement and became hypodense later in the course of the illness. It has also been claimed that corticosteroid therapy may suppress the contrast enhancement normally seen with cryptococcal granulomata, simulating these cystic lesions. However, as in the case described by Garcia,[12] our patient was not taking corticosteroids when the initial

CT scan was performed. It is feasible to assume that these cystic lesions may represent old granulomata in which tissue necrosis has occurred.

Hydrocephalus was seen in 20% of cases. Cryptococcal meningitis should therefore be considered amongst the other causes of chronic meningeal reactions which result in CSF obstruction. The CSF protein tended to be higher in patients with hydrocephalus, perhaps reflecting either a high organism load or a subarachnoid block. Most patients had a CSF pleocytosis, chiefly of lymphocytes; however this was not always the case, as in 2 of our patients. Both these patients had moderately severe lymphopaenia and were on immunosuppressant therapy, which helps to explain the absence of inflammatory cells in the CSF.

Indian ink staining of CSF smears has been the simple, time-honoured test for rapid diagnosis of cryptococcal meningitis. However measurement of latex agglutination by serological measurements has in most series proved to be a far more sensitive test.[16,17] Culture is also helpful but prolonged incubation is required for the highest detection rate and this is not always done if the diagnosis is not suspected. Occasionally cultures do not become positive for up to 4 days,[14] and in some cases culture may still be negative at this time.[18,19]

Positive blood cultures were seen in a small number of cases (4 of 8) and in all such cases there was a serious underlying illness. However, in contrast to other surveys,[4] this finding was not indicative of a poor outcome. Most of the poor prognostic indicators have been recognized in other series and include severe underlying disease,[5] changes in mental state,[2] a low CSF glucose level[4] and hydrocephalus[2] or other neurological deficit.

Hyponatraemia, attributable to inappropriate secretion of anti-diuretic hormone, is found in many conditions affecting the central nervous system. The 10% incidence in our series is similar to the incidence found by Stockstill,[20] compared with tuberculous meningitis where the incidence is much higher. A miliary infiltrate on chest x-ray examination, suggestive of tuberculous infection, was seen in 1 of our patients with cryptococcal infection.

Treatment often required long courses of AMB and 5FC. These 2 drugs are probably more effective if used together than if AMB is used alone.[21] In some studies raised serum cryptococcal antigen was found to correlate with a high incidence of relapse,[4] so that in many of our patients treatment was continued with the above drugs until a satisfactory fall in titre was observed. Despite this, about 21% of patients responding to the initial course of treatment later relapsed, a similar relapse rate to other series.[5,6] Relapse usually occurred within 6 months of cessation of treatment. The first course of treatment was given until CSF cultures had become negative, and declining CSF antigen and white cell counts had been demonstrated, providing the clinical course also was satisfactory. In patients with mass lesions, treatment was usually continued for longer periods until there was satisfactory resolution of the CT abnormalities. In the event of relapse, treatment with oral 5FC and ketoconazole was often used for many months after a second course of intravenous AMB. If 5FC is used alone there is a risk of developing resistant organisms.[22]

Transfer factor has been shown to be useful in some cases of cryptococcal meningitis.[23] Two patients were treated with transfer factor and clinical improve-

ment was noted. However it was difficult to assess the results of this treatment as there had been other changes in anti-fungal therapy at about the same time. Other anti-fungal drugs such as miconazole and clotrimazole were given to a few patients in this study, with poor results. However, these patients were already extremely ill and these drugs were used as a last resort. The efficacy of the newer anti-fungal agents is unknown and, until they have been assessed by controlled studies, they cannot be recommended for primary therapy.[24]

The mortality rate is in keeping with other studies[3,5] and in patients who have been cured the long term prognosis is excellent, provided there is no serious underlying illness. Successful management depends on early diagnosis, as well as on recognition of the complications which may occur as a result of the illness and the various treatment modalities. Management is often prolonged and taxing, both for the patient and for his or her attendant staff, but vigilant management with attention to detail is often rewarded with a very successful outcome.

Summary

Twenty cases of cryptococcal CNS infection treated at the Alfred and Fairfield Infectious Diseases Hospitals from 1975 to 1985 were reviewed. A predisposing immunological deficit was present in 40% of the cases and nearly half had evidence of pulmonary involvement. Severe headache was an almost universal presenting feature but fever and meningismus were not. Measurement of CSF cryptococcal antigen and CSF culture were far more reliable diagnostic markers than Indian ink smears. Cerebral CT scanning identified abnormalities in nearly 30% of cases, including 2 with cystic lesions and 2 with mass lesions. Combination therapy with amphotericin B and 5-fluorocytosine was used as first line treatment. Ventricular shunts were required for 2 patients with hydrocephalus, and persistently raised intracranial pressure often required frequent lumbar punctures and corticosteroids for control. Mortality was 30% and correlated with the presence of impaired conscious state, hydrocephalus or other neurological deficit, underlying immunodeficiency and low CSF glucose levels.

Acknowledgements

We thank Dr A. Kucers and the staff of the Fairfield Infectious Diseases Hospital for permission to review their cases and Mrs Faye Milburn for her expert secretarial assistance.

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Clobazam in the Treatment of Epilepsy

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Clobazam, a 1,5-benzodiazepine with anxiolytic properties, is claimed to be a potent anticonvulsant drug.[1-4] Its use in epilepsy, however, is limited by the frequent occurrence of tolerance and exhaustion of its antiepileptic effect.[1-3] It has been suggested that the use of smaller doses of clobazam may prevent or delay the onset of drug exhaustion and thus prolong the drug's anticonvulsant action.[2-4]

The aim of this study was to assess, by an open trial, the anticonvulsant activity of low dose clobazam in a group of patients with frequent intractable seizures. In addition serum concentrations of clobazam and its metabolite, *N*-desmethylclobazam, were assayed to investigate their correlation with therapeutic effect, adverse effects, drug dose and the development of drug tolerance.

Methods

Eleven patients were studied, 5 men and 6 women, aged 21 to 46 years. All patients had intractable seizures, having at least one seizure per week despite the use of multiple anticonvulsant drugs. Six patients had primary generalized epilepsy, 3 had secondary generalized epilepsy and 2 patients had partial seizures with secondary generalization.

Clobazam was given orally in addition to conventional antiepileptic agents, beginning with a dose of 20 mg at night. If the initial response was inadequate (less than a 50% reduction in seizure frequency), or if there was a subsequent deterioration in the level of control, the dose was increased by 10 mg daily every 2 weeks until an adequate response was achieved, side effects developed, or a maximum daily dose of 1.5 mg/kg was reached.

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Patients were seen at the outpatient clinic every 2 weeks for a minimum period of 3 months. The follow-up period ranged from 3 to 18 months. At each visit the number of seizures was noted, side effects were documented, and plasma levels of all anticonvulsant drugs, including clobazam, were measured. Electroencephalograms were performed on each patient before commencement of clobazam therapy and after 1 month and 2 months of treatment.

Clobazam and *N*-desmethylclobazam plasma concentrations were assayed by high performance liquid chromatography. One millilitre of plasma containing 0.5 μg of diazepam as internal standard and 200 μL of saturated Tris buffer, was extracted with 8 mL of chloroform. The chloroform was then evaporated to dryness at 60 °C and the residue reconstituted with 50 μL of the mobile phase, 35% acetonitrile in 0.01 mol/L phosphate buffer (pH 3.0). Chromatography was carried out on a Hewlett Packard 1090 Chromatograph using a 100 mm × 2.1 mm internal diameter Hewlett Packard Hypersil C-18 (5 μm) column, maintained at 50 °C. The mobile phase was run at 1 mL/min and monitored at 231 nm. The retention times of *N*-desmethylclobazam, clobazam and the internal standard were 1.72, 2.72 and 4.23 minutes, respectively.

Results

Seizure Control

A 50% or greater reduction in seizure frequency was noted, at least transiently, in all 11 patients.

In 6 patients there was an initial complete abolition of seizures. One of the 6 patients has maintained this level of control over a period of 18 months, 1 patient developed intolerable drowsiness despite a reduction in the dose of clobazam and the medication was withdrawn, and 4 of the 6 patients deteriorated within 3 months. In 2 of these patients, seizures recurred at 2 weeks, in 1 patient at 2 months and in 1 patient at 3 months after commencement of treatment. In 2 of these 4 patients the dose of clobazam was increased, with further improvement in epileptic control, but the development of intolerable drowsiness necessitated a reduction in the dosage and the seizures recurred. Two of the 4 patients experienced side effects on the lower dose (20 mg) and hence the dose of clobazam could not be increased.

A further 3 patients had a 75% or greater reduction in seizure frequency. All 3 patients deteriorated again within 3 months, 1 at 6 weeks, 1 at 2 months and 1 at 3 months. Two of these 3 patients, however, maintained a 50% reduction in seizure frequency. In all 3 patients the dose of clobazam could not be further increased because of side effects.

The remaining 2 patients had a 50% reduction in seizure frequency. One has maintained this level of control over a period of 6 months and the other deteriorated after 2 weeks of therapy. This latter patient did not respond to an increase in the dose of clobazam.

In the 11 patients studied there was no correlation between the type of epilepsy and the clinical response to clobazam.

Adverse effects were noted in 8 of the 11 patients. Six patients complained of drowsiness, 4 of these 6 patients requiring and responding to a dose reduction, while in one patient the drug was withdrawn. One patient developed behavioural problems which responded to dose reduction, 1 patient complained of intermittent ataxia and 1 patient, in addition to drowsiness, complained of weight gain.

Three patients reported positive side effects. Two commented on increased alertness and 1 patient's long standing depression improved.

Most of the patients had strikingly abnormal electroencephalograms with frequent paroxysmal activity. There was significant improvement, at least transiently, in the background rhythm, and suppression of paroxysmal activity in 7 of the 11 patients. The positive effect on the electroencephalogram usually correlated with the clinical response.

Plasma Levels

There was a significant linear relationship between the plasma concentrations of clobazam and its metabolite, *N*-desmethylclobazam ($r = 0.37, p < 0.01$) (Figure 1). The 8 outlying points, with disproportionately high clobazam concentrations, are from the 1 patient.

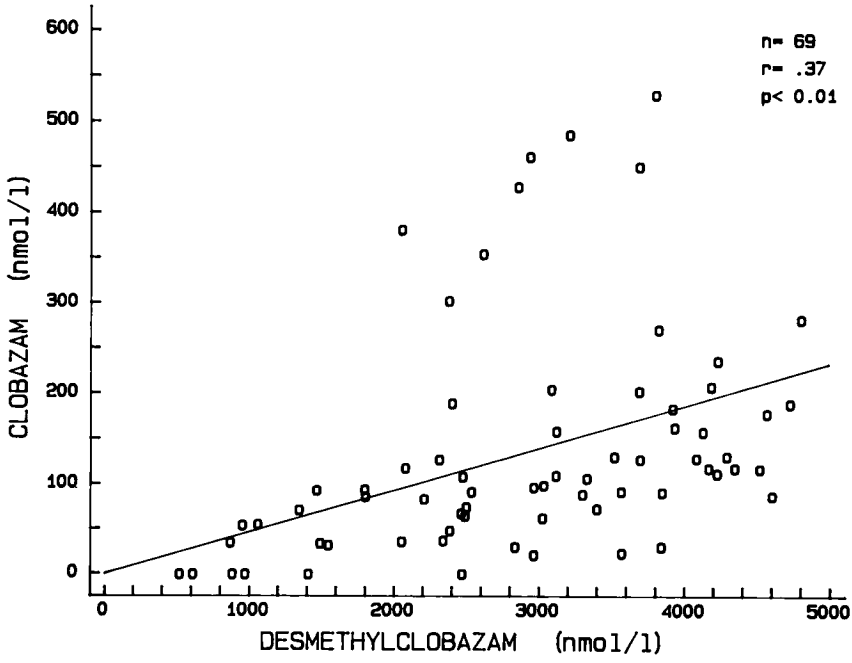

Figure 1. Relationship between plasma concentrations of clobazam and of *N*-desmethylclobazam.

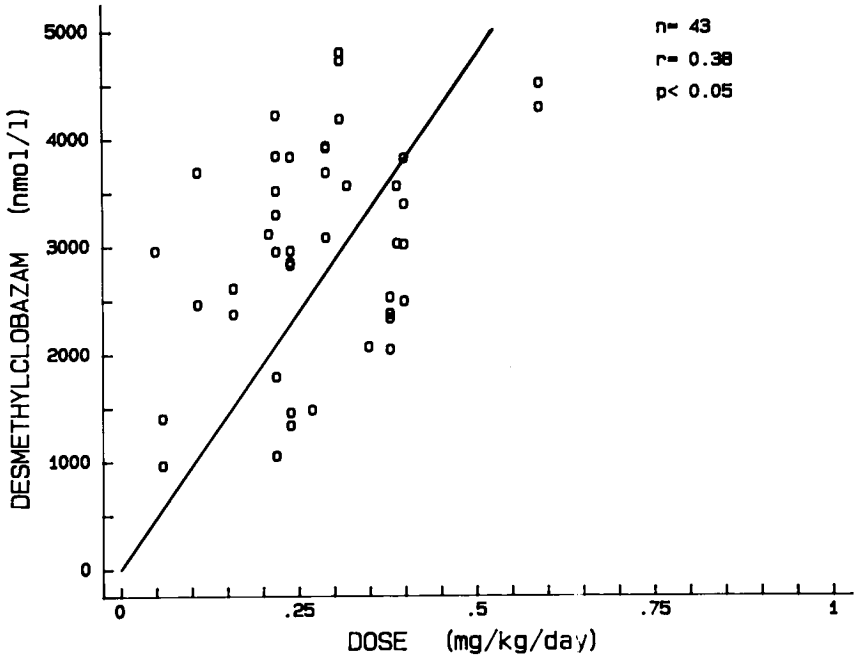

Figure 2. Relationship between daily dose of clobazam (mg/kg) and plasma concentrations of *N*-desmethylclobazam.

There was no correlation across the patient population between the daily dose of clobazam (mg/kg) and plasma clobazam levels. There was, however, a significant correlation between the daily dose of clobazam (mg/kg) and *N*-desmethylclobazam concentrations ($r = 0.38$, $p < 0.05$) (Figure 2).

There was no correlation between plasma clobazam concentrations and therapeutic and toxic effects. The mean steady-state plasma level of clobazam in the patients with 75% or greater reduction in seizure frequency was 101 ± 72 nmol/L compared with 262 ± 152 nmol/L in the patients with less than 50% reduction in seizure frequency. The mean plasma concentration of clobazam in the patients without adverse effects was 171 ± 132 nmol/L, and 86 ± 52 nmol/L in the patients who complained of drowsiness.

In contrast, the mean plasma levels of *N*-desmethylclobazam were higher in those with adverse effects (3373 ± 1015 nmol/L) compared with those who did not complain of side effects (2806 ± 951 nmol/L). Similarly, patients with 75% or greater reduction in seizure frequency had a mean *N*-desmethylclobazam concentration of 3199 ± 1035 nmol/L, whereas those with a poor response had a mean level of 2446 ± 818 nmol/L.

The development of drug exhaustion and relapse in control of epilepsy was not associated with a fall in the plasma concentrations of clobazam or of *N*-desmethylclobazam.

Discussion

Consistent with previous reports, this study has demonstrated clobazam to be a potent short-term anticonvulsant drug.[1–8] The effect, however, is usually not long standing and the drug rapidly loses part or all of its anticonvulsant activity. In the present study drug tolerance developed in 8 of the 11 patients (72%) and in half of these cases the tolerance was complete. Most previous studies have reported a lower incidence of drug exhaustion. Martin[2] reported escape from seizure control in 15 of 49 patients, Gastaut and Low[1] reported drug exhaustion in 38% of cases, whereas Allen *et al.*[8] did not observe drug tolerance during a follow up period of 9 weeks. It is possible that the high incidence of initial response and subsequent relapse observed in this study is in part a reflection of an initial placebo response.

The present study does not support the suggestion that the use of low doses of clobazam reduces the incidence of drug exhaustion.[2,4] The mechanism of the frequently observed loss of anticonvulsant activity is not known, although both a fall in plasma clobazam and *N*-desmethylclobazam levels and alteration in receptor sensitivity have been postulated.[9,10] The results from this study do not support the former postulate and suggest that the relapse is not of pharmacokinetic origin.

As with earlier reports, there was no correlation between plasma levels of clobazam and therapeutic and toxic effect.[6,7] However, as reported by Wolf *et al.*,[7] the plasma concentration of the metabolite, *N*-desmethylclobazam, did appear to correlate with anticonvulsant activity and adverse effects. These findings suggest that *N*-desmethylclobazam may be more relevant than the parent drug clobazam in therapeutic monitoring, and the significant correlation between dose of the parent drug and the plasma concentration of the metabolite supports this hypothesis.

In contrast to previous experience, adverse effects were common and frequently prohibited an increase in the dose of clobazam.[2,4] As with other studies, favourable side effects were occasionally seen.[1,2]

The lack of correlation between the type of epilepsy and anticonvulsant response may well be a reflection of the small number of patients studied. Some previous studies have reported the best response in patients with primary generalized epilepsy,[6] complex partial seizures,[3] and secondary generalized epilepsy[11] while others, like this study, have found the anticonvulsant activity to be independent of the type of epilepsy.

This study suggests that clobazam has a limited, but definite, place in the treatment of patients with intractable seizures and that its use may be facilitated by the monitoring of plasma levels of *N*-desmethylclobazam. Drug tolerance remains a major problem, however, despite the use of low drug doses, and further investigation into the mechanism of this phenomenon is needed.

Summary

Clobazam, a 1,5-benzodiazepine, is a potent anticonvulsant but the development of tolerance limits its use. It has been suggested that low dose clobazam may prevent or delay the onset of tolerance. This study aimed to assess, by an open trial,

the anticonvulsant activity of low dose clobazam in 11 adult patients with frequent intractable seizures. Serum clobazam and *N*-desmethylclobazam levels were assayed and correlated with clinical effect, adverse effects, drug dose and the development of tolerance. Clobazam was given in addition to conventional anti-epileptic therapy, beginning with a dose of 20 mg at night.

A 50% or greater reduction in the frequency of seizures was noted, at least transiently, in all patients. In 8 of the 11 patients there was a subsequent deterioration in control of epilepsy and in all patients this relapse occurred within 3 months of commencing treatment. There was a relationship between plasma concentrations of *N*-desmethylclobazam (but not of clobazam) and therapeutic and toxic effects. Tolerance was not associated with a fall in plasma levels. It is concluded that clobazam is of limited value as a long term anticonvulsant and that the high incidence of tolerance is not reduced by the use of low doses.

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The Management of Epilepsy in Women of Child-bearing Age and the Australian Experience of Valproate in Pregnancy

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A consideration in the therapeutic management of an epileptic woman of child-bearing age is her potential and wish, or otherwise, to become pregnant. The aim is to control the epilepsy during any pregnancy with minimal risk to the developing child.

From the point of view of the consulting physician it would be preferable to discuss any planned pregnancy with the woman before the event takes place.[1] The benefits and risks of treatment compared with the risks of untreated epilepsy may then be presented to the patient and the 'safest' course of action can be taken. Monotherapy with anti-epileptic medication is preferred[1] and a review of medication in patients who are pregnant, or planning to be so, has been recommended in order to implement the simplest possible effective drug regimen.[2]

A more common problem for the physician is the question of helping the woman of child-bearing age to prevent any unwanted pregnancy. If mechanical or local chemical methods are advised, then co-administered anticonvulsants will not be affected. There is evidence, however, that the efficacy of oral steroid contraceptives is impaired by anti-convulsant medicines[3,4] owing to their enzyme-inducing properties.[5] Breakthrough bleeding appears to be rare in women taking sodium valproate,[6] and this indication that oral contraceptives are not impaired by valproate has been confirmed by the measurement of steroid levels[7] in patients taking a daily dose of 400 mg of valproate. It has been suggested that sodium valproate should be substituted for phenytoin in patients receiving steroid therapy, including oral contraceptives.[8]

The question of whether or not to continue the treatment of epilepsy during pregnancy has been discussed in the literature. The consensus appears to be that if anticonvulsant treatment is required to control seizures then treatment should be

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continued.[9,10] Even in literature aimed at the general public this fact is quite clearly recognized[11,12] and the risk of damage to the foetus due to seizures is emphasized. There is no clear evidence that any one anticonvulsant drug is safer or more dangerous than any other[2] and the decision to treat, and which anticonvulsant drug to use, must remain the responsibility of individual physicians.

Treatment with Valproate

The 1983 WHO review of worldwide experience[13] of valproate in pregnancy commented on the significantly higher risk of malformation in women with uncontrolled epilepsy and the established risk of malformations with the older anticonvulsant drugs. The teratogenic potential of carbamazepine and valproate were examined specifically, but no significant conclusion could be drawn. Reports of spina bifida associated with valproate exposure from the Rhone–Alpes region of France were considered critically, and it was concluded that, although 'presumptive evidence of risk' is indicated, 'it does not, however, mark valproate as a more potent teratogen than other widely available anticonvulsants'. It was also observed that 'This association has been neither confirmed nor rejected in other surveys undertaken elsewhere'.

Before reports of neural tube defects in babies born to mothers with epilepsy who had taken valproate, it was considered that change in medication or reduction in dosage of anticonvulsants in pregnancy involved too great a risk.[10] The literature still recommends maintaining good control of seizures in pregnancy.[14] Open spina bifida may be detected *in utero* by alpha-foetoprotein measurements and ultrasound. Women taking valproate during pregnancy may be offered amniocentesis during counselling[14] and ultrasound scanning is now a routine procedure. It is thus possible to detect spina bifida cystica *in utero* at an early stage allowing further counselling and the opportunity to terminate the pregnancy electively. Lindhout[15] advised considering whether valproate could be replaced by another drug, but stated that the final choice depended not only on the type and severity of the seizures, but also on the parental attitude towards prenatal diagnosis and induced abortion.

Supervision of Therapy and Counselling

The relative teratogenic risks of anticonvulsant drugs are still not accurately known.[14] Decisions on therapy must, therefore, rest on careful supervision and clinical judgement.[14] Discussion between clinician and patient is of great importance to determine whether current treatment is suitable and, if not, to make the necessary changes.[12] Counselling should provide information about the teratogenic risks of anticonvulsants[15] and this counselling should occur before pregnancy to allow time for adjustment in any therapy. Pre-natal investigation may include foetal ultrasound and, where there has been exposure to valproate during the first trimester, measurement of serum and amniotic fluid alpha-foetoprotein levels.

Summary of Experience in Australia

Sodium valproate has been available to Australian clinicians for research since 1976. Since the general introduction of valproate into Australia in January 1978, an estimated 18000 patients have been treated for an average duration of 4 years. Extrapolating from population spread and disease incidence, it is probable that 5000 of these patients were women of child-bearing age. The manufacturer has taken active measures to encourage and facilitate reporting of birth defects and during this period 16 reports of congenital malformations in patients whose treatment included valproate have been notified to the Australian distributor.

Four of these patients had received valproate alone. One or more additional anticonvulsant drugs were taken during 11 of the pregnancies, 2 of these instances occurring in the same mother. One patient received chloroquine concurrently.

These 16 reports include 5 cases of neural tube defect. Three cases occurred where valproate had been co-administered with carbamazepine (1 case), phenytoin (1 case) and thyroxine and carbamazepine (1 case). One other case occurred in which valproate given early in pregnancy was followed by phenytoin. In the last case, the patient first received valproate followed by phenytoin and then by carbamazepine; the child was born with multiple severe congenital abnormalities which included a neural tube defect.

The other reported malformations are consistent with those observed in an untreated epileptic population. Thus the experience in Australia is in accordance with the data presented in and with the conclusions drawn from the WHO report.

Conclusion

The WHO report concerning the teratogenic potential of the newer anticonvulsants, including valproate, is still the most comprehensive summary of this perceived risk available. It has not yet proved possible to detect a specific association between neural tube defects and to exposure to valproate. The best way of minimizing the perceived risks to the woman with epilepsy who is of child-bearing age is effective contraception and close medical supervision both before and during a planned pregnancy.

Summary

Published opinion is reviewed and summarized with special reference to the teratogenic potential of the newer anticonvulsant drugs, treatment decisions and patient supervision. An Australian report covering a period of eight years, summarizing congenital malformations in births to patients whose treatment included sodium valproate (Epilim^{R}) is presented against the background of the WHO report on valproate and pregnancy.

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Intensive Neuromonitoring for Complex Partial Seizures: Focal Seizure Pattern Variability in Surgical Patients

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Recent years have seen the introduction into epileptology of techniques that enable long term neuromonitoring to be undertaken to capture patients' seizures on EEG and video-tape. This has allowed access to detailed seizure analysis and has highlighted deficiencies and inadequacies in the clinical history taken from both patient and relatives. Indeed, the introduction of these newer forms of investigation, in association with advances in neuropsychology, has permitted a fresh look at the application of surgery to the relief of refractory seizures. This is turn has emphasized the necessity of pinpoint accuracy in diagnosing the site and side of the epileptic focus to be removed, especially in temporal lobe epilepsy.

In view of the very stereotyped seizure pattern often described by the patient and the relatives, particularly in complex partial seizures, it comes as some surprise to discover that a considerable proportion of such patients exhibit variability in seizure pattern when studied by long term intensive neuromonitoring. Admittedly, the circumstances under which the seizures are recorded are somewhat artificial; the patients are in hospital and are often confined to one room, their anticonvulsant medication is withdrawn to a greater or lesser degree, and any emotional pressure upon the patients is low. Nevertheless, there is no substitute for this process and the results are of enormous value in lateralizing and siting any operable epileptogenic lesion.

We have studied the problem of variability in seizure pattern in 70 patients entering the Comprehensive Epilepsy Programme at the Austin Hospital and undergoing pre-surgical assessment for management of complex partial seizures. The results are presented below.

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Materials and Methods

The use of intensive neuromonitoring techniques in the assessment of patients referred for possible seizure surgery to the Comprehensive Epilepsy Programme at the Austin Hospital has been previously detailed. Data described here are derived from the last 70 patients assessed specifically for complex partial seizures; all these cases had video and EEG data which could be analysed (Table 1). Eleven patients (15%) showed multiple focal origins for various types of epileptic seizures. Seven of these patients showed seizures arising separately from both temporal lobes. Three showed 2 separate seizure forms, one arising from the temporal lobes and the other from the frontal lobes. One patient showed 2 separate types of focal epilepsy, temporal lobe epilepsy and a cortical focus in the facial area. Secondary generalization of complex partial seizures arising from the temporal lobes was an extremely common phenomenon in this series (and most series in the literature), and this aspect is not considered further. No doubt the withdrawal of medication, required for the neuromonitoring of most patients, accounted for this phenomenon.

Where varying seizure forms or multiple foci were found, the patient's personal history of seizure content and auras was confirmed and video-tapes were viewed by parents, relatives and spouses (where applicable) to determine (i) whether the seizure types had ever been witnessed before, and (ii) which seizure type had constituted the dominant pattern over the years. In addition, detailed analysis of the seizure patterns was undertaken, especially in the case of temporal lobe seizures, to determine whether there was any definite pattern which could be used to distinguish between the types and to determine the dominant variant.

Results

Temporal Lobe Foci (Table 2)

On intensive neuromonitoring, 7 patients exhibited separate seizures from either temporal lobe. In all 7 cases, positive identification by relatives of both seizure patterns was achieved and in most cases there was not a great deal of difference between the seizure patterns. In 3 patients the overwhelming number of seizures emanated from one side (a ratio of 4 or 5 to 1) and the decision was made to operate on the appropriate side. Of these 3 patients, 2 were completely freed

Table 1. Cases studied

Total number of subjects	70
Patients showing variable focal seizures	11
Separate bitemporal seizures	7
Separate frontal & temporal seizures	3
Separate forms of epilepsy	1

Table 2. Cases with bilateral temporal seizures

Separate bilateral temporal seizures	7
Both patterns identified by relatives	7
No successful lateralization: rejection	4
P300 potentials	
Not performed/not possible	2
Ablated both sides	1 (No operation)
Correct localization	3 (3 operations)
Localized	1 (No operation)
Neuropsychological test	
Patients tested	7
Firm lateralization	Nil
Operation	
Total ablation seizures	2
Seizures greatly reduced	1

Table 3. Cases with separate temporal and frontal foci

Separate temporal and frontal foci	3
Rejection for surgery	1
Temporal lobectomy	2
Cure of seizures	1
Cure of temporal seizures, retention frontal seizures	1
P300 potentials	
Present both sides	1 (reject)
Localized to side of surgery	2
Neuropsychological test	
No lateralization	2
Lateralized	1

from further seizures while 1 continued to suffer complex partial seizures at a much lower rate.

In 1 of the 7 patients P300 potentials proved impossible to obtain; in a further patient they were not measured. Of the remaining 5 patients, 1 showed evoked potentials on neither side and the other 4 showed P300 potentials well lateralized to one side, which served as a guide (partial) to operation in 3 cases.

In none of these patients did neuropsychologic testing provide a certain lateralizing guide and so operation was refused for 4 patients. However all 4 will be reassessed in the future.

Separate Frontal and Temporal Foci (Table 3)

Three patients exhibited both complex partial seizures (from the temporal lobe) and frontal seizures. The latter arose from one or other frontal lobe or, as was often

the case, from both simultaneously. The seizures comprised a curious psychoparetic form of fit which, though obviously different from the usually more vigorous temporal lobe attacks, nevertheless constituted a diagnostic problem.

In one of these 3 cases a dominance of the right temporal lobe type seizure pattern plus CT changes in this area indicated operation at this site. A small epidermoid cyst was removed with total relief from all further fits. The clinical picture was not so clear in the other 2 patients and no operation was contemplated.

In only 1 patient in this group was it possible to obtain P300 evoked potentials: in this case from both sides. Nor was neuropsychological testing helpful in lateralization of seizure origin.

In all 3 patients the referring neurologist was quite certain that the patient suffered from complex partial seizures and referral had been undertaken for consideration of seizure surgery.

Focal Facial Motor Epilepsy and Complex Partial Seizures

The patient in this category occasioned no diagnostic problem. The constant focal facial twitching was obviously divorced from the temporal lobe epilepsy arising from the same side. Routine resection of the temporal lobe was effected totally relieving the complex partial seizures but leaving the facial twitching unaffected. The patient has since resumed university studies.

Both P300 and neuropsychological testing confirmed a right temporal lobe abnormality in this patient.

Discussion

In any seizure surgery programme, the demand upon the recording and monitoring facilities dictates that the testing of patients be as rapid as is safe and possible. Consequently withdrawal of anticonvulsant medication is undertaken to expedite the occurrence of seizures.

The effect of withdrawal of medication on the character of seizures and hence upon their localization has not been widely considered, doubtless in view of the fact that intensive neuromonitoring is a relatively recent technique. Ludwig and Ajmone Marson[1] studied this problem as far back as 1975 in similar circumstances and found that there was a considerable spectrum of effects of anticonvulsant withdrawal upon EEG recordings. The changes sometimes involved non-specific activation and at other times showed heightening of the activity of the initial on-medication focus or caused the appearance of additional independent epileptogenic foci. Spencer *et al.*[2] found that in a series of 25 patients with a prior history of a set seizure pattern of a complex partial type only 1 developed an atypical clinical and electrical form of seizure. Engel and Crandall[3] described a patient who, with intensive neuromonitoring and drug withdrawal before surgery, experienced 6 mixed seizures arising from either temporal lobe but with an overwhelming localizational predominance pertaining to one side which was

subsequently removed at surgery and found to contain a small circumscribed tumour. Lateralization and localization of the epileptic focus in this case was helped considerably by positron emission tomography. Review of the patient data in the UCLA Seizure Surgery Programme revealed that in almost 30% of patients between 1978 and 1980 at least 1 seizure originated in the temporal lobe contralateral to the side that was eventually resected. The point was made that clinically these seizures differed from the seizure pattern usually seen in the patients. Our findings would indicate that bilateral, separate temporal lobe seizures do differ in pattern, but not markedly.

The observation of these seizure patterns in our patients towards the end of a significant burst of fits is probably important. In view of the 'cluster pattern' of occurrence of seizures, which is almost universal in these patients, it is conceivable that at some time or other 'maverick' seizure forms have arisen from the contralateral side, and that these forms may have been seen by the parent or relative. The use of the P300 evoked cerebral potential and of the positron emission tomography scan would seem to have considerable promise in resolving this problem.

In the present series, 7 patients showed complex partial seizures starting separately from either temporal lobe. In 3 patients the overwhelming number of seizures emanated from one side and this side was accordingly subjected to surgery. The other 4 subjects were temporarily rejected from the Seizure Surgery Programme.

At present the following criteria are used as practical bases for determining the side to be operated upon:

(i) the side giving rise to the overwhelming number of seizures captured on monitoring;

(ii) the opinion of relatives and eyewitnesses as to the typical nature (or otherwise) of the seizures captured on video-tape (although this can be misleading);

(iii) the subjective history from the patient (but amnesia can render this very unreliable);

(iv) the P300 evoked potential (which has only recently been introduced as a routine measure and is still under test);[4]

(v) neuropsychological testing and the WADA test (which may be unhelpful at times).

The combination of frontal and temporal lobe complex partial seizures is a rather more complex matter and has not been mentioned in detail previously. In 1 of our patients in this category, there was no doubt in the minds of the parents that the 'frontal seizures' were indeed foreign, and in view of the behaviour of the temporal lobe focus in this patient it was removed with splendid results. In the other 2 patients the relatives had seen both types of seizures and therefore further surgical endeavours were abandoned. This group of seizure sufferers obviously needs further study, but the existence of such a combination of seizure types is often not revealed by the clinical history because the relatives supply the doctor with a descriptive amalgam of the different seizure patterns. It is rare for them to refer to the niceties of the different forms of seizures and fortunate that most patients with complex partial seizures show a set pattern to their seizures. Indeed

the fine details of the various forms of seizure probably do not really have much impact upon the situation until a decision for or against surgery is to be made. One should also not be too surprised by other and rarer forms of seizure surfacing after temporal lobectomy has been undertaken for the dominant seizure type.

The problem of the patient's suffering from two distinct types of epilepsy can be perplexing. One patient described above suffered from an easily distinguishable left temporal lobe epileptic focus and the second focus in the facial motor area seemed (and was) independent. The former was easily resectable. For the latter, surgery was unthinkable. However, this problem is not confined to combinations of these two particular forms of epilepsy and the co-existence of two distinct forms of epilepsy in the one individual is currently being studied.

Summary

Intensive neuromonitoring of seizure surgery candidates, with its associated medication withdrawal, involves increased seizure susceptibility. This can cause a confusing array of seizure patterns. This problem was examined in the candidates for seizure surgery in the Austin Hospital Comprehensive Epilepsy Programme, emphasis being placed on focal seizures. Generalized seizures were very common. Eleven (15%) patients showed multiple focal seizure patterns. Seven patients showed temporal lobe seizures originating from either side separately. Three showed persistent frontal and temporal complex partial seizures. One patient showed 2 separate species of focal epilepsy. Whilst the simplest and most effective way out of this diagnostic problem was close consultation and video review with parent or spouse, this process was ineffective in 6 of 11 patients. In patients with bitemporal lobe epilepsy there was often little to distinguish the fit coming from one side from that coming from the other and often elements of the fit from either side were recognized by the relative. In all patients with frontal and temporal complex partial seizures, elements of the seizure had been seen previously and in only 1 was there any preponderance on neuromonitoring. Therefore it is suspected that the confusing seizure detail seen on intensive neuromonitoring may in fact exist in real life and render the clinical history suspect – a problem which can be avoided only by initial neuromonitoring.

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Tolerance to the Anticonvulsant Effects of Clonazepam and Clobazam in the Amygdaloid Kindled Rat

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A major problem that occurs in the treatment of clinical epilepsy with the benzodiazepines is the development of tolerance.[1] This is most marked with the 1,5-benzodiazepine, clobazam, but is also noted with the 1,4-benzodiazepine, clonazepam.

In the experimental epilepsy model, tolerance to several benzodiazepines has been studied using pentylenetetrazol (PTZ) infusions in a variety of animal species including the rat,[2] the mouse[3] and the dog.[4,5] No reports appear to exist describing tolerance to the benzodiazepines in the kindled animal model of epilepsy.

Kindling, first described by Goddard *et al.*,[6] refers to the phenomenon of progressive seizure development culminating in a generalized convulsive seizure after repeated low intensity brain stimulation. Using this model, it is possible to regulate the onset and intensity of convulsions. Moreover, this model allows the simultaneous observation of the behavioural seizure response and the electrophysiological aspects of the seizure, as measured by the after-discharge (AD) recorded on the electroencephalograph machine (EEG). Kindling provides a reliable model of focal and secondarily generalized epilepsy in animals and is a useful preparation for the evaluation of drugs thought to possess anticonvulsant properties.[7] The kindled amygdaloid seizures represent an animal model of epilepsy in which the seizures, in some ways, are thought to parallel human complex partial seizures progressing to generalized motor seizures.

The purpose of this study was to examine the effects of chronic treatment with

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clobazam, clonazepam, and the non-benzodiazepine sodium valproate in amygdaloid kindled rats.

Materials and Methods

Kindling

Kindling consists of the daily administration of brief, low intensity electrical stimulation to discrete brain regions by means of implanted depth electrodes. Initial stimulation produces a minimal response, but repeated daily stimulation elicits progressively greater seizure activity until each stimulation produces a generalized convulsion. The change in seizure susceptibility is essentially permanent and the amygdala is a particularly sensitive site for eliciting kindled seizures.[6]

The after-discharge duration (AD) is defined to be the period during which three or more spikes, of at least twice the maximal prestimulus amplitude, occurred at a frequency of one per second, or faster, in the amygdala.[8] The seizure severity is measured by a scale of five distinct stages,[9] as follows:

Stage 1 : Facial twitching
Stage 2 : Head nodding
Stage 3 : Fore-limb clonus
Stage 4 : Rearing
Stage 5 : Rearing and falling

Animals

Male Sprague–Dawley rats weighing 250–300 grams were used. Under barbiturate anaesthesia (methohexitone 25 mg/kg intraperitoneally plus amylobarbitone 45 mg/kg intraperitoneally), a stainless steel bipolar electrode was implanted into the right basolateral amygdaloid nucleus of each rat (co-ordinates: 2.8 mm posterior, 4.5 mm lateral, 7.8 mm ventral to the bregma). Following a 2 week post-operative rest, the animals were subjected to a daily (5 days per week) low intensity electrical stimulation (1 s of 60 Hz, monophasic square-wave pulses, 1 ms duration, 4.0 V). The stimulation was delivered to the animal by a Grass S88 stimulator. Electrographic recording was monitored from the same amygdaloid electrode before, and immediately after, the stimulation using a portable Nihon Kohden EEG machine.

On each day of stimulation the after-discharge duration and the seizure stage were recorded from each animal. An animal was said to be kindled when it exhibited a Stage 5 seizure (rearing and falling) on 2 consecutive days of stimulation.

Once an animal was kindled the stimulation intensity was decreased by 0.1–0.2 volts on each subsequent day until the stimulation could no longer elicit a Stage 5 convulsion. The lowest voltage that consistently produced a Stage 5 convulsion in a particular rat was said to be its seizure threshold.

Methods

Two sets of experiments are described. Each involved pre-treating the animals with the appropriate drugs at set time intervals before the application of the low intensity stimulus, and assessing the effect on blocking of the kindling response, both by clinical observation as defined above and by measuring the duration of the after-discharge on the EEG.

Experiment 1 (Pretreatment: clonazepam and valproate)

Days 1 and 2: Eighteen fully kindled rats were stimulated at 120% seizure threshold.
Days 3-14: Rats were assigned to one of 3 groups and given an intraperitoneal (i.p.) injection of saline (1 mL/kg), clonazepam (0.3 mg/kg) or sodium valproate (200 mg/kg). Sodium valproate (200 mg) was dissolved in 1 mL of distilled water and clonazepam (Rivotril®, Roche) was diluted to a concentration of 0.3 mg/mL with normal saline. Vehicle or drugs were administered twice daily (8 am and 8 pm) and each rat was stimulated at 120% seizure threshold 30 minutes *after the morning dose*. The amygdala after-discharge duration (recorded on a portable Nihon Kohden EEG machine) and the seizure stage were determined.

Experiment 2 (Pretreatment: clobazam)

Day 1: Twelve fully kindled rats were stimulated at 120% seizure threshold.
Days 2 and 3: Rats were assigned to one of 2 groups and given an intraperitoneal injection of either vehicle (1 mL/kg) or clobazam (4 mg/kg). Clobazam (4 mg) was dissolved in a vehicle containing 0.4 mL of propylene glycol, 0.1 mL of ethanol, 0.015 mL of benzyl alcohol, 50.0 mg of sodium benzoate, 2.25 mg of benzoic acid, and distilled water to 1 mL. Vehicle or drug was administered twice daily (8 am and 8 pm) and each rat was stimulated at 120% seizure threshold 60 minutes *after the morning dose*.
Days 4 and 5: The dose of clobazam was increased to 6 mg/kg on day 4 and to 8 mg/kg on day 5 to all rats in the drug group.
Days 9–17: The dose of clobazam was maintained at 8 mg/kg but the time interval between the morning dose and electrical stimulation was decreased from 60 minutes to 30 minutes.
Day 8: Clobazam treatment was ceased and the drug group was given clonazepam (0.3 mg/kg intraperitoneally) 30 minutes before electrical stimulation.
Day 19: The clonazepam dose was increased to 0.6 mg/kg, administered intraperitoneally.

The after-discharge duration and the seizure stage were determined in all rats over the course of the experiment.

Statistical Methods

The data were examined by analysis of variance with repeated measures.[10] This was followed by orthogonal partitioning of sums of squares for individual

comparisons of drug *versus* no drug and drug *versus* drug within the treatment period. The F ratio was calculated as $\Sigma x^2/EMS$ where EMS = error mean square term. The t-statistic was calculated as the square root of F, given 1 degree of freedom.

Results

Clonazepam (0.3 mg/kg), sodium valproate (200 mg/kg) and clobazam (8.0 mg/kg) all significantly blocked the kindled seizures in the initial stages of treatment (Table 1, Figure 1, Figure 2).

Table 1. Anticonvulsant effects of clonazepam, clobazam and sodium valproate in amygdaloid kindled rats.

		Pretreatment *vs* treatment			Tolerance		
EXPERIMENT 1		d.f.	t		d.f.	F	
Vehicle (1 mL/kg)	AD	51	1.12 NS	(No change)	1,44	1.2 NS	(No change)
	SS	51	0.76 NS		1,44	0.8 NS	
Clonazepam (0.3 mg/kg)	AD	51	7.88****	(Blockade)	1,44	3.4***	(Tolerance)
	SS	51	8.24****		1,44	3.2***	
Valproate (200 mg/kg)	AD	38	5.35****	(Blockade)	1,33	0.9 NS	(No tolerance)
	SS	38	5.67****		1,33	1.1 NS	
EXPERIMENT 2		d.f.	t		d.f.	t	
Vehicle (1 mL/kg)	AD	90	0.18 NS	(No change)			
	SS	90	0.04 NS				
Clobazam (4 mg/kg)	AD	90	0.58 NS	(No effect)			
	SS	90	1.57 NS				
Clobazam (6 mg/kg)	AD	90	1.51 NS	(No effect)			
	SS	90	1.51 NS				
Clobazam (8 mg/kg;1 hr)	AD	90	2.63**	(Blockade)			
	SS	90	2.87*				
Clobazam (8 mg/kg; 30 minutes)	AD	90†	3.79****	(Blockade)	90‡‡	4.20****	(Tolerance)
	SS	90	4.91****		90	5.18****	
Clonazepam (0.3 mg/kg)	AD	90‡	2.05 NS	(No effect)			
	SS	90	0.92 NS				
Clonazepam (0.6 mg/kg)	AD	90††	2.92***	(Blockade)			
	SS	90	2.62**				

*$p < 0.01$; **$p < 0.02$; ***$p < 0.005$; ****$p < 0.001$; AD = after-discharge duration; SS = seizure stage.

† Pretreatment days *vs* days 1 and 2 of clobazam (8 mg/kg; 30 minutes).

‡ Clonazepam (0.3 mg/kg) *vs* last 2 days of clobazam (8 mg/kg; 30 minutes).

†† Clonazepam (0.6 mg/kg) *vs* last 2 days of clobazam (8 mg/kg; 30 minutes).

‡‡ Days 1 and 2 of clobazam (8 mg/kg; 30 minutes) *vs* days 3–9.

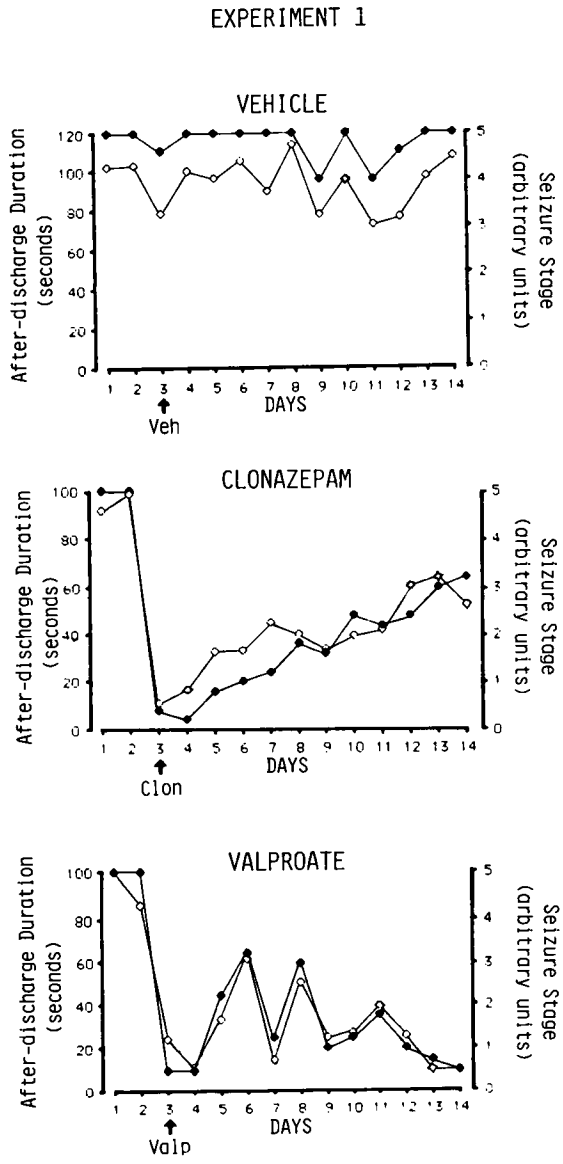

Figure 1. Effects of chronic treatment with vehicle, clonazepam and sodium valproate in amygdaloid kindled rats. ◇ = mean after-discharge duration; ◆ = mean seizure stage.

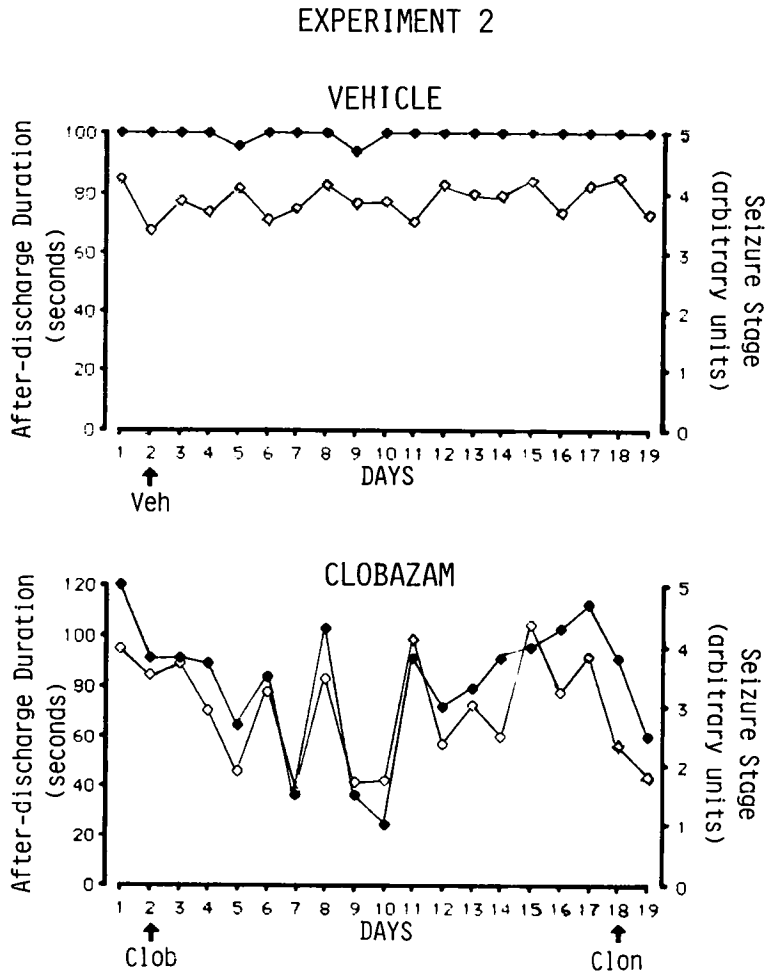

Figure 2. Effects of chronic treatment with vehicle and clobazam in amygdaloid kindled rats. ◇ = mean after-discharge duration; ◆ = mean seizure stage.

Tolerance developed to clonazepam and clobazam but not to sodium valproate. In the case of clonazepam, tolerance developed gradually and showed a significant linear trend ($p < 0.001$). Tolerance to clobazam, however, appeared as a single step to a residual protection after 2 days of treatment with 8.0 mg/kg administered intraperitoneally 30 minutes before electrical stimulation (Table 1, Figure 2).

Clonazepam (0.6 mg/kg) protected the rats that had become tolerant to clobazam with a significant reduction in after-discharge duration and seizure stage (Table 1).

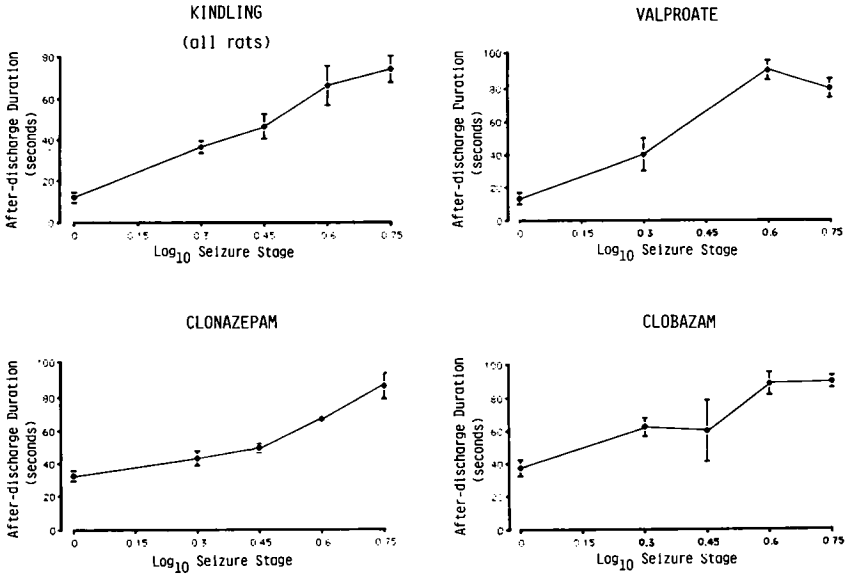

Figure 3. Electroclinical correlation. Only one animal in the clonazepam treated group exhibited a Stage 4 seizure and the standard error of the mean could not be calculated. No rats in the sodium valproate group had a Stage 3 seizure.

A strong correlation was seen between the after-discharge duration and the seizure stage in all 3 drug groups over the course of the experiment and during the kindling of the animals used in this study (Figure 3).

Discussion

Previous studies examining tolerance to the anticonvulsant effects of the benzodiazepines in animals have utilized the PTZ (pentylenetetrazol) infusion model. There do not appear to be any published reports describing this 'escape phenomenon' in the kindled animal model of epilepsy.

Our results indicate that tolerance to the benzodiazepines clonazepam and clobazam can be demonstrated in the amygdaloid kindled rat. These findings agree with those of Frey *et al.*[4] and Gent *et al.*[3] who found that clonazepam tolerance develops gradually over time whereas tolerance to clobazam occurs in a more abrupt fashion. Sodium valproate effectively blocks the amygdaloid kindled seizure in rats without the development of tolerance. Clonazepam can significantly prevent the amygdaloid kindled seizure in clobazam tolerant rats, although this phenomenon needs to be explored further.

The underlying mechanism of benzodiazepine tolerance remains unclear. Experiments are in progress to examine whether cross-tolerance occurs between

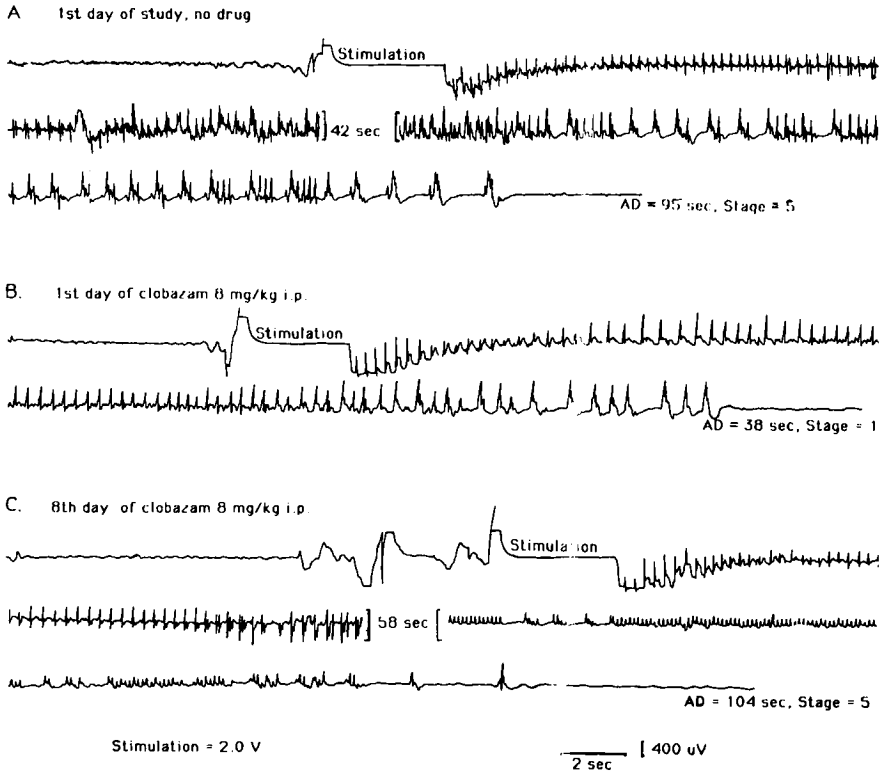

Figure 4. Effect of chronic treatment with clobazam on the same rat. EEG recordings made in the same rat on 3 separate days of the experimental procedure as indicated.
A – shows stimulation in absence of drugs (AD = 95 s, Stage 5 seizure observed).
B – shows stimulation 30 minutes after clobazam (8 mg/kg i.p.) on day 1 of treatment (AD = 38 s, Stage 1 seizure observed)
C – shows stimulation 30 minutes after clobazam (8 mg/kg i.p.) on eighth day of treatment (AD = 104 s, Stage 5 seizure observed).

benzodiazepines. If cross-tolerance does not occur, as our preliminary results with clonazepam suggest, then alternating drug therapy using these drugs could provide a means of overcoming the benzodiazepine 'escape phenomenon', which is a major problem in clinical epilepsy.

Summary

A major problem in the treatment of clinical epilepsy with benzodiazepines is the development of tolerance. This is most marked with the 1,5-benzodiazepine, clobazam, but is also noted with the 1,4-benzodiazepine, clonazepam. This study

examined the effects of chronic treatment with clobazam, clonazepam and the non-benzodiazepine sodium valproate on the amygdaloid kindled rat with a view to developing an animal model of tolerance.

Twice daily intraperitoneal injections of vehicle (1 mL/kg), clonazepam (0.3 mg/kg), clobazam (4.0–8.0 mg/kg) or sodium valproate (200 mg/kg) were given to fully kindled rats for 12 days, in the case of clonazepam and valproate, and for 16 days for clobazam. All rats were stimulated 30–60 minutes (depending on the drug) after the morning dose. The amygdala after-discharge duration (recorded on the EEG) and the seizure stage were determined.

While all three drugs initially blocked the kindled seizure, tolerance developed to clonazepam and clobazam but not to valproate. Statistical analysis of the results showed a significant linear trend in the development of tolerance to clonazepam after day 5, but tolerance to clobazam appeared in a more abrupt manner after day 2. The clobazam group were then given a further 2 days of treatment with clonazepam (0.3–0.6 mg/kg) and this blocked the kindled seizures.

The amygdaloid kindled rat is a suitable model for studying tolerance to the anticonvulsant effects of benzodiazepines. Further experiments are currently in progress to examine the effectiveness of change-over therapy between clobazam and clonazepam as a means of overcoming tolerance.

Acknowledgements

We thank Dr A. Curran of Reckitts Australia for generous support and Dr F. Rudolph for supplies of clobazam.

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Evaluation of the First 18 Months of a Specific Rehabilitation Programme for Those with Epilepsy

*R.G. Beran, M. Major and L. Veldze**

The role of rehabilitation in epilepsy management has been considered at a number of meetings[1–4] but very little has appeared in the literature.[5–7] Fraser[7] highlighted the four major requirements for successful epilepsy rehabilitation as:

(i) specialized vocational programmes which appreciate the particular problems of those with epilepsy,

(ii) psycho-educational programmes which address the anxiety and depression which accompany epilepsy,

(iii) state of the art understanding of the medical management of the condition, and,

(iv) the provision of transitional residential accommodation which minimizes the conflict of attaining full independence.

This report examines the first 18 months of operation of the epilepsy rehabilitation unit at the Mt Wilga Rehabilitation Centre in Sydney, Australia.

Background

The Commonwealth Rehabilitation Service, administered by the Department of Social Security, assists people who have a physical or mental disability that restricts their vocational and social independence and the ability to develop their maximum potential. The Mt Wilga Rehabilitation Centre, Hornsby, is a multi-diagnostic and multi-disciplinary centre offering comprehensive rehabilitation programmes with social, educational, vocational and medical components. The Centre caters for a maximum of 250 clients and residential facilities are available for country clients. A multi-disciplinary team, including a rehabilitation medical

*Mt Wilga Rehabilitation Centre, Hornsby, New South Wales.

consultant, physiotherapist, occupational therapist, speech therapist, rehabilitation counsellor, social worker and sister, identify the client's needs and together with the client, plan a suitable programme to meet his or her individual needs. Clinic meetings are held regularly to discuss each client's progress and to set goals to be achieved. The rehabilitation medical consultant in the unit involved with epilepsy rehabilitation is a neurologist with a special interest in epilepsy and who has access to clinical pharmacology and electroencephalography laboratories.

Clients are given the opportunity of participating in a wide variety of workshops to be assessed and to gain specific skills in assembly tasks, automotive and industrial spray painting, car detailing, woodwork, concreting and allied outdoor skills. Opportunity is also available for assessment on the switchboard, or as a kitchen hand, cleaner orderly, storeman gardener, housekeeper and physiotherapy aide.

For those interested in commercial or clerical fields, in further study or in the upgrading of their general education, the Centre offers teaching in basic and advanced office procedures, business English and mathematics, bookkeeping, typing, small business management, independent remedial work, migrant English, and preparation for Public Service examinations. Those clients for whom open employment is a realistic possibility are given the opportunity to experience 'work therapy' (on-the-job training) when considered ready for work. The purpose of their training is threefold: (i) to assess the client's ability to perform in open employment, (ii) to allow the client an opportunity to impress a prospective employer, and (iii) to bridge the gap between the rehabilitation centre and employment, giving the client confidence in a practical and supportive setting. During the training an allowance is paid to the client by the Department and expenses for fares, books and equipment are reimbursed.

For those clients who wish to attempt study at technical or university level or through practical courses, sponsorship may be considered by the Department. The goals must be vocationally realistic and the client capable of succeeding in those goals.

Mt Wilga does not cater exclusively for vocational rehabilitation. Improving the client's quality of life and level of personal and social independence is equally important. Opportunities are available to develop competence in activities of daily living such as self-care, home duties, mobility and avocational interests, and social and survival skills.

Clients are assessed again 6 months after discharge; this is to assist and support the client in the re-settlement period and to ensure there is no breakdown in the rehabilitation process.

Patients and Methods

Twenty-six patients (15 males, 11 females) attended the unit in its first 18 months of operation. Their age range was from 16 to 45 years (mean age of 24, modal age of 17 years). The period of follow-up was between 6 and 20 months, with a mean period of 14 months. Admission lasted between 2 weeks and 9 months, with

a mean of 4.5 months. Of the 26 patients, 13 were residential while 13 attended on a daily basis. Nine patients were referred by a doctor, 8 by community services, 4 by paramedical services such as social workers and hospital departments, and 3 by their family and for 2 the source of referral was unknown.

Follow-up data collection was by means of brief questionnaire, accompanied by a letter of introduction and explanation. Up to 3 mailings to the group of patients who attended the unit were undertaken and a subsequent personal approach, by a member of the therapeutic team, completed the task of data retrieval.

Results

Of the 26 patients, replies were obtained from 23 (85.5%) (Table 1). Eighteen of the 23 respondents were favourably impressed with the overall care provided at Mt Wilga while 5 (of whom 4 were non-residential patients) were undecided. The

Table 1. The findings of the survey together with demographic data of age and sex

Age (years)	Sex	Employment*	Results of follow up†			Medication‡
			Quality of life	Epilepsy control	Self-esteem	
Non-residential patients						
45	M	N	+/−	−	−	S
16	M	N	+	+/−	+	S
19	M	Y	+	+/−	+/−	S
35	M	Y	+/−	−	+/−	I
37	M	N	++	+/−	+	I
22	F	N	−	+/−	+/−	D
23	F	N	+/−	+/−	+/−	S
45	M	N	+	+/−	+/−	S
35	M	Y	++	++	+	S
17	F	Y	+/−	+/−	+/−	S
18	F	Y	+/−	+/−	+/−	S
Residential patients						
17	M	Y	+	++	+	D
16	F	N	+/−	+	+/−	S
33	M	Y	+	+/−	+	D
20	F	N	+	++	++	D
17	M	W	−−**	+	+/−	S
25	F	Y	+	+/−	+/−	D
19	F	N	+/−	++	+/−	S
23	M	Y	++	++	++	S
25	M	Y	+	+	+/−	S
25	M	Y	++	++	+	S
18	F	Y	++	++	++	S
22	F	Y	+	+/−	+	S

*Y = yes, N = no, W = was. †++ = much improved, + = improved, +/− = same, − = worse, −− = much worse. ‡S = same, I = increased, D = decreased. **This patient was in gaol at the time of the study.

major criticism of the services at Mt Wilga was the integration of more severely handicapped patients, from other units functioning at the Centre, with the epilepsy-affected group.

Responses were assessed with regard to whether the patient had been treated as a residential patient or as a day attendee. Five of the 11 non-residential patients were employed at the time of the study, as compared with 8 of the 12 residential patients. Another residential patient had been employed but was subsequently retrenched. Two of the 8 respondents, not employed, were undertaking further educative programmes designed to enhance their employment prospects. The overall success rate for employment was 59.1%. Those unemployed were fairly evenly distributed between males and females with the unemployed males being slightly older.

Quality of life was assessed on a comparative scale of 1 to 5 units which evaluated quality before and after admission. Overall, there was marked improvement in 6 subjects, some improvement in 9 patients, no change in 7 and deterioration in 2 (of whom one claimed marked deterioration because he had been gaoled). It is interesting to note that the patient who identified some worsening in her quality of life still wrote '. . The care given was terrific. . ' and indicated that her self-esteem was unchanged.

Comparison of residential and non-residential patients revealed greater improvement of quality of life for the residential group (Table 1). Self-esteem also showed significantly more improvement for the residential group as compared with the non-residential group. Only 1 patient stated that his self-esteem (also evaluated on a 5 point scale) had deteriorated. This patient was a non-resident who had no change in quality of life but claimed that his nerves had been bad and that he got upset easily. Overall, 43.5% identified an improvement in their self-esteem and 65.2% had better quality of life.

Comparison of state of employment with quality of life and self-esteem indicated that the patient with lowest self-esteem was an unemployed man in mid-life. Of the remaining 8 unemployed patients (including the temporarily employed male), 50% had improved quality of life and almost 50% had improved self-esteem.

Control of epilepsy was also examined and was assessed on a 5 point scale comparing the level of control before and after admission. Two non-residential patients identified a worse level of control. Of these 2 patients, 1 had his drug therapy increased during admission and the other had remained on the same regimen. Where therapy was reduced (5 patients), 2 patients felt that their seizure control had improved while the remainder felt that their control was unchanged. Of the 16 patients for whom no change to drug therapy had been made, 5 stated that their control of epilepsy was much improved and 3 identified some improvement.

Of the 11 patients who noted no change in seizure control, 6 were employed at the time of the study. Seven of the 11 noted improved quality of life and 4 claimed improved self-esteem.

Respondents were given the opportunity to answer open-ended questions asking for either positive or negative remarks concerning their rehabilitative programme. Positive comments focused on the willingness of staff to attend to indi-

vidual problems. Criticism of staff was directed towards the patronizing attitude of a minority of staff members and some patients were critical of the excessive 'spoon feeding' which was incorporated into their programme. The disciplinary code of the Centre received both positive and negative comment with the balance favouring the need for a defined domain of rules and expectations.

Discussion

Our results highlight areas of interest in the rehabilitation of those with epilepsy. As mentioned above, Fraser[7] raised 4 points necessary for the successful outcome of rehabilitation in epilepsy. Research directed at patients and doctors[8] disputed the need for a half-way house in a rehabilitation programme. Fortuitously, there was an even distribution between residential and non-residential patients in our survey. The success rate of rehabilitative outcome favoured the residential group who showed a greater level of employment, improvement in quality of life, control of epilepsy and enhanced self-esteem. Thus, 'half-way' accommodation may be an important factor in the rehabilitation of those with epilepsy. Fraser *et al.*[9] identified the specific benefits that accrue from a specialized unit directed specifically at the rehabilitation of those with epilepsy. Our figures would support the findings of these workers.

There is more to the management of epilepsy than manipulation of therapy (drugs or surgery). Half of those who had no change made to their drug regimen acknowledged either some or marked improvement in their seizure control following their admission to Mt Wilga. This occurred despite 2 of these patients not becoming employed. The majority of those who had no change in seizure control still experienced an improved quality of life, one of the most important aims of rehabilitative medicine.[10] Six of the 16 patients who had no change in seizure control were employed at the time of the survey; the majority of these indicated improvement in other areas as well.

This survey adds weight to the observations of Fraser *et al.*[9] that there is a need for the establishment of units dedicated to the rehabilitation of those with epilepsy. These figures would further suggest the benefit of a residential programme in which the patient is admitted for a short period into a therapeutic environment designed to meet his or her special needs and to aid transition to full independence. This is of major importance at a time when the current vogue is to disband all residential services in rehabilitation therapy.

Summary

This survey examined the outcome of the first 18 months of the specialized rehabilitation programme at Mt Wilga Rehabilitation Centre, which was designed to cater for the needs of those with epilepsy. Almost 60% of those who underwent the programme were employed at the time of the study, 65% had improved quality of life, approximately 45% acknowledged enhanced self-esteem, and about 45%

had an improved control of epilepsy despite the fact that only 30% had their drug therapy altered and of these more than half had either the same or worse control of their seizures.

The findings revealed that those patients who were admitted into the residential accommodation, rather than being provided with transport to allow daily attendance while living in their own homes, achieved greater benefit from the rehabilitative programme.

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Impairment of Consciousness in Migraine

*P.A. Kempster, R. Iansek and J.I. Balla**

Impairment of consciousness during episodes of migraine has previously been recognized in the form of a number of clinical syndromes, including basilar artery migraine,[1] confusional migraine of late childhood and adolescence,[2] migraine stupor[3] and possibly transient global amnesia.[4] It has been our experience that the range of clinical features of migraine associated with impaired consciousness is wide in terms of age incidence and frequency and pattern of episodes, and that such episodes often do not conform to categories described in previous studies.

Although affecting only a small fraction of the migraine-prone population, this type of disturbance does not appear to be rare in neurological practice. To define the clinical syndrome further we report details of 25 patients with attacks of migraine that were accompanied by impaired conscious states.

Methods

Cases were selected from inpatient admissions to the Neurology Unit at Prince Henry's Hospital from 1981 to 1985 and also from patients seen in outpatient private practice by one of the authors (J.B.) over the 12 year period 1974 to 1985. Clinical features were studied retrospectively by review of the medical records. A migrainous explanation for episodes of impaired consciousness was based on consideration of the following factors: the history of prior periodic headache and associated neurological features, the patient's description of the prodrome and aftermath of attacks, eyewitness accounts and the absence of an alternative likely diagnosis. Patients with short-lived syncopal impairment of consciousness were not included.

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Results

Twenty-five patients (11 male and 14 female) were thought to have had episodes of altered consciousness related to migraine. Their ages ranged from 9 years to 58 years with a mean of 28 years. Descriptions of episodes fell into 3 main categories: confusional episodes, episodes of unconsciousness and amnesic episodes.

Clouding of consciousness with confusion was seen in 15 cases and was often associated with disturbance of personality or behaviour. Eyewitness descriptions of irritable, child-like or aggressive behaviour were commonly employed. Five patients became comatose for at least part of the duration of an attack, while five patients experienced episodes in which complex behaviour was preserved but for which the patient was subsequently amnesic. Eyewitness descriptions usually suggested that the disturbance involved more than short term memory function and 4 patients had episodes of briefer duration than typical transient global amnesia. The following Case Reports are characteristic.

Case Reports

A 15 year old girl had been prone to periodic generalized throbbing headache accompanied by nausea and fragmentation of vision since the age of 13. Both parents and her brother suffered from migraine. On 2 occasions her usual headache was preceded by a disturbance lasting for 20 minutes, during which she was said to be delirious and to have behaved aggressively.

A 49 year old man had experienced periodic frontal headache for many years, infrequently accompanied by shimmering visual distortion and sensory symptoms in right face and arm. On one occasion similar sensory symptoms plus dysphasia were succeeded by confusion and progressive obtundation over an 8 hour period. At the height of the attack he was unrousable.

A 33 year old man had been prone to periodic headache accompanied by visual scintillation since his teenage years. One day at work he experienced his usual visual symptoms plus headache and was observed to be vague and unsteady on his feet, as if drunk. He apparently drove himself home and woke in his bed 36 hours later with no recollection of events over this time, although he had changed all of the tyres on his car and performed several other tasks. Dull headache persisted for 10 days.

The frequency and duration of attacks in all patients are displayed in Tables 1 and 2, respectively. Eight patients aged 15 years or younger developed attacks of

Table 1. Frequency of attacks

1 episode	16 patients
2 episodes	4 patients
⩾ 3 episodes	5 patients

Table 2. Duration of attacks

< 1 hour	15 patients
1–6 hours	7 patients
6–24 hours	1 patient
⩾ 24 hours	2 patients

impaired consciousness either as an initial manifestation of migraine or within several months of the onset of migrainous headache. By way of contrast, 8 older patients had a history of migraine which predated the onset of episodes of altered consciousness by at least 10 years. Fifteen patients gave a family history of migraine. Focal central neurological symptoms were reported with previous headache in 17 cases and with attacks of altered consciousness in 19 cases; 5 of this latter group had brainstem disturbances. Thirteen patients reported that attacks with disturbed consciousness were followed by prolonged headache or lethargy.

Discussion

Previous reports of basilar artery and confusional migraine have emphasized the tendency of these disorders to occur in young patients near the time of onset of migraine, the frequency of occurrence of a family history of migraine, and the occurrence of features of brainstem dysfunction in attacks. Lee and Lance[3] reported 7 cases with confusion or stupor due to migraine that did not show a predilection for younger age groups although brainstem symptoms or signs were seen in the majority. Our series of 25 cases shows a considerable range of impaired consciousness phenomena related to migraine. Although many patients were of the younger age group usually associated with basilar artery or confusional migraine, about one-third of subjects were over the age of 35 years and often had had a well established migrainous tendency for some years before developing episodes of altered consciousness. Brainstem neurological dysfunction was not encountered often in this study. A prominent feature of the attacks of impaired consciousness in over half of our cases was the subsequent prolonged headache and/or lethargy, often persisting for some days and considerably outlasting the usual duration of the migrainous headaches.

We suggest that migraine be considered as a possible cause for transiently impaired consciousness in any patient with a prior history of migraine.

Summary

A series is reported of 25 subjects with migraine, whose attacks on some occasions involved impairment of consciousness. The disorder did not necessarily involve younger people, or occur early in the course of the malady.

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Cervical Spondylosis and Headaches

*R. Iansek, J. Heywood, J. Karnaghan and J. I. Balla**

Cervical spondylosis may be defined as a degenerative disease affecting the intervertebral discs and apophyseal joints of the cervical spine. Many reports have detailed the major clinical features of this disease, including the presence of headache. The reported incidence of headache in this condition is variable. Brain's[1] original description failed to mention the presence of headache in any of 45 patients with documented myelopathy or radiculopathy. Similarly Balla *et al.*,[2] in a review of 40 cases of cervical myelopathy and radiculopathy, did not find any cases presenting with significant headache symptoms. A further paper by Brain[3] documented the incidence of headache in cervical spondylosis as being 28%. Other reports[4–6] have described an incidence of headache of up to 79%, a figure quoted for patients with radiculopathy.

The mechanism of headache in cervical spondylosis is also of significance in assessing the relevance of cervical spine degenerative disease in the pathogenesis of headache. Pain from the diseased joints has frequently been implicated as the source of headache in this condition. However, the commonly affected joints in the cervical spine (C_5, C_6, C_7) have not been shown[7] to refer pain to the head when manipulated or injected during surgical exploration of the neck. Furthermore, for the upper three (less commonly affected) intervertebral discs and apophyseal joints, there is no positive evidence showing that the pain sensation from these structures radiates to the head. The radiation of pain to the head from the upper cervical spine appears to originate from muscle nociceptors.[8]

Taking into consideration the wide range of incidence of headache reported in cervical spondylosis, and the doubts about whether the headache originates from joints of the cervical spine, we re-investigated this problem. A personal series of clinically diagnosed muscle contraction headaches was reviewed, and the features

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of these headaches were then compared with the headaches described by a group of patients with cervical spondylosis.

Methods

We reviewed retrospectively a personal series of 59 cases with a diagnosis of cervical spondylosis and 50 cases with a clinical diagnosis of tension headache.

All cases with cervical spondylosis had degenerative disease of the cervical spine present on plain radiographs. Those diagnosed as having radiculopathy had radiation of pain into an arm, in some instances associated with neurological abnormalities. Those with myelopathy had evidence of paraparesis and abnormal myelograms. The cases without neurological abnormalities had significant limitation of neck movement with localized tenderness in the neck. The case histories of 50 patients over the age of 45 years diagnosed as having tension headaches were retrospectively reviewed to assess the pattern of headache in addition to the possible role of cervical spine pathology. Tension headache was diagnosed on the basis of the chronicity of the headache, the absence of nausea or other neurological symptoms, and the presence of anxiety or tension. The comparison of headache types was performed on a qualitative basis.

Results

The incidence of headache in patients with cervical spondylosis is shown in Table 1. Overall, 13% of patients with cervical spondylosis had headache as a prominent symptom. Four patients had headaches in a setting of radiculopathy and in 2 of the patients the root pain was in the C_7 distribution. In the other 2 cases it was more diffuse, but was again in the lower cervical segments. In all 8 cases the headache was occipital, with radiation to the frontal regions in 2 of these patients. Four patients complained of a constant ache, whilst another 4 had twinges and stabs of pain. Movement appeared to precipitate or aggravate the pain in 4 cases. In 1 patient the headache was exacerbated by bending forward and also by the maintenance of a sustained posture such as during reading or developing films. Two patients had tender spots in the sub-occipital region in addition to limitation of head movement. One patient had visual blurring associated with the headache and in another patient headache was precipitated by lying down.

Table 1. Cervical spondylosis headache group

Presenting feature	Number	Number with headache
Radiculopathy	30	4
Myelopathy	9	1
Neckache	20	3
Total	59	8

Table 2. Summary of descriptive features of tension headache group

Duration	12 months
Side	Bilateral 25 Unilateral 17
Type	Pressure 13 Dull 2 Ache 1
Location	All over 3 Top of head 9 Frontal 6 Occipital 7 Occipital-frontal 8
Precipitating factors	Head injury 2 Tense 3
Aggravating factors	Bending 3 Lying in bed 8 Neck movement 2 Standing 1 Cold 1
Ameliorating factors	Standing 6 Heat 1 Valium use 1 Lying 1
Associated factors	Blurred vision 2 Unsteady 2

All 50 patients with tension headache had clinical evidence of anxiety or depression. Cervical spine disease was thought to be a significant contributing factor in 9 of the 50 cases diagnosed as having tension headache. Table 2 summarizes the features of the headache in the tension headache group of patients. The mean duration of the headache in this group was 12 months. The headache was unilateral in a large proportion of the patients, and was frequently located in the occipital region. Various precipitating and aggravating factors were described, including bending forwards, lying in bed, standing, and neck movement. Associated features included blurred vision and unsteadiness. It is apparent that the headaches in the patients with tension headache had many features that were similar to the headaches described by our group of patients with cervical spondylosis.

Discussion

This retrospective review emphasizes the low incidence of headache associated with cervical spondylosis and also illustrates the often indistinguishable features of the headaches of such patients compared with those of patients with tension headache. These findings suggest that nociceptors from deranged joint structures are not

directly responsible for headache in cervical spondylosis. We suspect that the headaches in cervical spondylosis are caused by secondary muscle contraction, either owing to the presence of associated tension and anxiety, or arising from a reflex muscle contraction due to the joint derangements and local pain that occur in this condition. The pronounced muscle contraction would in turn lead to ischaemia as a result either of the sustained muscle contraction or of the associated vasoconstriction that has been described in some patients.[9]

We are well aware of the problems in arriving at this conclusion from our retrospective review, problems which relate predominantly to the absence of a 'gold standard' of diagnosis for both these clinical entities. Unfortunately, this problem affects all analyses based on clinical diagnosis. Within these constraints, however, we can say that in our series the incidence of headache in cervical spondylosis was low and that the clinical features of the headache were indistinguishable from those of muscle contraction headache.

Summary

The incidence of headaches in well documented cases of cervical spondylosis with neurological disability was reviewed. This was compared to that in a series of cases with a clinical diagnosis of tension headache in order to determine if there were any identifiable differences between the two types of headache. Fifty-nine cases of cervical spondylosis were reviewed. Five of these patients had headaches. Fifty patients with tension headaches were also reviewed. No differences were seen when location or other qualitative features of the headaches were compared between the two groups of patients. We conclude that the incidence of headache is low in cervical spondylosis and that the pattern of headache has no features that distinguish it from that of tension headache, suggesting that the pathogenesis is similar. We therefore suggest that the basis of headache in patients with cervical spondylosis is secondary muscle contraction.

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Whiplash Headache

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Headache in the Acute Whiplash Syndrome

The whiplash syndrome comprises a collection of symptoms and disabilities that follow any neck strain where there has been an abrupt movement of the cervical spine. It is usually seen as a result of motor vehicle accidents.

Patients

We have studied prospectively 122 patients with whiplash headache presenting within 4 weeks of a motor vehicle accident, seen by the Whiplash Study Group of the Motor Accidents Board of Victoria and in whom a description of the headache was available.

Results

The location of the headaches in the 122 subjects studied was occipital in 46%, generalized in 34% and elsewhere in 20%. The pain was present more than half the time in 50% of patients. Its quality varied and there were trigger spots in the neck and shoulder regions in about 50% of the patients. At 12 weeks, one-third of patients had pain more than half of the time, while headache persisted in 73% and in these latter cases it was present more than half the time in 36%.

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Headache of the Late Whiplash Syndrome

This syndrome was defined as an inability to return to normal activities for 6 months or longer after a whiplash injury. The incidence of headache in a retrospective analysis of 300 cases was 97%.[1]

Patients

One hundred consecutive patients from a single neurological practice seen more than 6 months after a whiplash injury were reviewed retrospectively. Of these subjects, 90% were seen within 3 years of the accident and 80% were still having headaches at the time of review. There were 55 females and 45 males in the series and 80 cases were analysed in detail. Since the study was retrospective, some information was missing, but the general characteristics of the headache were consistent throughout.

Results

The headaches were constant in more than half the cases analysed in detail and occurred once a week or more often in 40%. Half of the subjects woke with headache and in two-thirds it was most prominent in the mornings. The other headache characteristics are shown in Tables 1 and 2.

Pathogenesis of Headaches Following Whiplash

Adequate data on the pathogenesis of acute whiplash headache in human subjects are not available. Neuropathological studies of primates involved in high acceleration injuries were reported by Unterharnscheidt.[2] He found that the

Table 1. Time to onset of headache after accident

Time	Percentage of cases (N = 80)
Immediate	11%
Within 1 day	62%
Within 1 week	86%

Table 2. Factors aggravating headache in the late whiplash syndrome

Aggravating factor	Percentage of cases (N = 80)
Any activity	55%
Specific neck move	28%
Anxiety	12%
Concentration	5%

severity of the pathological changes found at autopsy was related to the severity of the trauma. There was contusion in the muscles and ligaments of the neck and also, in more severe cases, in the spinal cord and cerebral cortex. The relationship of these findings to the generally less severe injuries seen in humans is open to question. Radiological reports have indicated possible malalignment of joints demonstrable only on specialized functional views.[3] This work needs to be supported by further clinical correlations before any generalizations can be made. Furthermore, it is uncertain if these structures do refer pain to the head; if they do, discharge from joint nociceptors would be expected to take place at the time of extreme movement, not long after the injury, as is so often the case in clinical practice.

An alternative explanation is that the greater occipital nerve may be traumatized by forcible extension of the neck in the nerve's course through the upper two vertebrae. However, even the most severe traumatic disruptions of the craniospinal region failed to show evidence of damage to the C_2 nerve in these conditions.[4]

On the evidence, the clinical features of headache following whiplash injury are in keeping with muscle contraction headache. This is likely to be the result of localized trauma and, in some instances, associated anxiety.

Similarly, the pathology of the late whiplash syndrome has not been adequately documented. There is no evidence to link pre-existing degenerative changes in the cervical spine with the development of chronicity. The relative sparing of older age groups and the lack of correlation between x-ray findings and symptoms is in keeping with this view. It is difficult to escape the conclusion that there must be a relationship between the severity of the impact and the development of the late whiplash syndrome, but this has not yet been confirmed. There are some indications that socio-cultural factors may account for a number of cases going on to chronicity. Retrospective studies[1,5] have suggested that various ethnic groups have a differential distribution of the illness and also that there is an increase in the upper middle, as opposed to the lower and higher, occupational categories. This would fit in with the concept of differential illness behaviour in these groups. Further studies are required to substantiate these early hypotheses.

Summary

This study considers the natural history and characteristics of headache occurring after whiplash injuries. Previous descriptions generally failed to distinguish between the headaches seen at various stages after the injury. In a prospective study of 180 cases of acute whiplash injury, it was demonstrated that 82% suffered from headache. One hundred and twenty-two cases were analysed to describe the type of headache seen and it was shown that in the majority rapid improvement occurred over a matter of some weeks.

In a retrospective analysis of over 5000 cases of whiplash injury, about 25% developed chronic disability. Practically all of these had headaches. A retrospective analysis of 100 cases describes a spectrum of headaches different from those seen after the acute illness. The pathogenesis of the two types of headache is likely to

be different and this needs to be investigated before rational treatment can be instituted.

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Diagnostic Strategies of Fifth Year Medical Students in a Neurological Case. The Importance of the First Hypothesis

M. Gibson,[†] *J. Kaaden*[†] *and J.I. Balla*[*†]

One major difference between the expert and the novice in their diagnostic processing is their first diagnostic formulation.[1] The early hypotheses correlate closely with the final hypotheses,[1] so that the more correct the first hypothesis, the more likely it will be that the final hypothesis will be the right one. It is therefore important to understand the source of the first hypothesis, and the problems that lead to faulty early formulations in the diagnostic process. This study looks at the source of the first hypothesis made by fifth year medical students.

A Prescriptive Decision Analysis Model

According to a prescriptive model, the first formulations should be based on (i) prior probability and (ii) utility considerations.[2] These factors should be combined with knowledge and understanding derived from anatomical, physiological and pathological considerations.

Diagnostic Process of the Novice

It has previously been shown that the novice is very poor at using his (or her) anatomical and physiological knowledge, even very shortly after passing examinations which tested the relevant knowledge.[3] We also know that the novice is very quick at developing early diagnostic formulations.[2] In this study we examine this

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process, as it may lead to insights into student learning, thus helping us to improve teaching methods.

Methods

Fifth year medical students were used as subjects. Over 40 were studied, but the present report concerns the first 20 cases only.

Two simulated patients were devised with two neurological and two medical conditions. Each student saw one neurological and one general medical problem. The first three minutes of the diagnostic interview were video-taped. Stimulated recall was then used to carry out an in-depth interview between the student and research worker. An ethnographic method was used to analyse the cognitive processes used by the students whilst going through the process of diagnosis.

Neurology Case 1 was a middle aged woman with episodic aphasia and right facial twitch followed by weakness of the right leg. Neurology Case 2 was a middle aged woman with an acute onset of numbness of both hands after an abrupt hyper-extension injury to the neck. This was followed by the gradual onset of weakness in the legs.

Results

The students formulated early hypotheses as previously demonstrated.[2] The first formulations varied and centred mainly on tumour, psychiatric problem, and transient ischaemic attack in Case 1, and diabetes, neuropathy, and a psychiatric problem in Case 2.

It was of interest that a number of students were convinced that in a neurological case one could obtain most information from the examination findings. They made comments such as 'I would have gained more from examination' and 'A lot of neurological diagnosis is made on examination'.

Source of First Hypotheses

Recent Exposures to Clinical Cases

Comments made were 'Diabetes has been drilled about constantly',

'Taught in [bedside] tutorials to clarify and localize, especially in neurology tutorials' and

'There was a CVA recently in the ward'.

Outside Influences

The comments made included

'Neighbour's daughter had multiple sclerosis',

'People and friends ask about certain problems which might trigger off certain things in your mind', and

'Experience of your own family, for instance grandmother had sciatica and so you read up about it'.

Anatomy

The comments included

'Pathology is reinforced in the clinical teaching. Anatomy and physiology I suppose is somewhere in the back',

'They keep telling us how bad we are, yet they do not reinforce what we learnt a long time ago' and

'Previous pre-clinical work had to be rapidly revised with clinical work when we realised the significance of it. I have had to re-read neuroanatomy. I had to realise it was important and had to read it'.

Psychiatry Exposure

The following comments were made:

'Since most of the interviewing we are doing are in psychological and behavioural science, I think about those things',

'You think of psychological because that is all we have in tutorials',

'If I get desperate, I get into psychological, I leave it till later sometimes', and

'I could not think of what it could be, so I thought of something non-organic'.

Their Personal Prior Probability

Remarks such as the following were made:

'I got really desperate for questions, I would probably have got onto more common things like carpal tunnel, but this year we are doing things like diabetes' and

'The most common cause of a neuropathy is diabetes'.

Discussion

It was particularly significant that students exposed to identical learning experiences gave different interpretations of the same experiences. These differences were possibly dependent on their own previous experiences, particularly with relevance to their understanding of medical problems. It was clear that students did not use utility considerations or prior probabilities, except for those that they generated from their own limited exposures. Nor did they routinely refer back to their pre-clinical learning, though they were often aware of its importance. It was also clear that students could not generalize from their previous experience.

Implications

It is important to look at ways of teaching more generalizable knowledge, so that students with relatively little experience can use this experience when they meet hitherto unseen cases. It is likely that more interplay between theory and clinical cases with real life and clinical exposures in the wards would result in more meaningful learning experiences for students.[4] The present practice of case demonstrations in campus lecture theatres has not proved effective. This needs to be taken into account by curriculum planners.

Summary

The problem-solving strategies of fifth year medical students were studied using two simulated cases. One of these cases involved a neurological problem which was unfamiliar to the students. With the use of stimulated recall the study looked at the origin of the first hypothesis.

The symptoms given by the patient did not trigger an appropriate hierarchy of questions and the students resorted to problem-solving techniques, such as drawing on commonsense. In some cases they matched symptoms against clinical cases they had seen previously. Recall from lectures was used occasionally. Instead of rational methods of hypothesis generation, they were most likely to be influenced by recent clinical exposures. Students having identical experiences may have had differing perceptions of these exposures. As a result, their early hypothesis formation showed marked individual variation. These findings need to be considered in the light of how students learn and the content of the teaching that is meaningful to them.

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An Analysis of Cranial Computerized Tomography Scanning in Private Neurological Practice

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The decade 1976–1985 has seen the introduction of 11 computerized tomography (CT) scanners to radiological services in Perth, Western Australia. The use of this facility has increased dramatically, in proportion, it seems, to the number of CT scanners becoming available. With this increased usage it appeared that the pattern of referral by general practitioners to neurologists had altered and that a significant number of patients had already had a cranial CT scan before neurological consultation.

A one year prospective study of patients referred to a neurologist was performed to evaluate the usage of the cranial CT scan in private neurological practice.

Methods

A total of 826 new cases presented between 1 January 1985 and 31 December 1985. Information was recorded about their age, sex, referring doctor, reason for referral, prior investigations, clinical history, examination findings, provisional diagnosis, subsequent investigations, final diagnosis and follow-up. Two groups were studied: Group A were patients who had had a cranial CT scan before referral and Group B were patients who were subsequently referred for CT scan.

Results

The outcome of the study is summarized in Table 1.

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Table 1. Outcome of the study in the two groups of patients

	Prior CT scan Group A No. (%)	Subsequent CT scan Group B No. (%)
Number of cases	60	81
Females	40 (67%)	58 (72%)
Males	20 (33%)	23 (28%)
Referrals by general practitioner	55 (92%)	76 (94%)
Provisional diagnosis attempted by referring doctor	20 (33%)	33 (41%)
Neurologist's diagnosis in agreement with that of referring doctor	10 (50%)	17 (52%)
No diagnosis attempted by referring doctor	40 (67%)	48 (59%)
Abnormal clinical signs elicited by neurologist	17 (28%)	26 (32%)
CT scan – normal	57 (95%)	74 (91%)
– abnormal	3 (5%)	7 (9%)
: cortical atrophy	1	3
: cerebellar atrophy		1
: corpus callosum lipoma		1
: left hemisphere tumour		1
: old right frontal traumatic area		1
: left parietal infarct	1	
: normal pressure hydrocephalus	1	
Further investigations* by neurologist		
: EEG	2	15
: Serum carbamazepine	2	1
: BAEP	1	1
: VEP		1
: VDRL, serum B_{12}		2
: TFT		1

*EEG = electroencephalogram, BAEP = brainstem auditory evoked potentials, VEP = visual evoked potentials, VDRL = venereal disease research laboratory test, TFT = thyroid function test.

Discussion

This study indicates that some general practitioners (GPs) now tend to order a CT scan before attempting a provisional diagnosis and seeking neurological consultation. The possible reasons include:

(i) time: there may be a long waiting time to see a neurologist and it takes more time to complete a thorough history and examination than to arrange for a CT scan;

(ii) cost: there is no direct cost to the patient under the current health system;

(iii) patient expectations: patients may not be satisfied until they have had a CT scan, and

(iv) GP education: the GP may wish to be involved in the investigation of his or her patient.

Headache was the most frequent symptom in the subjects studied. A form of headache was diagnosed in 40% of cases in Group A (migraine 18%, muscle contraction headache 17%, post-traumatic headache 5%) and in 34% of cases in Group B (migraine 28%, muscle contraction headache 4%, post-traumatic headache 2%). The presence of a normal CT scan in almost all of these patients supports the statements of Ashworth that in migraine and non-specific headache without abnormal neurological signs the scan is seldom of diagnostic value.[1]

Five CT scans in Group B were performed at the patient's request in view of family histories of neurological disease such as arteriovenous malformations or tumour. All of these scans were normal and again support Ashworth, 'scans are unrewarding in patients with trivial symptoms who sometimes demand, and are prepared to pay for the investigation'.[1] Also, indiscriminate scanning sometimes detects asymptomatic lesions and raises difficult questions in investigation and management.

The neurologist's reasons for performing a CT scan in the other 76 patients were mainly to exclude a posterior fossa lesion (26%), to investigate epilepsy (20%) and to exclude a structural hemisphere lesion (16%).

This study also highlighted the finding that, although CT scanning is an important advance, it was abnormal in only 7% of all scans and in 1% of all cases. Its availability has therefore not removed the need for a thorough clinical assessment. The questions to be addressed are the following.

(i) What is the cost–benefit ratio of CT scanning in private practice if only 7% of scans are abnormal?

(ii) Is it acceptable to perform CT scanning at the patient's request only and is a 0.6% (5/826) incidence of so doing acceptable?

(iii) What are the indications for CT scanning?

Summary

A one year prospective study was undertaken to evaluate the usage of the cranial CT scan in private neurological practice. The impetus for the study emanated from a general impression that patterns of referral to neurologists were changing with regard to the nature of the patients' condition and that a large number of patients had already had a cranial CT scan before neurological consultation.

A total of 826 cases were reviewed. Sixty (7%) had had a recent cranial CT scan before consultation, and 90% of these cases were referred by the patients' general practitioners. A provisional diagnosis was attempted by the GP in 36% of cases, and 50% of these were correct. Ninety-five per cent of the CT scans were normal. Eighty-three (10%) patients were referred for cranial CT scan after neurological consultation. The neurologists' reasons for CT scanning included investigation of epilepsy (20%) and exclusion of a structural cerebral hemisphere lesion

(16%), acoustic neuroma (10%) and other posterior fossa lesions (16%). Ninety-one per cent of these CT scans were normal.

In all, 143 (17%) patients underwent cranial CT scanning; of these almost half (42%) had been referred for the CT scan by the general practitioner before neurological consultation. This study contrasts the CT scan referring patterns of general practitioners with that of a neurologist and questions the possible overuse of this facility.

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Acute Encephalopathy following Petrol Sniffing in Two Aboriginal Patients

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Although the psychological and neurological complications of petrol sniffing have been documented in Australian Aboriginals,[1] the most devastating toxic effect, acute encephalopathy, has not previously been reported. This toxic effect is infrequent but may result in fatalities and permanent sequelae.[2] The most toxic component of petrol is lead, which is present in an organic form as tetraethyl-lead. The clinical presentation and treatment of poisoning due to tetraethyl-lead differ from those of inorganic lead poisoning. The toxicity of tetraethyl-lead is much greater than that of inorganic lead because of its high lipid solubility[3] and the molecule has different effects in the body from those of inorganic lead.[4] Lead poisoning due to petrol sniffing commonly presents as cerebellar dysfunction, tremor, brisk tendon reflexes and, less commonly, hallucinations.[5,6]

We describe two instances of petrol sniffing encephalopathy in Australian Aboriginals.

Case Reports

Case 1

An 11 year old Aboriginal was referred to Alice Springs Hospital from an outlying area following a seizure, having been noticed 4 days previously to be sniffing petrol. He had a 1 year history of petrol sniffing.

He had further seizures, dizziness, headache, hallucinations, involuntary movements of face and limbs, enuresis and bizarre behaviour, and was transferred to Adelaide Children's Hospital.

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There he was encephalopathic and unable to respond to commands (although he could respond to painful stimuli) and he appeared to be hallucinating, with frequent bursts of activity interrupted by brief periods of sleep. There was repetitive lip pursing, with choreo-athetoid movements of his face and limbs; the deep tendon reflexes were overactive. He had several further seizures, which were treated with phenobarbitone; intravenously administered diazepam in the acute phase rapidly induced a peaceful sleep. Haematology, long bone x-ray examination and a CT brain scan were normal. Plasma zinc concentration was low. His EEG showed an excess of slow rhythms for his age and was of low voltage. Nerve conduction studies were normal.

Treatment was commenced with dimercaprol (450 mg/m^2 daily) and calcium edetate (150 mg/m^2 daily) both given intramuscularly in twice daily divided doses. A second course of chelation therapy with these agents was given 2 days after the first because of increasing blood lead levels; a subsequent blood lead elevation was treated with penicillamine.

The faecal lead concentration in the first sample collected after commencement of treatment was 0.17 μmol/g. Intravenous and oral magnesium supplements were required because of low magnesium levels (minimum value 0.5 mmol/L; normal range 0.70–1.05 mmol/L). Liver function tests, mildly elevated before treatment, became more elevated.

Clinical improvement was slow. He remained in a semi-comatose state with hallucinations for 5 days. On recovery of consciousness, marked choreo-athetosis made independent walking impossible. He was discharged 6 weeks later with only mild improvement. His intellect at discharge was apparently intact. His EEG was much improved, but still mildly abnormal.

Case 2

A 22 year old man was referred to Alice Springs Hospital from Ernabella Mission in northern South Australia with seizures. He had a 2 year history of chronic petrol sniffing. The blood lead level was reported as 4.7 mmol/L (normal < 1.4 mmol/L) and he was treated with penicillamine, edetate and dimercaprol.

After discharge he promptly resumed petrol sniffing and was admitted to the Queen Elizabeth Hospital, Adelaide, after further seizures. He was confused, appeared to be hallucinating, and was unable to respond appropriately to questions. He had a marked tremor of the lips, bilateral intention tremor of the hands with dysmetria, dysdiadochokinesia, heel–shin ataxia, a flapping tremor of the outstretched hands (which showed choreiform movements) and an ataxic, widebased gait.

There was no nystagmus and no limb weakness. He responded appropriately to painful stimuli, to cold and to light touch on the extremities. There was no clinical evidence of a peripheral neuropathy; all tendon reflexes were brisk, plantar responses were flexor and Romberg's sign was negative. Visual acuity was 6/5 in both eyes.

His blood lead concentration was 3.5 mmol/L (normal range < 1.4 mmol/L). The haemoglobin was 11.8 g/L with some basophilic stippling of red cells. Otherwise haematology, serum biochemistry, plasma zinc and magnesium levels and urinary magnesium and calcium contents were normal. A chest x-ray examination was also normal.

His EEG showed a marked bilateral excess of low to medium voltage at 2–3 Hz activity and some slow wave activity in the theta range with some poorly sustained alpha components at 8–9 Hz, suggesting a generalized encephalopathy of some severity. Nerve conduction studies showed significant slowing of motor conduction in the right median nerve to 51 m/s (normal range 53–66 m/s) and of sensory conduction in the left sural nerve to 37 m/s (normal range 42–60 m/s).

Visual evoked potentials were of small amplitude with absolute latencies of the P100 component from each eye at 137 m s (reference range for age-matched Caucasian controls 99–129 m s).

Treatment was begun with dimercaprol (200 mg, 4 times daily, reduced after 3 days to 200 mg, 3 times daily, for 6 days) together with edetate (1.2 g in 24 hours) in a constant intravenous infusion to a total dose of 6.6 g. During this treatment, liver function tests were carried out and AST, LDH and ALT levels all became mildly elevated. Serum magnesium levels fell.

Clinical improvement occurred rapidly, with disappearance of the choreiform movements, and

reduction in the tremor and ataxia by the third day, although the heel–toe gait was still unsteady. A striking improvement in the EEG was recorded on the sixth day, 5–7 Hz rhythms now predominating with some 3–4 Hz low voltage activity continuing to occur intermittently. The background high voltage very slow activity was much less conspicuous.

Treatment was withheld for 9 days but there was no rebound in blood lead levels. He was discharged 9 days after completion of his treatment, free of ataxia and inco-ordination. On clinical review one month later there were no signs of an encephalopathy. He was cheerful and alert with no tremor, inco-ordination, reflex depression or evidence of peripheral neuropathy. He claimed to have stopped petrol sniffing.

Discussion

Encephalopathy is an infrequent but serious consequence of petrol sniffing. It usually affects chronic petrol sniffers, reflecting a widespread abuse of this toxin in the community.

Boeckx *et al.*[10] estimated that there was a 100% prevalence of petrol sniffing in the 4–18 year old group in an isolated North American community, although only a small number of cases of encephalopathy have been reported. Eastwell[11] reported that one-half to one-third of adolescents in Maningrida, an Arnhem Land Aboriginal coastal community, were chronic petrol sniffers, although petrol sniffing encephalopathy has not previously been reported in Aboriginals. The social and physical ramifications of this practice are alarming, and huge savings in the cost of health care would result from its control.

Suggested measures to achieve control have included the substitution of diesel fuel, or of lead-free petrol, or the addition of dimercaptane to the local petrol supplies. Such measures have not always received strong community support, and communities have proved unable to regulate the problem by other means, such as by social censure or by invoking tribal custom.

Summary

Two instances of acute encephalopathy following petrol sniffing in Australian Aboriginals are reported. In one case recovery was incomplete 6 weeks after cessation of exposure to the toxin.

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Bilateral Intracerebral Haemorrhage Presenting with Supranuclear Ophthalmoplegia, Bradykinesia and Rigidity

*G.J. Hankey and E.G. Stewart-Wynne**

The clinical manifestations of an intracerebral haemorrhage vary with its site and size. The common sites for hypertensive intracranial haemorrhage are the putamen and adjacent internal capsule in 50% of cases and various parts of the deep central white matter, sometimes extending from the adjacent putamen. This results in the unilateral hemiparesis and/or hemisensory syndrome and/or dysphasia and/or conjugate gaze palsies.[1]

A case of bilateral intracerebral haemorrhage is described. The patient presented with supranuclear ophthalmoplegia, bradykinesia and rigidity which resembled progressive supranuclear palsy.

Case Report

A 70 year old man recovered from a left putamenal haemorrhage in 1984 with a residual mild right hemiparesis (Figure 1). A year later he presented following the sudden onset of an inability to stand. His past history included myocardial infarction in 1975, hypertension, and pulmonary tuberculosis treated with isoniazid, rifampicin and ethambutol.

His heart rate was 75 per minute and his blood pressure was 130/90 mmHg. He was right handed. He spoke with a soft voice, his speech was monotonous and dysarthric and he had diminished facial expression. He had no neck bruits. His mental state was normal. Visual acuity in the right eye was N18 and in the left N6. Visual fields were full to confrontation. The eyelids were retracted and blinking was infrequent. Fixation instability was present in the primary position of gaze. Convergence was poor. Vertical and horizontal eye movements were initially limited but after 6 days improved with normal pursuit movements to the left and vertically, although saccadic pursuit was present on right lateral gaze. Vestibulocular reflexes were normal. Mild right central facial weakness was present but cranial nerve examination was otherwise normal. The glabellar tap was positive and the grasp, palmo-mental and pout reflexes were prominent. Extensor tone of the neck

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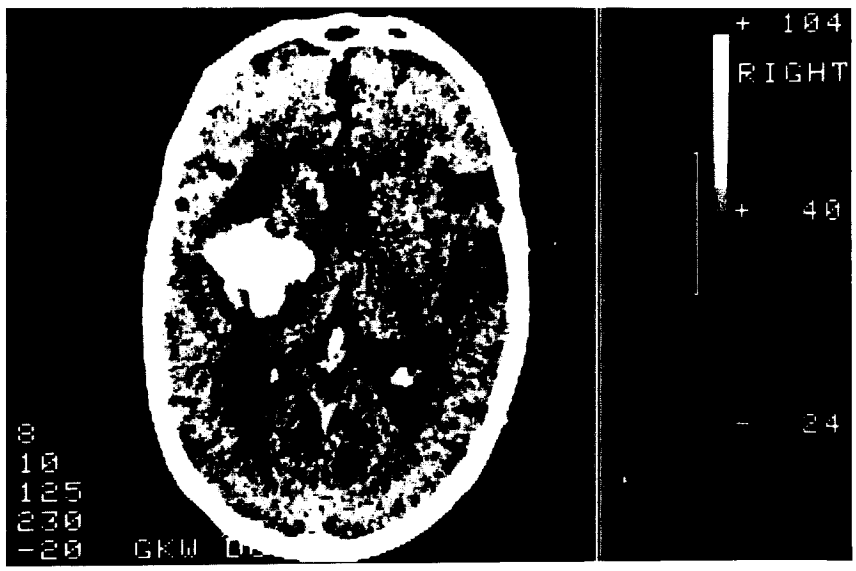

Figure 1. CT head scan demonstrating the left putamenal haemorrhage.

and rigidity in the trunk and limbs were marked. The jaw jerk was very brisk and bilateral corticospinal tract weakness, hyperreflexia and extensor plantar responses were present. He was slow to initiate movement. Fine finger movements were bradykinetic and of reduced amplitude. He was unable to sit up from the lying position, bridge or roll. He had poor sitting balance and posture, falling backwards and to the left. He walked with small shuffling steps, a flexed posture and diminished arm swing, particularly on the left. He had grossly impaired righting reflexes. Tremor was absent. A cranial CT scan in June 1985 revealed a small haematoma in the white matter of the right cerebral hemisphere above the roof of the lateral ventricle. On the left side there was considerable enlargement of the Sylvian fissure and a low density in the adjacent grey matter of the basal ganglia region, marking the site of previous intracerebral haemorrhage (Figures 2 and 3). Extensive calcification in the carotid arteries and basilar arteries was noted together with basilar artery ectasia.

Discussion

Acute bradykinetic and rigidity syndromes are an uncommon manifestation of cerebrovascular disease. Since Critchley's original report,[2] the term 'vascular Parkinsonism' has been used to describe the akinesia and rigidity of patients with clinical evidence of extensive cerebrovascular disease, as suggested by a history of several strokes and the presence of associated pyramida and pseudo-bulbar signs and dementia.[3] However this entity has been questioned because of the lack of conclusive clinicopathological studies,[4] but since the introduction of CT scanning a sub-acute Parkinsonian syndrome has been described in patients with CT evidence of basal ganglia infarcts.[5]

The majority of bradykinetic and rigidity syndromes have a chronic or sub-

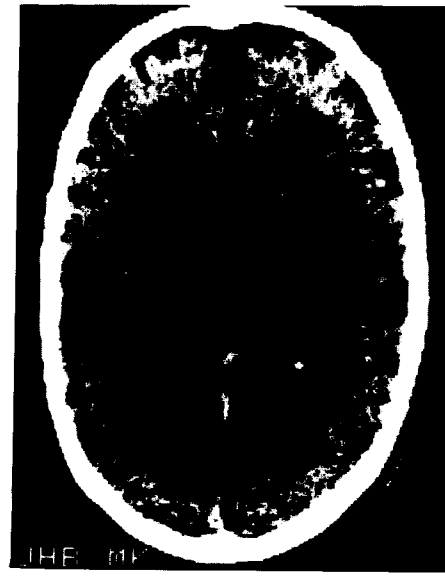

Figure 2. CT head scan demonstrating considerable enlargement of the left Sylvian fissure and a low density in the adjacent grey matter of the left basal ganglia region marking the site of previous left intracerebral haemorrhage.

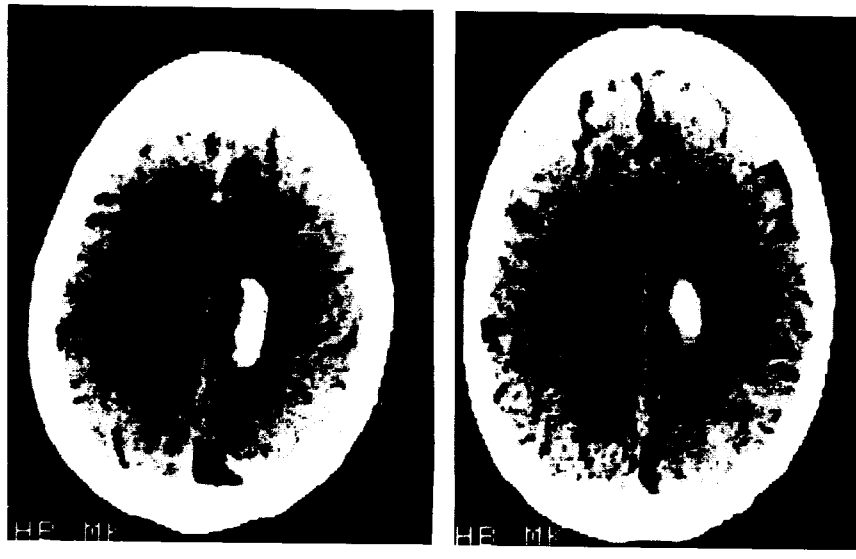

Figure 3. CT head scan demonstrating a small fresh haematoma in the deep white matter of the right cerebral hemisphere above the roof of the lateral venticle.

acute onset and are a manifestation of progressive supranuclear palsy (failure of downward gaze and marked rigidity of the neck), normal pressure hydrocephalus (urinary incontinence and gait ataxia), multi-system atrophy (autonomic dysfunction, pyramidal, extra-pyramidal and spinocerebellar degeneration), Alzheimer's disease (memory loss, personality change and intellectual impairment), drug-induced Parkinson's disease (bilateral symmetrical rigidity and akinesia with little tremor) or multilacunar state (pseudo-bulbar palsy).

The case here described presented with an acute bradykinetic rigidity syndrome and supranuclear ophthalmoplegia following a right lobar intracerebral haemorrhage superimposed on a previous left putamenal intracerebral haemorrhage. It is well recognized that thalamic haemorrhage, by virtue of its extension into the subthalamus, may cause a series of ocular disturbances including forced deviation of the eyes downward and palsies of vertical and lateral gaze.[2] However, the right lobar intracerebral haemorrhage in our patient was high in the deep white matter of the right cerebral hemisphere. The rapid and total resolution of vertical and horizontal eye movements within 6 days of onset suggested an acute and irritative, but not destructive, effect of the haemorrhage on the supranuclear gaze pathways.

The acute onset, resolution of supranuclear ophthalmoplegia and subsequent clinical improvement of bradykinesia and rigidity made the diagnosis of progressive supranuclear palsy or other degenerative extra-pyramidal syndromes untenable. Hence, diagnostic investigations such as electro-oculography were not performed. Other causes of Parkinsonism, such as neuroleptic toxicity or normal pressure hydrocephalus, were also excluded.

The CT scan findings in this patient suggest that bilateral intracerebral haemorrhage can cause the clinical picture of bradykinesia, rigidity and supranuclear ophthalmoplegia.

Summary

A 70 year old man recovered from a left putamenal haemorrhage in 1984 with a residual mild right hemiparesis. In 1985 he presented following the sudden onset of inability to stand. The clinical findings of supranuclear ophthalmoplegia, bradykinesia and rigidity resembled those of progressive supranuclear palsy. CT scan revealed a recent haemorrhage deep in the right hemisphere white matter in addition to a low density change in the left basal ganglia reflecting the site of previous haemorrhage. The patient's course was uncomplicated and the ophthalmoplegia resolved. Bradykinesia and rigidity persist.

This case illustrates an unusual clinical presentation of bilateral intracerebral haemorrhage with supranuclear ophthalmoplegia, bradykinesia and rigidity.

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Amnesia Following Right Thalamic Haemorrhage

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Memory disturbance as a presentation of thalamic haemorrhage is unusual. We have been able to find only 5 previous case reports, 2 of these haemorrhages being in the left thalamus and 3 in the right.[1,2] However, detailed neuropsychological assessment of these patients was not performed and the observations were limited to the acute hospitalization period. We report here a case of predominantly right medial thalamic haemorrhage causing persistent memory impairment.

Case Report

A 52 year old housewife suffered a sudden onset of slurring of speech and dizziness without vertigo 3 days before admission to hospital. She was also noticed to be slightly drowsy and had no recollection of the events of the past week. She had had essential hypertension for over 10 years and received regular medication from her family doctor. There was no relevant family history and she was a non-smoker.

Examination revealed an obese, right-handed woman. Her pulse was 90/min and regular, blood pressure 130/90 mmHg, heart was normal and there were no cardiac bruits. She was alert but disorientated in space and time and her concentration span was short. Both short term and long term memory were markedly impaired, although immediate recall remained intact. She could not perform the serial 7 test or other simple calculations and her current knowledge was poor. She appeared unconcerned about her illness. There was mild dysarthria but no dysphasia. A right Horner's syndrome was present, but the cranial nerves and motor and sensory functions were normal.

A CT scan (Figure 1) showed an intracerebral haematoma in the medial aspect of right thalamus reaching the genu of the internal capsule; a small amount of blood was also present in the third ventricle and possibly in the medial aspect of the left thalamus.

She was treated conservatively and gradually improved. When reviewed 3 months later at the

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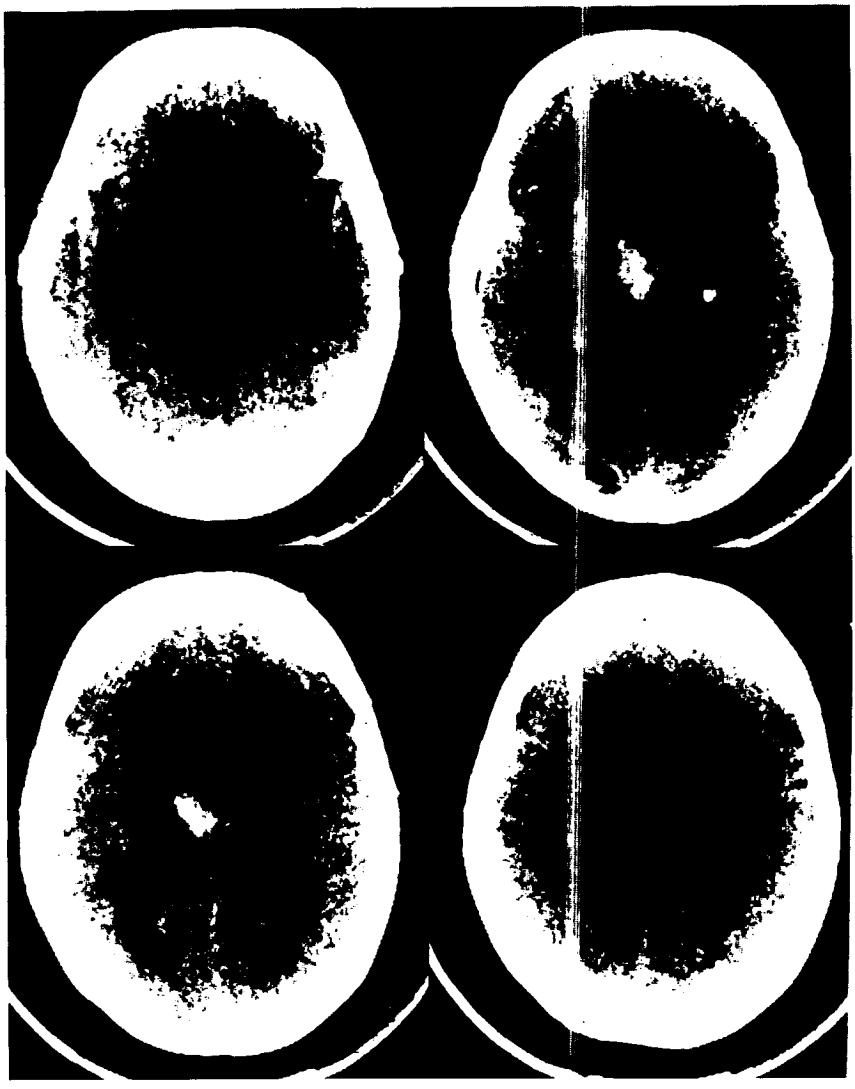

Figure 1. Computed tomographic scan. The 4 consecutive slices show a haematoma in the medial aspect of the right thalamus and the genu of the right internal capsule, measuring 2.2 cm anteroposteriorly, 1.4 cm transversely and 3 cm cephalocaudally. There is a small amount of blood in the third ventricle and possibly in the medial aspect of the left thalamus.

out-patient clinic, she was fully orientated with good concentration, but her memory was severely impaired. There was no dysarthria and signs of the Horner's syndrome had resolved.

The patient was given psychological assessment 4 weeks after the ictus and was reassessed 3 months and 3 years later.

Results

The patient had a full scale IQ of 66 on the Wechsler Adult Intelligence Scale (WAIS), a verbal scale IQ of 71 and a performance scale IQ of 60. Her performance was low on all subtests and she had notable difficulties in the digit symbol, block design and object assembly subtests, all of which suggested perceptual-motor deficiency.

She had a memory quotient of 62 on the Wechsler Memory Scale. She was limited in various aspects of memory functioning, but her poorest performance was with visual reproduction. Problems with perceptual-motor skills and memory for visual material were confirmed by equally poor performance on the Rey–Osterrieth test. Her copy of the figure was distorted and was rotated at an angle of 90° (Figure 2). She was unable to reproduce any parts of the figure after 40 minutes' delay.

Figure 2. The patient's copy version of the Rey-Osterrieth figure at her first assessment.

Further assessment on the Bender-Gestalt test and the Benton Visual Retention test strongly indicated that the patient's visual-motor co-ordination and visual perception and retention were much impaired. Of these, the most notable aspects were omission of all the peripheral figures in the Benton Visual Retention test, both for immediate and 15-second delayed recall, and a perseveration tendency.

In addition to the test results, the patient's daily activities were seriously affected. Her family reported that she forgot to carry out routine housework, was unable to operate a washing machine and forgot the recipes of her favourite dishes.

On reassessment, she did not show any improvement on the 2 visual memory tests, the Rey-Osterrieth (Figure 3) and the Benton Visual Retention test and the WAIS. There were also signs of persistent visual field restriction with omission of peripheral figures in the Benton Visual Retention test, and angulation difficulty.

While the patient did not improve on her previous WAIS performance (full scale IQ = 72; verbal scale IQ = 68; performance scale IQ = 67), persistent configural anomalies were detected in her constructions in the block design subtest. She rotated the blocks by 90 to 360 degrees in 5 of the items, which was not obvious in the first assessment, confirming the perceptual difficulties that have already been mentioned (Figure 4). There was however a gain of 15 points on the Wechsler Memory Scale and the improvement spread across all the subtests.

When the patient was reassessed 3 years after her second assessment, she had made no further improvement on any test administered.

Discussion

This is an instance of persistent verbal and non-verbal anterograde amnesia subsequent to a predominantly right thalamic haemorrhage. The patient showed marked inability to recall non-verbal material and had perceptual motor deficits. Her difficulties were more than her limited intelligence and educational background could account for.

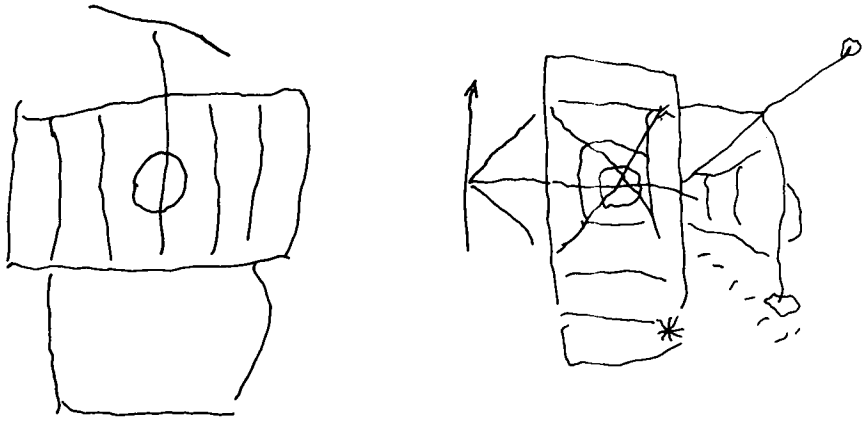

Figure 3. The patient's copy version (left) and 40 minutes delayed recall version (right) of the Rey–Osterrieth figure on reassessment.

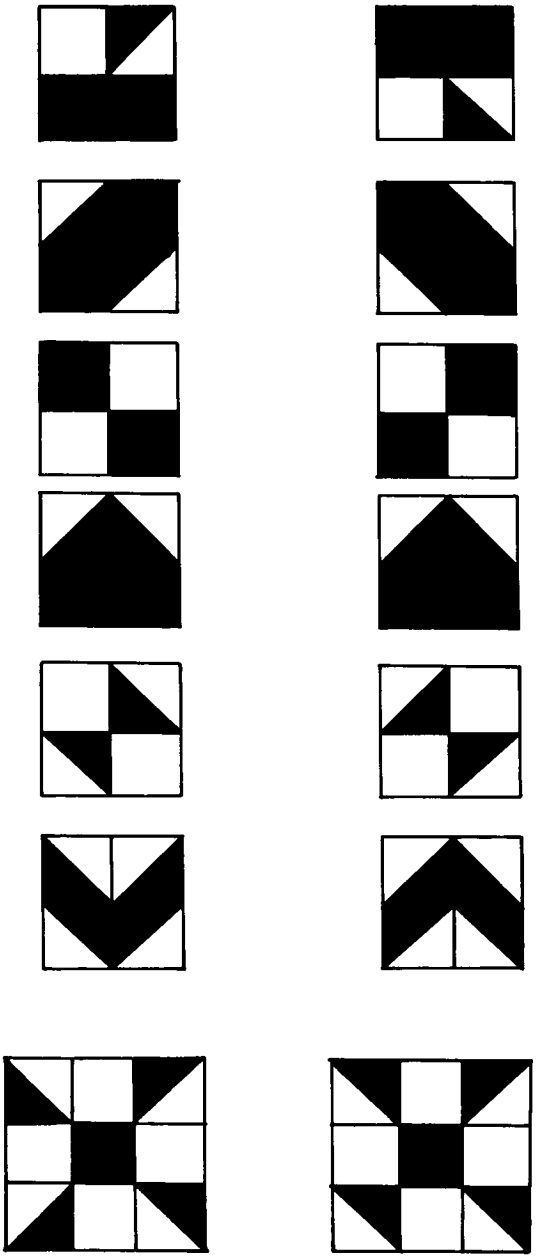

Figure 4. Reproductions of the patient's block design performance (left-hand column) and the original designs (right-hand column).

The thalamus is the major correlation centre for most sensory information going to the brain.[3] In terms of lateral asymmetry, the thalamus parallels cortical organization in that the right thalamus is more implicated in non-verbal aspects of cognitive activities and the left thalamus in verbal activities.[4] This belief has received support from studies of thalamic stimulation[5] and of tumours, haemorrhage or infarction of the right or left thalamus.[1,6,7] In addition, the dorsal medial thalamic nucleus appears to have a critical role, with limited local lesions causing amnesia.

Despite the fact that the lesion seen on the CT scan was largely confined to the right medial thalamus, the memory dysfunction applied to both non-verbal and verbal material. This can be explained by the extension of the haemorrhage across the midline so that the left medial thalamic nucleus may have been affected to some degree, thus causing the verbal memory disturbance.

On the other hand, it is still possible that some verbal memory processing is performed by the right thalamus, since Case 3 reported by Choi *et al.*[1] had a right thalamic haemorrhage and verbal memory impairment. Unfortunately that patient had a previous left caudatoputamenal haemorrhage as well as a pontine infarct, and the period of observation was limited.

Our patient fared notably worse than the patients reported by Speedie and Heilman[6] and by Squire and Slater[8] in non-verbal memory tasks. Both the latter patients suffered from lesions in the left thalamus. A patient who suffered from bilateral thalamic lesions[9] also surpassed the present case in non-verbal memory. Furthermore, in the present patient there was no improvement up to 3 years after a slight improvement at 3 months on the Wechsler Memory Scale.

The extent of the lesion was relatively focal in the present case and yet there was extensive impairment of non-verbal and verbal memory. One possibility is that, at thalamic level, functional asymmetry is not completely defined. Thus, a patient who suffered a stab wound damaging the left dorsal thalamus had antegrade amnesia for both verbal and non-verbal material, albeit much more severe for the former.[8,10,11] Similar findings were noted in a case of left thalamic infarction.[6] Another possibility is that, although the lesion was both focal and limited in size, the interconnectivity of this area of the brain with cortical structures may be important.[12] Given the nodal position of the thalamus, a lesion of this part of the brain may cause extensive psychoneurological disturbance because the functions of closely connected areas will be compromised also.

Summary

A 52 year old patient with a right thalamic haemorrhage is described. She suffered from anterograde amnesia and memory impairment for both visual and verbal material. At follow-up after 3 months, despite being fully oriented and having good concentration, her memory impairment was still evident. Reassessment 3 years afterwards showed persistent deficits and no further improvement.

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Ventriculo-Peritoneal Shunting of Acute Hydrocephalus in Vein of Galen Malformation

*K.K. Pun, Y.L. Yu, C.Y. Huang and E. Woo**

The vein of Galen malformation is an uncommon vascular abnormality. It results from either a direct arteriovenous shunt or, less commonly, an arteriovenous malformation that drains into and dilates the vein of Galen.[1] The symptoms vary according to the age at presentation. In neonates, shunting of blood leads to heart failure,[2] and in infants blockage of the aqueduct causes obstructive hydrocephalus.[3] In older children and adults the presenting complaint is usually recurrent headaches or subarachnoid haemorrhage.[1,4] This report describes a case of acute hydrocephalus due to a vein of Galen malformation in an adult and discusses the observations associated with the shunting operation.

Case Report

A 26 year old female secretary was admitted with subacute headache, vomiting and drowsiness for 4 days. There was no previous history of headache, blurring of vision or convulsions. The family history was negative. Examination revealed a mentally dull patient responding to verbal commands. A dense left homonymous hemianopia was present and fundal examination showed early papilloedema. The left upper limb power was grade 4/5. Tendon reflexes were brisk bilaterally with bilateral extensor plantar responses. There was no neck rigidity and Kernig's sign was negative. Cranial bruits were not detected.

Haematological and biochemical tests and x-ray examination of the skull and chest were normal. Electroencephalography showed a mild to moderate bilateral disturbance with right-sided emphasis. Computed tomography (CT) of the head (Figure 1, upper) revealed an extensive arteriovenous malformation over the right temporal and parietal regions in continuity with a markedly dilated vein of Galen. Acute hydrocephalus with grossly dilated lateral and third ventricles and periventricular lucency was present, with the pathological vein of Galen compressing

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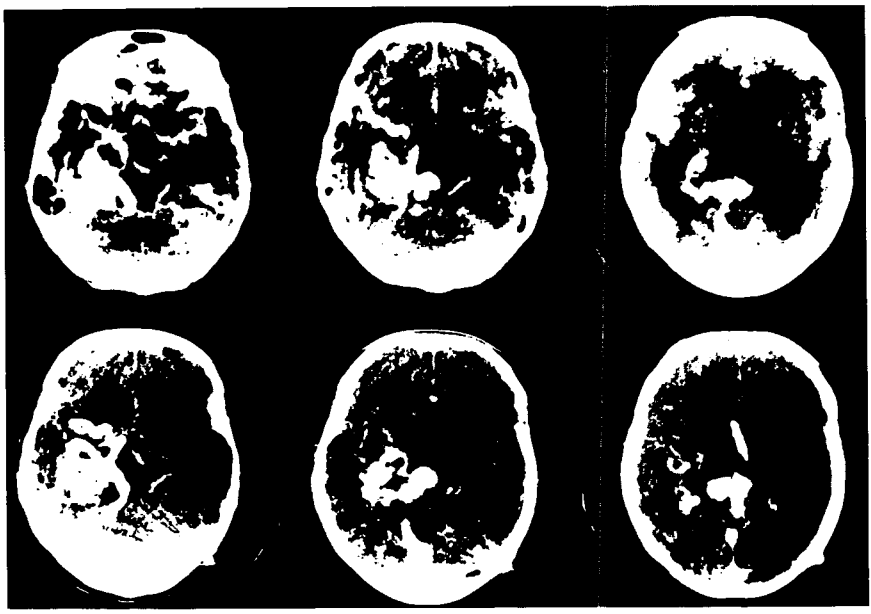

Figure 1. (Upper) CT scan on admission showing both an extensive arteriovenous malformation in continuity with the enlarged vein of Galen and an acute obstructive hydrocephalus. (Lower) Repeat CT scan showing shrinkage of the malformation and successful drainage of the hydrocephalus.

the rostral end of the aqueduct. There was no evidence of haemorrhage in the plain or enhanced films.

In view of the rapid deterioration resulting from the acute hydrocephalus, a ventriculoperitoneal shunt was inserted through a left posterior parietal burr-hole. The cerebrospinal fluid was under high pressure, but was not blood-stained or xanthochromic. The patient recovered gradually after surgery and the only detectable neurological deficit a week later was a small left upper quadrantic visual field loss. She returned to full-time work after 7 weeks' convalescence. Re-examination conducted 8 months later revealed no change in the residual visual field defect.

Subsequent carotid and vertebral angiography revealed an extensive arteriovenous malformation over the right temporal and parietal regions supplied mainly by the right posterior cerebral artery and, to lesser extent, by the right anterior and middle cerebral arteries; it drained into the dilated vein of Galen (Figure 2). A repeat CT scan (Figure 1, lower) showed shrinkage of the malformation and successful drainage of the hydrocephalus. Owing to the extensive vascular supply, the arteriovenous malformation was considered to be inoperable

Discussion

The vein of Galen malformation in our patient is of the less common variety as the dilated vein of Galen was the major draining vessel of the arteriovenous malformation. The shrinkage of such a malformation after a shunting procedure is an interesting observation which has hitherto received little attention. Anatomical-

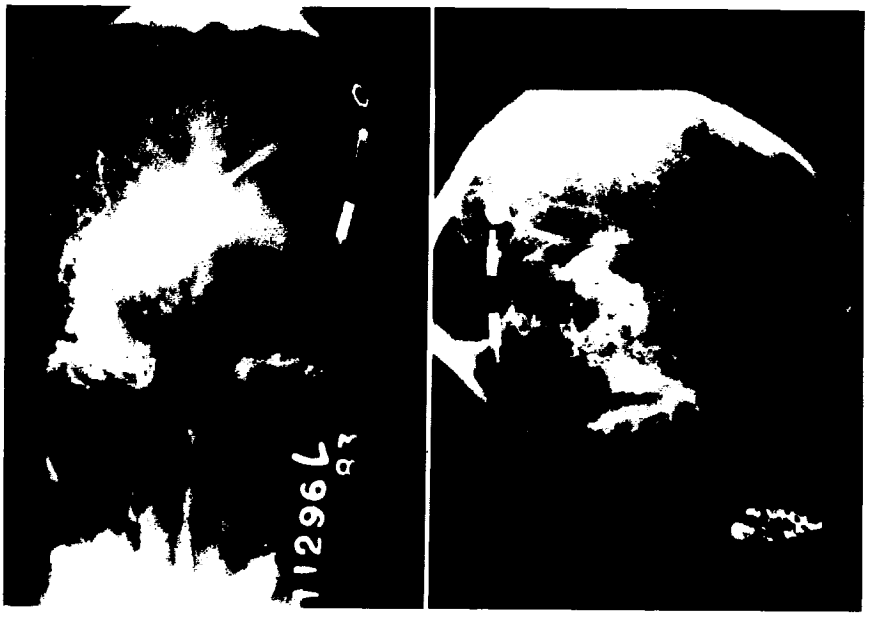

Figure 2. Right carotid angiogram, (right) PA and (left) lateral views. The arteriovenous malformation is draining into the vein of Galen.

ly the vein of Galen is situated anterior to and 1–2 cm above the tentorium and near the aqueduct.[5] An enlarged vein of Galen will cause compression of the aqueduct leading to dilatation of the third and the lateral ventricles. The dilated ventricular system in our patient further displaced the vein of Galen towards and against the tentorium. This impeded the drainage of blood to the straight sinus and caused congestion of the malformation, leading to further compression of the aqueduct and more marked hydrocephalus. The deleterious effect was self-perpetuating and quickly raised the intracranial pressure to a dangerous level. Relief was provided by a prompt ventriculo-peritoneal shunting of the hydrocephalus. The malformation shrank in size after the shunting procedure. Acute hydrocephalus may also result from haemorrhage from the malformation, but in our patient there was no evidence of haemorrhage in the CT appearance or the cerebrospinal fluid.

A related feature in this patient was the visual field disturbance. In obstructive hydrocephalus due to blockage of the aqueduct, the dilated third ventricle may compress the visual pathways, leading to a variety of visual field defects including unilateral and bilateral scotomata, incongruous bitemporal hemianopia[6] and junctional scotoma.[7] Homonymous hemianopia has also been described by Weinberger and Webster in 4 patients with an enlarged third ventricle resulting from cerebellar tumours.[8] These authors suggested that downward pressure on the optic tract by the dilated third ventricle against the posterior communicating artery might

be the mechanism of the field defect. Moreover, with a concomitant rise of intracranial pressure, occipital lobe ischaemia from strangulation of the posterior cerebral artery at the tentorium may occur. The dense homonymous hemianopia in our patient could be explained in part by these 2 postulated mechanisms. In addition, there probably was a significant contribution from the space-occupying effect of the congested arteriovenous malformation. Therefore, once the hydrocephalus was relieved, the visual field defect resolved almost completely. The residual visual field defect could be the result of damage to the posterior optic pathway or occipital lobe, or may have simply been a feature of the arteriovenous malformation itself.

Summary

The case of an adult patient with acute hydrocephalus due to a vein of Galen malformation is reported. Ventricular shunting, apart from relieving the hydrocephalus, also resulted in shrinkage of the malformation and of the visual field defect. The possible mechanisms involved in this phenomenon are discussed.

Acknowledgements

We thank Miss Mary Chan for typing the manuscript.

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Isolated Unilateral Hypoglossal Nerve Palsy due to a Chondroid Chordoma

K. Millingen and M. Prentice†*

An isolated unilateral hypoglossal nerve palsy due to a lesion within the skull is quite rare. Intramedullary lesions usually involve adjacent nuclei or tracts and peripheral lesions usually involve other lower cranial nerves. Extracranial causes of an isolated hypoglossal nerve palsy are slightly less rare. We now report an isolated unilateral hypoglossal nerve palsy due to a tumour in the hypoglossal canal.

Case Report

The patient was a 57 year old woman who had noticed a sensation as if a crumb had lodged in her throat on a couple of brief occasions in the past month. No abnormalities were found apart from weakness, wasting and fasciculation of the left side of the tongue (Figure 1). In particular the lower cranial nerves were not involved and there were no long tract signs. The responsible lesion was considered to be in the hypoglossal canal.

A CT scan, with contrast, through the base of skull with 0.5 mm cuts, showed erosion of the apex of the petrous bone and widening of the left hypoglossal canal. No soft tissue mass was evident (Figure 2). Bone scans and angiography were normal. There was no involvement of the clivus or central bone structures.

At operation a mucinous-looking tumour was found, involving the hypoglossal canal and extending down towards the occipital condyle. This was totally removed without complications and two years later the patient remains well, although the appearance of the tongue is unchanged.

Pathological Report

Macroscopically the specimen consisted of multiple fragments of pale gelatinous tissue, the largest fragment measuring up to 6 mm.

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Figure 1. Wasting of the left side of the tongue.

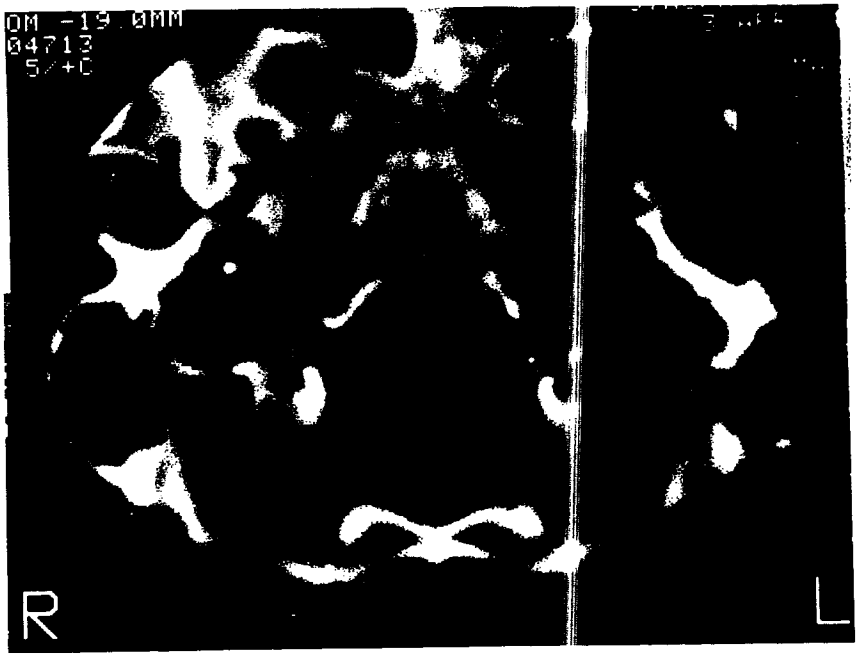

Figure 2. CT scan through the base of the skull showing erosion around the hypoglossal canal on the left side.

Figure 3. The tumour showing two distinct populations of neoplastic cells, the chondroid region (inferiorly) and the chordoma component (superiorly). Haematoxylin and eosin (H & E).

Figure 4. Predominantly chondroid region of the tumour with neoplastic cells situated in well defined lacunae. Some physaliferous chordoid cells are also present. (H & E).

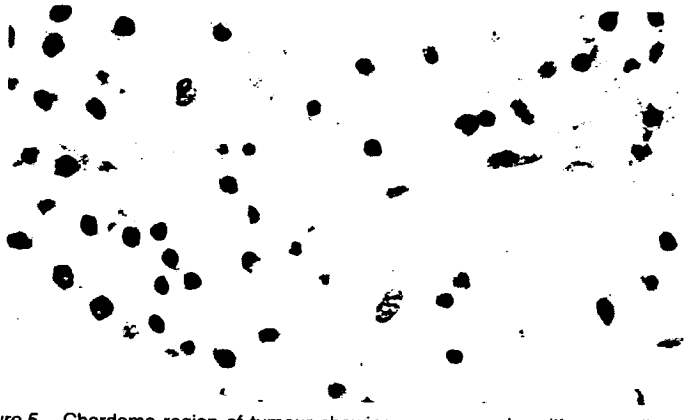

Figure 5. Chordoma region of tumour showing numerous physaliferous cells. (H & E).

Histological examination revealed multiple, relatively well defined, variably sized nodules of neoplastic chondroid tissue which were separated by a more cellular but myxoid tissue. In some regions the two morphological forms merged without clear demarcation. Within the chondroid areas the neoplastic cells were distributed in lacunae separated by typical chondroid matrix. Nuclear features in this region were bland, consisting of ovoid to spherical nuclei with finely vesicular chromatin and inconspicuous nucleoli. Binucleation and mitotic activity were not present. The cytoplasm was clear in most cells in this region. However some cells showed physaliferous type vacuolation.

The more cellular intervening myxoid tissue showed the typical features of a chordoma. Numerous physaliferous cells were apparent and were separated by an acid mucopolysaccharide ground substance. In some regions, the neoplastic cells were lined together forming short strands. Nuclei in this region showed a moderate variation in size and shape: again, binucleation and mitotic activity were not observed.

The above appearances demonstrated extensive chondroid differentiation in an otherwise typical chordoma. The chondroid regions appeared histologically benign and formed the dominant morphological component of the tumour which can thus be classified as a chondroid chordoma. It was unusual pathologically in that it appeared to have arisen laterally, close to or within the left hypoglossal canal.

Discussion

An isolated unilateral hypoglossal nerve palsy due to a lesion within the skull has been reported as being due to intracranial metastasis,[1] infectious mononucleosis[2] (site of lesion thought to be around 12th nerve nucleus), associated with influenza vaccination,[3] and associated with the common cold[4] (exact site of lesion unclear). The only one of these conditions in which a definite pathological lesion has been demonstrated is intracranial metastasis. Rubinstein described three cases in which isolated unilateral hypoglossal nerve palsy was the first sign of an intracranial metastasis, all the palsies being due to local meningeal infiltration. The primary lesions were, respectively, Hodgkin's disease, bronchogenic carcinoma and acute leukaemia. As far as we are aware unilateral hypoglossal palsy has not previously been described as a result of chrondroid chordoma.

Chondroid chordomas were first[5] described as a distinct entity in 1973, in a major review of chordomas and cartilaginous tumours occurring at the skull base. This study included 55 chordomas arising in the spheno-occipital region of the skull. Of these tumours, 19 showed evidence of chondroid differentiation, which varied from multiple, small scattered foci of cartilaginous differentiation in a predominant chordoma background to lesions in which the chondroid component dominated the histological appearance. The chondroid component showed features which ranged from the benign to the chondrosarcomatous in the different tumours. In addition to the histological difference, these tumours were clinically distinct in that they showed a slight female predominance compared with the usual male predominance seen in typical chordomas and they were diagnosed at a slightly younger average age (35 years as compared with 42 years). Of the 19 chordomas showing chondroid differentiation, all but one arose in the mid-line in the spheno-occipital synchondrosis. The remaining tumour appeared to originate just lateral to the clivus which showed no definite radiological evidence of destruction.

The importance of distinguishing the chondroid chordoma group from the

typical chordomas arising in the spheno-occipital region is the significantly better prognosis of the former group. Despite similar treatment programmes which included surgery and radiotherapy, alone or in combination for each group, the average survival time for the chondroid chordoma patients was 15.8 years as compared with 4.1 years for the typical chordomas.

Summary

A case is described of an isolated unilateral hypoglossal nerve palsy due to a tumour which was removed surgically from the hypoglossal canal. The pathological findings showed the features of a chondroid chordoma.

This case is unusual because intracranial causes of isolated unilateral hypoglossal nerve palsies are rare, and because the chondroid chordoma had arisen laterally, either close to or within the hypoglossal canal.

Acknowledgements

We thank Mr David Lees, University Clinical Photographer, for the preparation of the photographic material and Mrs Sandra Petrie for typing the paper.

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Herpes Zoster Arteritis: Pathological Findings

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Herpes zoster ophthalmicus is occasionally followed by contralateral hemiparesis. This begins some weeks or months after the initial virus infection and is sometimes accompanied by other evidence of ipsilateral hemisphere deficit.[1-5] Angiography has revealed a characteristic segmental constriction of basal arteries on the ipsilateral side.[3,6] Occasionally patients with herpes zoster ophthalmicus develop symptoms of a generalized inflammatory encephalopathy, and post-mortem studies of such cases have revealed the presence of a granulomatous angiitis.[7,8,18] It has been assumed that this pathological process is responsible for the segmental changes seen in the angiograms of patients with the contralateral hemiplegia syndrome.[3,9] However, necrotizing arteritis of large and small cerebral arteries has recently been described in typical cases of the syndrome[10-12] and virus-like particles have been identified in association with this arteritis.[10]

We report here the pathological findings in two cases of delayed contralateral hemiparesis following herpes zoster ophthalmicus. Both patients died of cerebral haemorrhage resulting from a localized arteritis; no features of generalized encephalopathy were present before death and no features of granulomatous angiitis were found in the post-mortem material. The features of the localized arteritis are described.

Case Reports

Case 1

A 66 year old normotensive Caucasian man had a 2 week history of left sided headaches. Four days before admission he developed a vesicular eruption in the skin area supplied by the ophthalmic

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division of the left trigeminal nerve. Examination disclosed evidence of conjunctivitis and keratitis of the left eye; the pupil was semidilated and did not react to light, and adduction and elevation of the eye were absent. The day after admission he became febrile and confused; the cerebrospinal fluid contained 367 white blood cells, almost all monocytes, but there was no clinical or electroencephalographic evidence of focal disturbance. His confusion cleared within a few days, and he was then well, apart from pain in the left eye and over the left forehead. Three weeks later, he was transferred to a convalescent hospital for continued pain management and for local treatment to the left eye. He remained afebrile, with gradual control of pain and general improvement. Six weeks after the onset of the infection he was found unconscious in bed with a flaccid right hemiplegia. A computerized tomography scan of the head showed extensive recent haemorrhage in the left frontal region. He died 18 hours later without regaining consciousness.

Post-Mortem Report

The brain was removed intact and the external features were carefully examined before fixation. There was no evidence of subarachnoid bleeding and no aneurysms were seen. The left frontal lobe was pale and swollen; the left trigeminal ganglion was grossly enlarged with an area of haemorrhage within it and the proximal trigeminal nerve trunk was also swollen and haemorrhagic. Sectioning of the brain after fixation revealed that a large intracerebral haemorrhage had destroyed the inferior portion of the anterior part of the internal capsule and adjacent structures. The haemorrhage extended forwards to destroy most of the inferior portion of the central white matter of the frontal lobe and had ruptured into the ventricular system, which was filled with blood. There were secondary haemorrhages into the midbrain and anterior portion of the pons.

The heart, systemic blood vessels, lungs, gastrointestinal tract, genitourinary system, endocrine glands and haemopoietic systems showed no macroscopic abnormalities. Similarly, there were no microscopic abnormalities in the systemic organs, or in sections of cerebral tissue and coverings apart from the area of haemorrhage. The left trigeminal ganglion contained a haemorrhagic area with an acute inflammatory focus infiltrating around the nerves. Sections of more proximal left trigeminal nerve trunk revealed foamy macrophages and an inflammatory infiltrate, while other areas of the left trigeminal nerve showed a mild inflammatory reaction. Sections of right trigeminal ganglion and nerve were normal. Electron microscopy was performed on tissue from both trigeminal ganglia and nerves as well as both internal carotid arteries. No viral particles were seen. Viral cultures performed on tissue from left and right trigeminal nerves and ganglia as well as from both internal carotid arteries yielded no growth.

Sections of left proximal internal carotid artery, left proximal middle cerebral artery and left proximal anterior cerebral artery showed a mixed inflammatory infiltrate consisting almost completely of lymphocytes; the cells assumed a predominantly periarterial distribution (Figure 1). The left distal internal carotid artery showed regular thrombus in conjunction with the perivascular changes described above. The left distal anterior cerebral artery showed narrowing of the lumen by eccentric fibrosis with thickening of the intima and perivascular changes as already described. The right internal carotid artery and all major branches, both vertebral arteries and the basilar artery and a cerebral vein over the left frontal lobe showed no microscopic evidence of inflammation.

Case 2

A 71 year old Caucasian woman, previously in good health, developed right herpes zoster ophthalmicus. The right eye was treated with local atropine and steroids but 6 weeks after the onset of the infection she was admitted to hospital because of progressive debility and continuing pain in the right eye. She was lethargic, afebrile and normotensive; there was scarring in the distribution of right ophthalmic nerve and the right pupil was dilated and unreactive.

Twelve days after admission and 8 weeks after the onset of the right herpes zoster she suddenly developed slurred speech and weakness of the left face and arm. Computerized cerebral

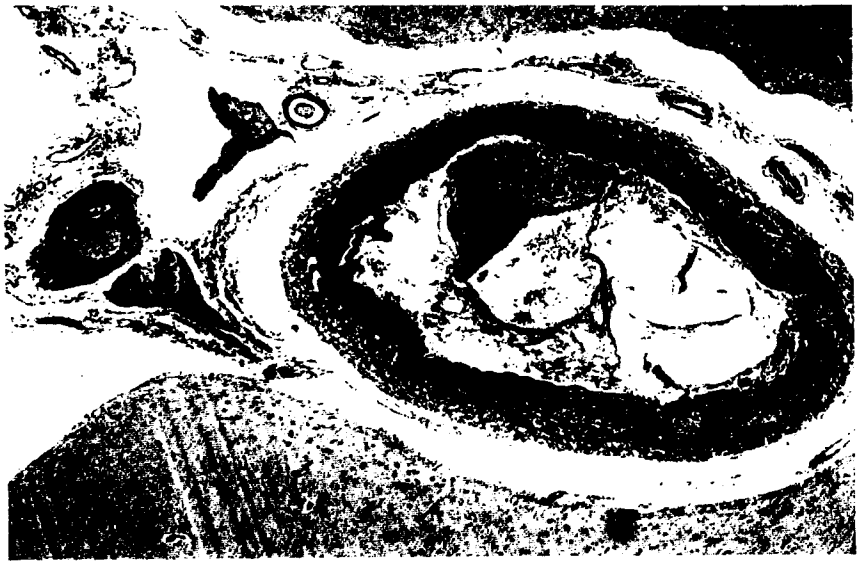

Figure 1. Case 1. Periarterial cellular reaction, predominantly lymphocytic. (H & E)

tomography showed a recent haemorrhage into the right basal ganglia. Three days later the patient became comatose with flaccid quadriparesis and bilateral extensor plantar responses; she died 36 hours later.

Post-Mortem Report

A massive left fronto-parietal haemorrhage had occurred with secondary rupture into the left lateral ventricle. Microscopic examination revealed an inflammatory process of left hemisphere vessels. The left middle cerebral artery was especially affected (Figures 2 and 3), showing an acute medial inflammatory necrosis. There was also a more diffuse meningeal lymphocytic infiltration.

Discussion

This paper presents the post-mortem findings in 2 patients who suffered ipsilateral intracerebral haemorrhages 7 and 8 weeks after the development of herpes zoster ophthalmicus. Microscopic examination of the basal arteries revealed a multifocal segmental inflammatory process largely confined to the side of the herpes infection. In Case 1 the inflammatory infiltrate consisted almost completely of lymphocytes and assumed a periarterial distribution; in Case 2 the process was more severe and acute medial inflammatory necrosis was seen.

Delayed contralateral hemiparesis following herpes zoster ophthalmicus is increasingly recognized as a complication of that disorder.[1,5,13] The syndrome is thought to be caused by spread of the inflammatory process from the trigeminal

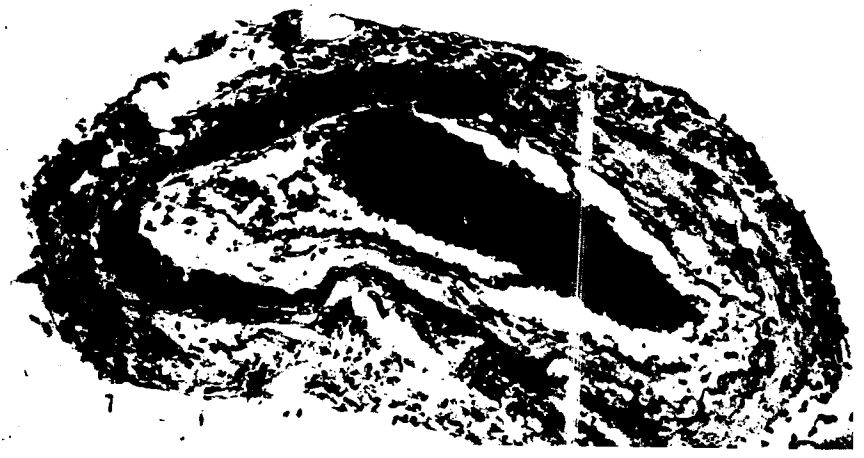

Figure 2. Case 2. Acute inflammatory medial necrosis, left middle cerebral artery. (H & E)

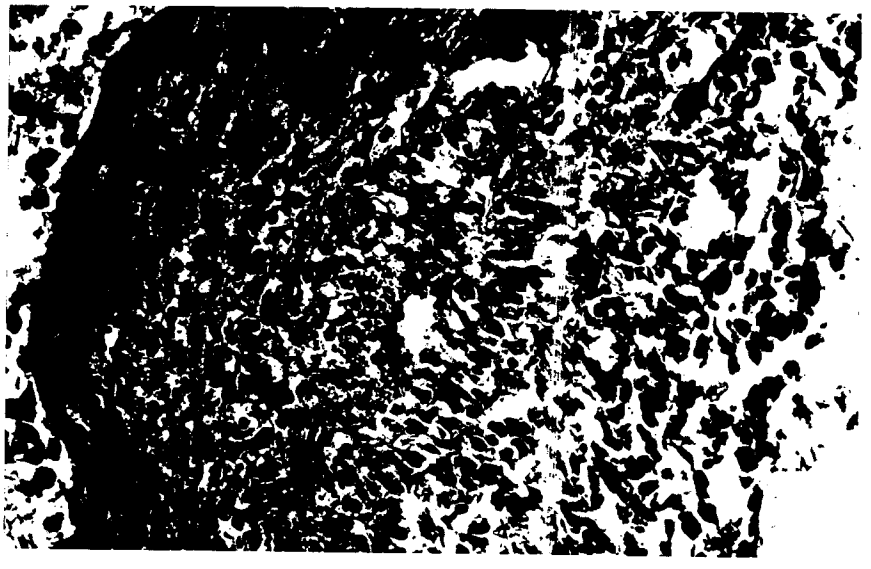

Figure 3. Case 2. Higher power view of the medial necrosis. (H & E)

ganglion to nearby blood vessels leading to thrombosis and distal embolization.[2] Evidence for such spread has come from angiographic studies which have shown segmental constriction of basal cerebral arteries on the ipsilateral side[3,6,14] and computerized tomographic scans have demonstrated ipsilateral cerebral infarction in the affected middle cerebral artery territory.[15] Most patients with such deficits will not die and those who do are often assumed to have had atherosclerotic cerebrovascular disease and no post-mortem examination is performed. Thus, pathological reports on this condition are rare. There is, however, a report in the German literature[16,17] of a patient with clinical and pathological features remarkably similar to those in our 2 cases. Their patient was a 71 year old woman who suffered an ipsilateral hemispheric infarction 2–3 months after herpes zoster ophthalmicus; post-mortem examination revealed a necrotizing arteritis affecting 65% of intracerebral and meningeal vessels on the ipsilateral side. The infiltrate mainly involved the adventitia, which led the author to compare the process with periarteritis nodosa. These findings are similar to our own except that both our patients suffered intracerebral haemorrhage, presumably secondary to the arteritis.

In recent years several reports have appeared detailing the pathology of typical cases of the syndrome.[10–12] The features were not those of a granulomatous arteritis, the pathology suggested as underlying these cases by Gilbert,[3] but were those of a focal necrotizing arteritis, as reported here. The anatomical distribution of the lesions seen in these cases would correspond to spread the virus along intracranial branches of the ophthalmic nerve and thence to the cerebral arteries, as suggested by Mackenzie and Karnes.[6]

Summary

This paper describes the pathological findings in two cases of delayed contralateral hemiparesis following herpes zoster arteritis. Both died of cerebral haemorrhage and a necrotizing angiitis was found involving the major vessels of the ipsilateral cerebral hemisphere. No feature of granulomatous arteritis or of encephalitis was found. It is likely that the virus spreads along intracranial branches of the ophthalmic nerve supplying the major arteries and causes the inflammatory reaction by direct invasion of vascular muscle.

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Otocerebral Mucormycosis – A Case Report

R.A.L. Macdonell, G.A. Donnan,* R.M. Kalnins,† M.J. Richards‡ and P.F. Bladin**

Mucormycosis is an uncommon infection caused by saprophytic and ubiquitous organisms of the order Mucorales. Infection of humans most commonly arises as a complication of unstable diabetes, particularly in patients who are ketoacidotic, but may also occur as a complication of other immunosuppressed states.[1–6] Organisms of this order typically cause a rapidly progressive necrotizing infection, invading arteries and veins directly to cause infarction of tissue and subsequent spread of the infective process. The most common presentation of this infection is as an orbital cellulitis. In this situation the infection is virtually always fatal unless treated rapidly and aggressively because of contiguous spread through the cribriform plate to involve the brain and major cerebral vessels.

We here report a case of mucormycosis with neurological involvement arising as a result of spread from the parotid gland through the petrous temporal bone to involve the brainstem and cavernous sinuses. This presentation of mucormycosis has not, to our knowledge, previously been reported.

Case Report

A 72 year old man was admitted to a country base hospital following an episode of haematemesis and malaena. One week before this he had presented to his local doctor after the sudden onset of left sided facial weakness which had been diagnosed as 'Bell's palsy' and treated with aspirin.

Diabetes mellitus had been diagnosed five years previously and managed with diet alone; he also had hypertension. According to his wife he had consumed 6 pots of beer a day (100 g of alcohol a day) for many years.

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On admission he was drowsy and had an obvious left sided lower motor neuron facial palsy. The remainder of the neurological examination was normal. His pulse was 80 per minute and regular and his blood pressure 170/90 mmHg with no postural drop. Examination of his abdomen revealed three fingersbreadth of hepatomegaly and numerous spider naevi were present.

Initial investigations included a full blood count which showed a normal haemoglobin level (14 g/L), an elevated white cell count (17 000/mm^3) with a neutrophilia and a normal platelet count (133 000/mm^3). His blood sugar level was elevated (18 mmol/L) and liver function tests were abnormal (total protein 57 g/L, bilirubin 35 mol/L, alkaline phosphatase 851 U/L, aspartate transaminase 149 U/L, γ-glutamyl transpeptidase 238 U/L). Urea and electrolyte levels were normal.

A gastroscopy was performed which showed severe gastritis and oesophageal varices but no bleeding point was identified.

Over subsequent days he became increasingly drowsy but did not develop a foetor or a flap. His malaena persisted.

Five days after admission he developed a fever and a swollen hot left cheek over the parotid gland. A clinical diagnosis of parotitis was made. At the same time, in view of his persisting drowsiness and fever, it was decided to perform a lumbar puncture. The cerebrospinal fluid was clear and colourless but microscopy and biochemistry of the fluid were abnormal (65 leucocytes/mL, 50% lymphocytes, 50% polymorphs; protein 1.18 g/L; glucose 5.5 mmol/L) at a time when his capillary blood glucose level was 15.6 mmol/L. A Gram stain was negative, as were cultures. The finding of meningitis prompted his transfer to the Austin Hospital for further investigation and management. On arrival he was drowsy and jaundiced. The left parotid area was tender, erythematous and indurated and this induration extended behind the left ear. No cervical nodes were palpable. Neurological examination disclosed left VI and VII nerve palsies but no other abnormalities apart from drowsiness. There was no neck stiffness and pus could not be expressed from the left parotid gland duct.

CT scanning showed a possible low density area in the left pons (Figure 1).

The patient was given intravenous flucloxacillin and gentamicin after surgical opinion opposed formal drainage of the parotid gland. A neurological opinion was sought the following day. At this stage the patient's conscious state had deteriorated further although he was still responding specifically to questioning. An incomplete left ptosis was now present in addition to the left VI and VII nerve palsies. There was a bloody discharge from the left ear and this was found to be arising from the external ear canal, the tympanic membrane being intact and transparent.

Further CSF was obtained and on this occasion there were 41 lymphocytes/mL with a protein level of 0.95 g/L and a glucose level of 2.7 mmol/L. Gram stain and Indian ink stains were again negative, as was culture.

The next day he developed a left sided palatal palsy, left sided facial hypoaesthesia, right sided arm and leg weakness and an upgoing right plantar. His pupils were small bilaterally and reacted sluggishly. The CT scan was repeated and this time a definitely hypodense area occupying the left side of the pons was demonstrated as well as decreased aeration of the left mastoid air cells (Figures 2 and 3). A pontine abscess was suspected and chloramphenicol, rifampicin and isoniazid were added to his antibiotic regimen to cover the possibility of tuberculous meningitis as he was too unwell for surgical exploration.

He continued to deteriorate and over subsequent days became progressively more obtunded. Skew deviation of the eyes appeared, followed by total ophthalmoplegia of the left eye and a complete left ptosis. Twelve days after admission he did not respond to painful stimuli and developed Cheyne–Stokes respiration. He died shortly afterwards.

At post-mortem examination he was found to have macronodular cirrhosis of the liver, splenomegaly and oesophageal varices. The parotid gland was extensively necrotic owing to invasion of vessels, parenchyma and fat by large, irregular, non-septate, branching hyphae consistent with mucormycosis. In some areas a granulomatous reaction to fungus, with giant cells, was noted (Figure 4). The infection extended to involve the left petrous temporal bone and middle ear, which showed areas of necrosis as a result of fungal invasion of vessels and tissue. The left facial ganglion was necrotic.

Inspection of the brain showed an acute basal meningitis. After sectioning and histological

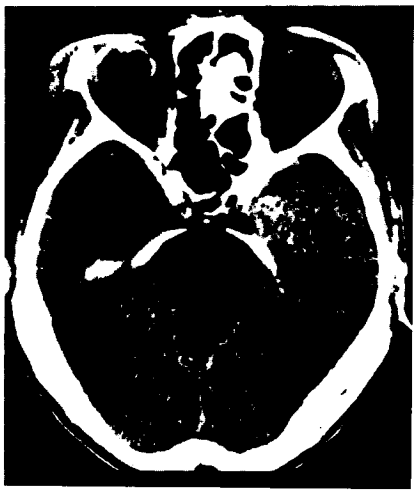

Figure 1. Initial CT scan demonstrating a possibly hypodense lesion in the left pons.

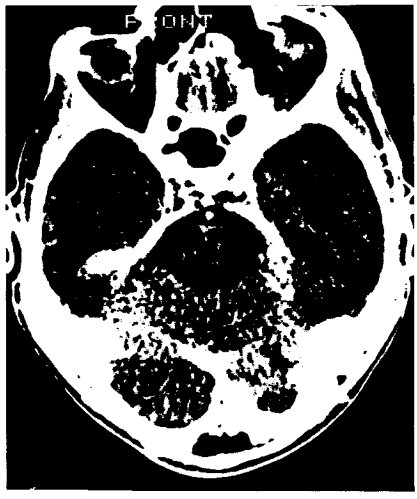

Figure 2. CT scan performed 4 days later showing a definitely hypodense area in the left pons.

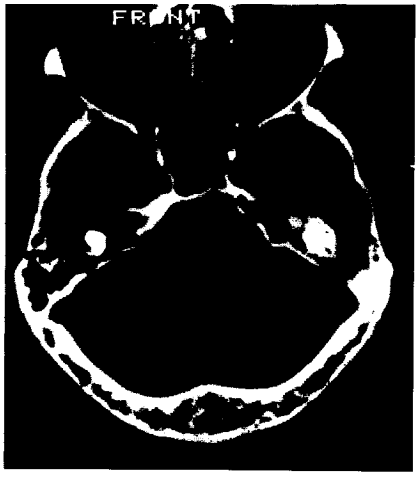

Figure 3. CT scan performed at the same time as that in Figure 2, using bone window settings, showing homogenous soft tissue infiltration of the left mastoid air cells.

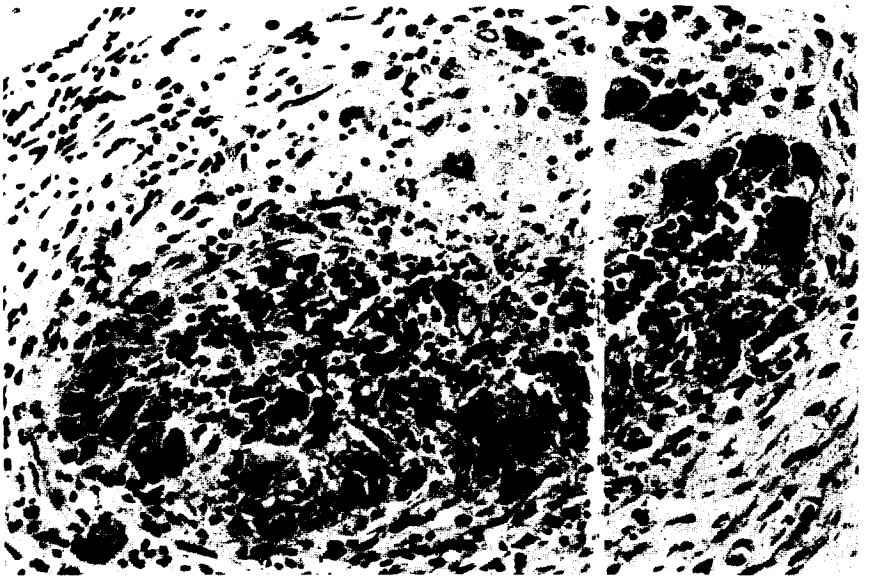

Figure 4. Parotid gland showing focal granulomatous response to the presence of fungal hyphae. (H & E, × 175)

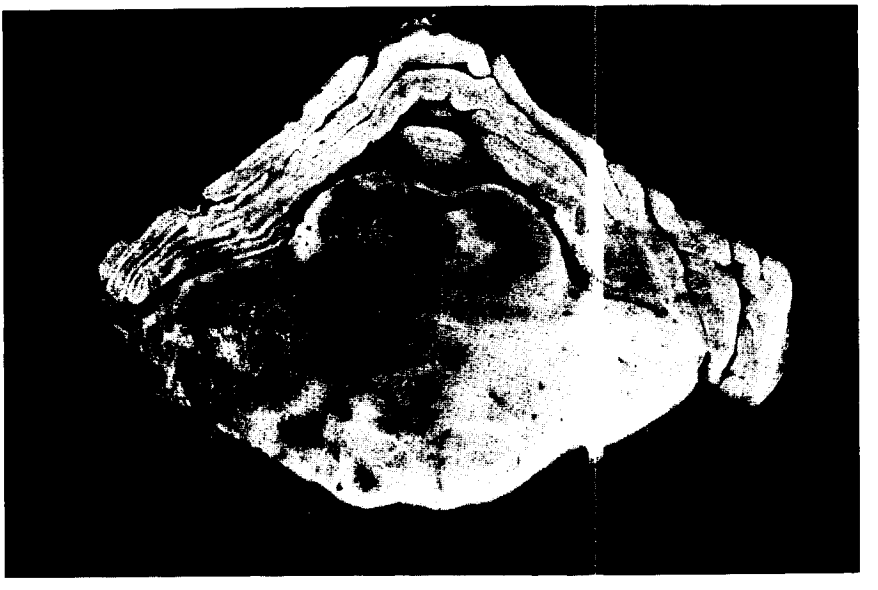

Figure 5. Transverse section of the pons showing predominantly left sided haemorrhagic necrosis.

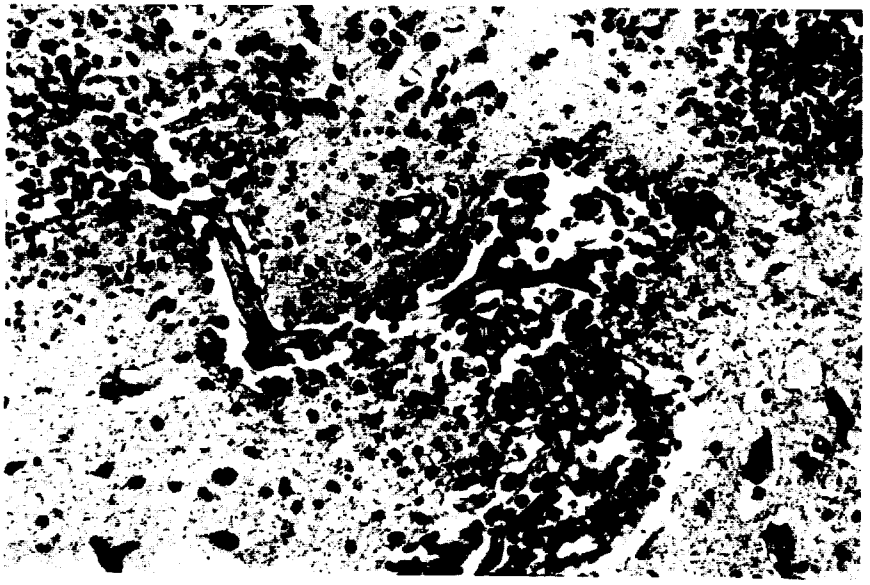

Figure 6. Pons, showing focal necrosis of parenchyma, with inflammatory infiltrate. Fungal hyphae seen focally. (H & E, × 200)

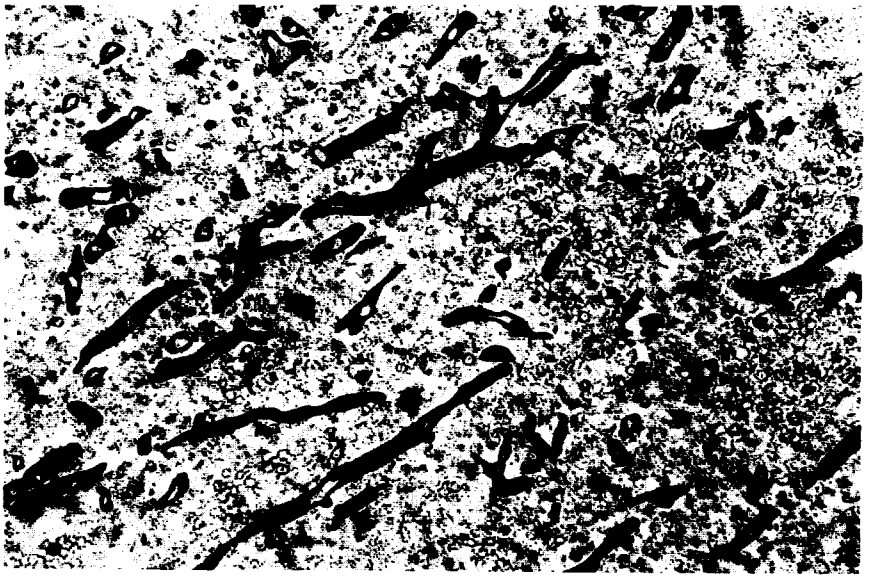

Figure 7. Pons, showing extensive infiltration by coarse, irregularly branching, non-septate fungal hyphae. (Silver methenamine, × 200)

examination the cerebral cortex, white matter and basal ganglia showed mild anoxic changes only. In the brain stem there was macroscopic necrosis of the left basis pontis (Figure 5) and histologically acute inflammation of the left side of the pons, midbrain and medulla oblongata. This was due to invasion of vessels and perivascular tissues by Mucor (Figures 6 and 7).

The anterior inferior cerebellar artery and both cavernous sinuses had been invaded by the organisms to cause septic thromboses of these vessels. In addition the left internal carotid artery in its intracavernous portion was acutely thrombosed.

Discussion

Intracerebral infection by mucormycosis following initial infection in the parotid gland has not been reported previously. The organisms probably gained access to the gland through the parotid duct and then spread to the petrous temporal bone along blood vessels accompanying the facial nerve. Further spread then led to infection of the left brain stem and cavernous sinuses. The case is also unusual because, although the blood glucose was moderately elevated on admission, at no stage was the patient ketoacidotic.

Unstable diabetes with ketoacidosis is the most often reported predisposing cause in the rhinocerebral form of the disease. *In vitro* work suggests that it is the acidosis rather than hyperglycaemia which is the more important factor.[7,8] However cerebral involvement with Mucor may also be seen in well controlled diabetics who are not acidotic.[1,9] Other predisposing conditions to Mucor infection include uraemia,[2] severe burns,[3] leukaemias and lymphomas,[4] immunosuppression[5] and multiple organ failure.[6] The common factor in all these is a degree of immunosuppression. Acidosis would appear to be an additive risk factor.

Our patient, although not acidotic, was immunocompromised as a result of diabetes and liver cirrhosis. The immunocompromised host loses natural resistance to organisms of the order Mucorales which are ubiquitous in soil and debris. Three genera of this order have been reported to cause intracerebral infections: Mucor, Rhizopus and Cunninghamella.[10] They may also cause infections of the skin, lungs or gastrointestinal tract in the susceptible host.

Mucor differs from other fungi in its marked tendency to invade blood vessels, stripping the intima from the media to produce thrombosis, infarction and necrosis.[6] The organisms tend to migrate along blood vessels and into infarcted, necrotic areas which provide an excellent acidotic medium for further growth of hyphae and spread of the infection.

Intracerebral mucormycosis was considered universally fatal after Paultauf's[11] original description in 1885, until the first reported survival in 1955.[12] Since then there has been a considerable improvement in prognosis such that at present rhinocerebral mucormycosis has an 89% cure rate if managed in an aggressive fashion before direct central nervous system involvement. This requires extensive debridement of dead and infected tissues, correction of systemic acidosis and hyperglycaemia and intravenous amphotericin B therapy.[13] However if intracerebral infection is present at the time of diagnosis the mortality is still high.[4]

Laboratory confirmation of the clinical diagnosis may be difficult. Cultures of superficial swabs and cerebrospinal fluid are unsuitable and cultures of biopsied

tissue must be performed on special isolation media and even then are often negative. This is in part because many of the hyphae in infected tissues appear not to be viable. Serological techniques are as yet not well developed and in particular antibody levels tend to be low or absent in early acute infection when there is most need to confirm a suspected diagnosis.[14]

The radiological appearances of rhinocerebral mucormycosis have been well described.[15] In particular the CT scan findings may suggest the diagnosis.[16–18] Homogenous infiltration involving the infratemporal fossa is seen with widening of the pterygomaxillary fissure. In the orbit the medial rectus may be displaced laterally by a soft tissue mass[16] and the superior ophthalmic artery and vein may not be opacified by intravenous contrast media. This latter feature may be specific for orbital mucormycosis.[18]

At present, however, confirmation of the diagnosis requires a biopsy of affected tissue. This shows the characteristic intravascular invasion through vessel walls by fungal hyphae.

This case illustrates that mucormycosis may infect the central nervous system by means other than by the classical rhinocerebral route. Infection due to this group of organisms should be considered in any patient with a facial cellulitis, particularly if predisposing conditions are present.

Summary

Mucormycosis is an often fatal infection caused by ubiquitous organisms of the order Mucorales. Infection is most commonly seen in the immunocompromised host, particularly in the setting of diabetic ketoacidosis.

The most common presentation is with rhinocerebral involvement. We here report a case of otocerebral mucormycosis occurring in an elderly man with maturity onset diabetes who was not acidotic. The unusual site of infection delayed diagnosis until the pons had been invaded by the infecting organism which was demonstrated as a hypodense area on CT scan. Consequently radical excision of infected tissue was not feasible and the patient died. At post-mortem examination there was extensive infection and infarction of the parotid gland, inner ear and pons associated with arterial invasion by the fungus and septic cavernous sinus thrombosis.

The case is described to demonstrate the existence of other modes of neurological presentation of mucormycosis apart from the well recognized rhinocerebral form. Early diagnosis is the key to successful therapy.

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Lumboperitoneal Shunting as a Cause of Visual Loss in Benign Intracranial Hypertension

B.J. Brew, R. Garrick* and T.J. Connelley†*

The causes of visual loss in benign intracranial hypertension are related to long standing papilloedema, ischaemic optic neuropathy[1] or haemorrhage into a subretinal neovascular membrane.[2] Decompression procedures generally preserve or improve visual acuity but surgical treatment by subtemporal decompression may lead to visual impairment.[3] To our knowledge treatment with lumboperitoneal shunting leading to further significant visual loss in this condition has not previously been reported. We now report a patient in whom this occurred and suggest a possible mechanism.

Case Report

A 17 year old female was admitted for assessment of recurrent headache. Nine years previously she had been diagnosed as having benign intracranial hypertension related to tetracycline therapy. She had remained well until one week before admission when she had gradually developed generalized dull headache and neck stiffness. Two tablets of vibramycin had been given for non-specific symptoms at some time before this illness.

Examination revealed that she was alert and afebrile. Marked bilateral papilloedema was present with haemorrhages on the left. Visual fields and acuity were normal. Neck stiffness was present. There were no other abnormal neurological findings.

Investigations included a CT scan of the brain and cerebral angiography. Neither showed any abnormality and there was no evidence of venous sinus thrombosis. Cerebrospinal fluid (CSF) pressure was higher than 44 cmH_2O. There were no cells and the CSF sugar and protein levels were normal.

Treatment with dexamethasone, frusemide and acetazolamide was instituted. Over the subsequent 7 days her vision deteriorated. New retinal haemorrhages were seen. On the tenth day after admission her visual acuity had declined to 6/9 bilaterally. As a result of the failure of drug

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therapy, lumboperitoneal shunting was advised. This was performed on the tenth day. There were no intraoperative complications; her blood pressure did not fall during the operation.

Over the next 24 hours she gradually lost the vision in both eyes leading to a visual acuity of 6/60 bilaterally with sluggishly reactive dilated pupils. A repeat brain CT scan and lumbar puncture showed no abnormalities, although the CSF pressure and intraocular pressure were at the upper limits of normal. Consequently timolol eyedrops were given to reduce intraocular pressure and thereby improve retinal and optic nerve perfusion.

Ten days after her initial visual loss, she had regained some sight; the visual acuity on the right was 6/9, and on the left 6/24. By day 29 her visual acuity was 6/9 bilaterally. There has been no further improvement over 5 months. Two more CT scans have not shown any abnormality. Progress CSF studies including pressure measurements have been normal. Visual evoked responses (Figure 1) showed persisting abnormalities consistent with retinal or optic nerve damage.

Discussion

The fact that the visual loss and the insertion of the shunt occurred at the same time suggests that the two were related. This is supported by the lack of any identifiable local cause of the visual loss such as haemorrhage or raised intracranial

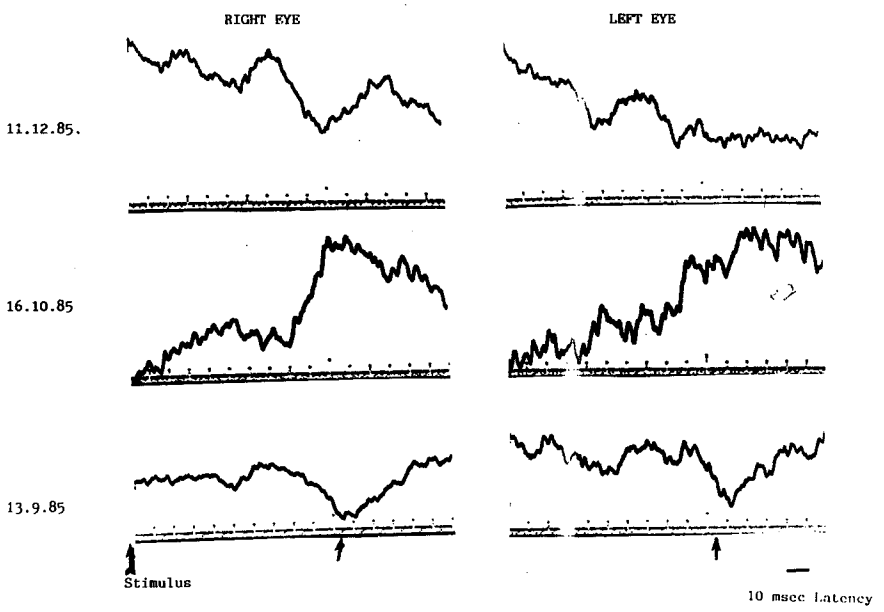

Figure 1. Serial visual evoked potentials showing distorted wave forms and loss of clear definition of the P100 wave form and subsequent partial recovery without delay in latency. The changes are consistent with retinal or optic nerve disease.

pressure. Blindness after craniotomy or ventriculography has been well recorded.[4] Some cases are undoubtedly due to the effects of brain herniation and the consequent distortion of the posterior cerebral arteries. However, cases have been recorded in which there has been no evidence of herniation.[5,6] Several mechanisms have been proposed including direct trauma, spasm of vessels supplying the visual cortices and retinal vascular disturbance. The prognosis is variable, but often there is some improvement.[7]

The present case gives credence to the last mentioned mechanism. By the very nature of the operation of lumboperitoneal shunting, there is no direct trauma to the brain and serial CT scans did not show any evidence of occipital infarction in our patient. The visual evoked responses suggested a retinal or optic nerve disorder.[8]

This rare complication of shunting should be kept in mind when considering treatment in patients with raised intracranial pressure. The likely mechanism appears to be local retinal vascular disturbance.

Summary

The causes of visual loss in benign intracranial hypertension are related to long standing papilloedema, ischaemic optic neuropathy or haemorrhage into a subretinal neovascular membrane. Decompression procedures generally preserve or improve visual acuity but surgical treatment with subtemporal decompression may lead to visual impairment. Such a deficit has been recorded in the past as occurring with ventriculography. Postulated mechanisms have included brain herniation, spasm of vessels supplying the visual cortices or retinal vascular disturbance. To our knowledge treatment with lumboperitoneal shunting has not previously been reported as leading to further significant visual loss in this condition. This report describes such an occurrence in a patient. Retinal vascular disturbance is postulated on the basis of several normal CT scans, normal CSF pressure measured after surgery and visual evoked responses suggesting retinal or optic nerve damage.

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Abstract

The Epidemiology of Multiple Sclerosis in Australia: a 20 Year Follow-up Study

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An epidemiological survey of multiple sclerosis (MS) in Australia was undertaken to compare the status of the disease in 1981 with surveys conducted in a number of regions of Australia 20 years previously. The national census day on 30 June 1981 was used as the prevalence day. The methods employed in collecting medical data in our study were similar in each centre, and standardization of procedures was ensured by regular meetings of survey co-ordinators from each area. The major sources for case ascertainment in each area were hospital diagnostic indices, neurologists, general practitioners and MS societies. All patients were interviewed and examined by members of the survey team and those in whom the diagnosis was considered to be correct were classified into clinically definite, probable or possible groups. Patient disability on prevalence day was assessed according to the Kurtzke disability status scale (DSS) and to a 'Stairs' and 'Wheelchair' DSS. Data were recorded on a standard protocol form and were subsequently entered into a computerized data base.

The general relationship between increasing prevalence and increasing south latitude found in 1961 was confirmed in our study. Standardized prevalence rates per 100 000 of population in 1981 were 18.6 in the State of Queensland, 29.9 in

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Perth, 36.5 in Newcastle, 29.7 in the State of South Australia and 75.6 in Hobart. Particular attention was paid to Perth, Newcastle and Hobart because of the comprehensive nature of the 1961 survey in these cities. Prevalence rates had substantially increased in each city (by factors of 1.5, 1.9 and 2.3 in Perth, Newcastle and Hobart respectively) and the high risk status for MS (prevalence rate of 30 +) previously only found in Hobart now applied to all 3 cities. Incidence rates had also risen substantially in Newcastle and Hobart but remained essentially stable in Perth. However it is unlikely that this rise reflected a real increase in disease frequency. A number of factors with varying influence from city to city were identified which together probably accounted for the change. These factors included better case ascertainment, increased disease duration and a lower mortality rate, increased recognition of less severely disabled cases, and an increased contribution from migrants from high-risk areas of the northern hemisphere.

Despite the latitude-related differences in the relative risk of acquiring MS the clinical features of the disease were very similar in each area. In particular, disability profiles of the clinically definite patients indicated that after a mean disease duration of 14.3 years about 40% were moderately or mildly disabled only whilst about 30% were disabled to the extent that constant assistance was required in activities of daily living.

Abstract

A Syndrome of Two 'Funny Hands': Loss of Intermanual Co-operation and Motor Inhibition after Anterior Cerebral Artery Occlusion

*A.W. McNabb, W.M. Carroll and F.L. Mastaglia**

In three elderly right-handed women, occlusion of the dominant anterior cerebral artery led to a distinctive disturbance of motor control in both upper limbs. In each case the right upper limb, which was paretic, exhibited forced grasping and other intermittent non-purposive or goal-directed movements; in the left hand there was dyspraxia, agraphia and astereognosis. At times there was evidence of conflict between the motor behaviour of the 2 upper limbs ('intermanual conflict'), the right hand interfering with tasks being performed by

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the left hand, or the left hand restraining the unwanted activity of the right hand. A transcortical motor dysphasia was also present in each case. The significance of the motor abnormalities is discussed in terms of impaired inhibitory motor control and hemispheric disconnection. The results of movement-related cerebral potential studies in one case are presented.

Abstract

A Comparison of Brainstem Auditory Evoked Responses Evoked by Rarefaction and Condensation Stimulation in Control Subjects and in Patients with Wernicke-Korsakoff Syndrome and Multiple Sclerosis.

S.R. Hammond, C. Yiannikas† and Y.W. Chan†*

Brainstem auditory evoked responses (BAERs) evoked by monaural rarefaction and condensation wide-band click stimulation were recorded from 37 male and 40 female control subjects to investigate the interaction between sex and click polarity. Rarefaction stimulation produced significantly shorter wave I latencies in females only and this was reflected in significantly longer waves I–III and I–V interpeak latencies in females with this stimulus mode. Condensation stimulation produced significantly larger wave III amplitudes in females and wave V amplitudes in both sexes. However rarefaction stimulation produced significantly better separation of waves IV and V and this was independent of sex. This part of the study indicates the importance of taking into account sex and click polarity when establishing BAER control values.

Rarefaction and condensation evoked BAERs were compared in 25 patients with Wernicke-Korsakoff syndrome (WKS) and 20 patients with multiple sclerosis (MS). Rarefaction and condensation stimulation defined abnormalities in 12 (48%) and 10 (40%) WKS patients, respectively, whilst each click polarity detected abnormalities in 10 (50%) MS patients. More importantly, click polarity-related differences in topodiagnosis were found in 6 (24%) WKS and 8 (40%) MS patients. In 10 of these (6 WKS, 4 MS) the responses were abnormal with one click polarity

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but normal with the other. These results suggest that for maximum information BAERs need to be recorded routinely with both stimulus polarities separately, if practicable.

Abstract

A Comparison of Somatosensory Evoked Potentials Evoked by Median and Posterior Tibial Nerve Stimulation in 112 Patients with Multiple Sclerosis

S.R. Hammond and C. Yiannikas†*

Somatosensory evoked potentials (SEPs) were recorded from median and posterior tibial nerve stimulation in 112 patients with clinically definite or probable multiple sclerosis (MS), to compare their relative sensitivity and to investigate whether SEP abnormalities correlate with clinical disability. A further aim was to assess the value of analysing the cortical P23 component of the median nerve SEP in terms of increasing the sensitivity of the test. Control data for median and posterior tibial nerve SEPs were obtained from 32 and 42 control subjects, respectively. Significant correlations were noted in the control median nerve SEP data between arm length and absolute latency of the potentials recorded over Erb's point (N10), cervical spine (P/N13)and contralateral cortex (N19 and P23), and also the inter-peak latencies N10–P/N13, P/N13–N19 and N10–N19. Similarly, in the control posterior tibial nerve SEP data, significant correlations were noted between height and the absolute latency of the potentials recorded over L1 (N20) and the cortex (P37), and also the N20-P37 inter-peak latency. Results for MS patients were evaluated against control nomograms constructed for each of these parameters and abnormal inter-side differences were also used to determine abnormality. Median and posterior tibial nerve SEP abnormalities were present in 64.3% and 71.4% of patients, respectively. Analysis of the P23 component of the median nerve SEP increased its abnormality rate to 72.3%. Importantly, 12.5% of patients had abnormal posterior tibial nerve and normal median nerve SEP whilst the reverse was true in 13.4% ; 84.8% of patients showed abnormalities when the tests were combined. Abnormalities in median and posterior tibial nerve SEP were both found to correlate strongly with patient disability.

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Abstract

Pathophysiology of Experimental Allergic Encephalomyelitis in the Lewis Rat

*M. P. Pender**

Experimental allergic encephalomyelitis (EAE) is widely studied as an animal model of multiple sclerosis (MS). In MS, demyelination of the central nervous system contributes significantly to the production of neurological signs. However, because of reports of the absence of demyelination in some animals with neurological signs of EAE, it has been suggested that the signs of EAE are due not to demyelination but to other factors such as oedema or an impairment of serotoninergic neurotransmission. But these reports have been based on studies which have either failed to use adequate histological techniques to assess demyelination or failed to examine thoroughly the whole nervous system, particularly the lumbar, sacral and coccygeal spinal cord segments, and the peripheral nervous system which is known to be involved in EAE. Histological and electrophysiological studies have therefore been performed in Lewis rats with whole cord-induced EAE or myelin basic protein-induced EAE to determine the cause of the neurological signs. These studies show considerable demyelination in the spinal cord, dorsal and ventral roots and dorsal root ganglia, and focal nerve conduction abnormalities in the regions of demyelination. Therefore demyelination readily accounts for the neurological signs of EAE, and there is no need to invoke other factors such as oedema to explain them.

Abstract

Fatal Adrenal Haemorrhage during Controlled Heparin Anticoagulation

A. Weinmann and B.S. Gilligan†

Bilateral adrenal haemorrhage associated with heparin and warfarin anticoagulation is difficult to diagnose before death, owing to a low index of suspicion on

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the part of the clinician and the relatively non-specific and insidious onset of clinical features.

A 64 year old man is described who was anticoagulated initially with heparin and then with warfarin for a cerebral ischaemic episode following acute myocardial infarction. At all times the daily whole blood clotting time and later the prothrombin time were in the therapeutic range. Vague back and flank pain associated with mild abdominal distention and lethargy developed on the sixth day of anticoagulation and was associated with progressive hyponatraemia, hyperkalaemia and uraemia. A computerized tomography scan of the abdomen on day 10 suggested equivocal enlargement of the left adrenal gland. The patient died on day 15. Post-mortem findings revealed recent myocardial infarction, bilateral pulmonary oedema and bilateral adrenal gland infarction and haemorrhage.

It is vital to suspect this condition in a patient who deteriorates within the first few days of anticoagulation; blood cortisol levels should be estimated and vigorous steroid replacement instituted, if indicated.

Abstract

The Sydney Multicentre Study of Parkinson's Disease: the First 18 Months

M.A. Hely, J.G.L. Morris,* S.A. Genge,† D. O'Sullivan,‡ P.M. Williamson,** W. Reid,†† D. Rail†† and G.A. Broe‡‡*

The efficacy and side effects of low doses of bromocriptine (< 30 mg/day) and low doses of levodopa–carbidopa (< 600–150/day) in the treatment of idiopathic Parkinson's disease are being compared in a double-blind, long term study. An attempt is being made to identify subgroups of Parkinson's disease by their clinical features and response to treatment. The incidence and nature of dementia in this group of patients are also being studied.

Preliminary data on 94 patients who had entered the study by January 1986 are presented. Fifty patients have been followed for 6–18 months. Of these, 27 (54%) have improved, the condition of 15 (30%) is unchanged and 8 (16%) have deteriorated. The mean doses for the groups were 15 mg/day of bromocriptine or 300–75 mg/day of levodopa–carbidopa. Of the 23 patients who did not improve, or deteriorated, 8 had mild disease, 5 had significant dementia and 4 were able to tolerate only very low doses. Patients with symmetrical rigidity and akinesia

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showed less overall improvement than those with tremor as a prominent initial symptom.

Seventeen of the 94 patients have been withdrawn from the double-blind part of the study. Three patients, all receiving levodopa–carbidopa, developed dyskinesia. Six patients receiving bromocriptine had an inadequate response. A further 6 patients receiving bromocriptine developed confusion (3) or postural hypotension (3).

As expected, the initial improvement resulting from low doses of bromocriptine and levodopa–carbidopa is less than that which occurs with conventional doses of these agents. It is hoped, however, that this therapeutic approach will reduce the incidence of long term side effects such as dyskinesia and performance fluctuations.

Abstract

Debatable Aspects of 'Pure' Alexia

*T.J. Day and A. Fisher**

Although alexia without agraphia is believed to be adequately explained by the disconnection hypothesis, difficulties in nomenclature and analysis abound. These problems were exemplified in a right-handed patient who developed alexia without agraphia from a deeply placed right occipito-parietal haemorrhage. The presence in the patient of other 'parietal' symptoms and of mild verbal and auditory dysmnesia made the use of the term 'pure alexia' unsatisfactory. Limb dominance was assessed quantitatively using the Edinburgh Handedness Inventory.[1] Language laterality could be inferred only by the presence initially of a Gerstmann's syndrome. A Wada[2] test was not performed. The results of our study of this patient lend no support to the proposition that there is bilateral representation of reading capability.

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Abstract

Neural Mechanisms in Symbol Development

*D.L. Rail**

Symbol formation is the key to the mental life which characterizes human beings. Understanding of the development of normal and abnormal speech and cognition depends on the formulation of a model couched in terms of neurophysiological processes. The model is based on the development of the symbol for an object.

In ontogeny the object is internalized before the development of its symbolic representation. Action on the object produces a functional dissection of the object which is then resynthesized. The object is delivered to distributed groups of degenerate receptors (see Edelman and Mountcastle). Further action on the object extends and atomizes its transforms within neural space. The object becomes unfolded and displayed, thereby producing a vast array of implicate ontological and logical relationships at each part of the manifold.

The word is used to refer to the object. A gradual match occurs between the word and the object-related neural space. Symbol realization occurs as the object's representations are consolidated. The symbol develops the structure of the intensional space thereby acquiring (a) an internal systematicity, (b) a sensory signature and (c) an operational capacity.

Speech develops around the functional nucleus of the symbol's intensional space. Psychical operations on this 'object' explicate propositional relationships. Disorders of speech and cognition relate to (a) inability to acquire the appropriate nucleus for sentence generation and (b) difficulties in operating on the procured nucleus.

Abstract

Foveal Pattern-reversal Visual Evoked Potentials Improve the Detection of Visual Pathway Demyelination

W.M. Carroll†

Multichannel visual evoked potentials were recorded from two groups of selected patients using a battery of 10 different visual stimuli; these stimuli comprised pattern-reversal (wide-field, foveal and low luminance), pattern onset

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and offset and foveal luminance. The first group was of 20 patients with monocular optic neuritis and prolonged P100 latencies (mean 147 ms); the second group was of 27 patients with optic neuritis or multiple sclerosis who had high-normal P100 latencies (110–115 ms) from 12 symptomatic and 16 asymptomatic eyes. From the 20 patients with optic neuritis, the P100 latency rates of abnormality (including the interocular latency difference) to pattern-reversal stimulation ranged from 90% (wide-field) to 95% (foveal) compared to rates of 55% to 82% for foveal luminance stimuli and 70% to 90% for pattern offset and onset. Whilst the mean P100 latency to pattern-reversal stimuli increased from 147 ms (wide-field) to 157 ms (foveal), the interocular latency difference did not change significantly (43 ms and 41 ms). By comparison, abnormality rates from the symptomatic and asymptomatic eyes of the second group of patients increased from 34% (symptomatic eyes) and 20% (asymptomatic eyes) for wide-field pattern reversal to 83% (symptomatic eyes) and 50% (asymptomatic eyes) with low luminance foveal pattern reversal. In demyelinated visual pathways, pattern reversal results in a higher rate and greater degree of abnormality than foveal luminance or pattern onset and offset, and foveal pattern reversal frequently unmasks an abnormal latency in patients with borderline–normal P100 latencies to wide-field pattern reversal.

Abstract

Pseudo-absences and Drop Attacks due to Self-induced Syncope

E.R. Somerville and P.G. Procopis†*

Self-induced epileptic seizures are well recognized but self-induced syncope is rare. A 7 year old, mentally retarded girl experienced episodes of unresponsiveness and a vacant facial expression, often with staring or upward deviation of the eyes. There was occasional loss of tone, causing head nodding. She also suffered drop attacks, injuring herself on many occasions. More than 100 attacks occurred per day and did not respond to anticonvulsants. During a 5½ hour telemetry recording, 66 episodes were captured. Each was preceded by vigorous hyperventilation for 10–30 seconds, followed by a Valsalva manoeuvre lasting 10–20 seconds, during which the peripheral pulse became impalpable. With loss of consciousness, the Valsalva manoeuvre ended and the pulse returned. The EEG revealed high voltage rhythmic 2–3 Hz delta activity at the onset of unconsciousness, which lasted 8–20 seconds. Voluntary hyperventilation alone did not produce syncope. This child suffered self-induced syncope as the result of hyperventilation followed by a Valsalva manoeuvre. The confusion with absence seizures was due to several factors: the episodes were brief, usually consisting of a vacant stare with

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interruption of activity and unresponsiveness and were not accompanied by a post-ictal state; they were preceded by hyperventilation and were associated with drop attacks, which we assume were also the result of syncope. Gastaut recently reported 8 children with self-induced syncope. However, these children had autistic features and the mechanism of syncope was prolonged apnoea, at times after hyperventilation or a Valsalva manoeuvre. The reason these children repeatedly induce syncope is unknown. Our patient often smiled after her episodes and they abated when she was upset, suggesting that they were pleasurable to her.

Abstract

Out-patient Video-EEG Telemetry: Results, Advantages and Indications

*E.R. Somerville**

Video-EEG telemetry has become well established in the diagnosis of epilepsy, in its differentiation from other episodic disturbances of brain function and in the evaluation of intractable epileptics before surgery. While its use is largely confined to the in-patients of teaching hospitals, I have used video-EEG telemetry to study 119 out-patients over a 24 month period. The patients' ages ranged from 13 months to 75 years. A 16-channel cable telemetry unit was synchronized with a domestic video system. Each patient was accompanied by a relative or friend during the 8-hour recording and was not continuously supervised. In some cases the patient was sent home overnight with the disconnected electrodes in place. Only ictal portions of the recordings were replayed. Sixty-four of the 119 recordings (54%) captured a typical attack. Where episodes were occurring daily, 44 of 54 (82%) recordings were positive. Of patients whose episodes occurred every 2–7 days, 9 of 24 (38%) recordings were positive, while no recording of 28 patients who suffered fewer than one episode a week was positive. In 8 patients, efforts were made to induce an episode and were successful in each case. In 5 patients, the episodes were predictable and the timing of the recording was arranged accordingly. Of these, 3 (60%) were positive. Recorded events included complex partial seizures (10 patients), simple partial seizures (7), myoclonic seizures (6), absence seizures (4), tonic seizures (3), atonic and atypical

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absence seizures (1 each), pseudoseizures (20), syncope (4), extensor spasms (1) and familial paroxysmal kinesigenic choreoathetosis (1). In 8 patients no firm diagnosis was possible. Video-EEG telemetry of out-patients has several advantages: cost is greatly reduced, disruption to patients is minimized, the reduction in seizure frequency which may accompany admission to hospital is avoided and the procedure does not depend on the availability of hospital beds. The procedure is particularly useful where seizures are occurring daily, are predictable or can be induced.

Abstract

Leber's Optic Neuropathy. A Longitudinal Neuro-ophthalmic and Visual Evoked Potential Study of Symptomatic and Asymptomatic Family Members of a Six Generation Kindred

*W.M. Carroll, F.L. Mastaglia, G.W. Thickbroom, H.D. Davies, R. Stell and A. McNabb**

Fifty-six members of a 6 generation family with Leber's optic neuropathy were studied in 1977 using single-channel foveal visual evoked potentials (VEPs) and a semi-quantitative neuro-ophthalmic examination. At that time there were 16 symptomatic and 40 asymptomatic members. Subclinical abnormalities were identified in 10 (50%) female lineage descendants who were at risk of developing the disease. The family was re-examined in 1985 when multichannel VEPs were recorded to wide-field, half-field and central-field stimulation. Two members of the family had become symptomatically affected; both of these had shown subclinical neuro-ophthalmic and/or VEP abnormalities at the earlier examination. Multichannel half-field VEP studies of these and other symptomatic members showed 'scotomatous' abnormalities rather than true delay of VEP subcomponents. Half-field VEPs also showed that macular and paramacular subcomponent interaction was responsible for the 'bifid' VEPs recorded from clinically asymptomatic members in the 1977 study. The evolution of clinical, neuro-ophthalmic and VEP abnormalities in both symptomatic and asymptomatic members is presented.

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Abstract

Spatio-temporal Mapping and Dipole Modelling of Epileptic Spikes

*H.D. Davies, G.W. Thickbroom, F.L. Mastaglia and W.M. Carroll**

Spatio-temporal mapping and dipole modelling techniques have been applied to study the scalp fields and sources of focal spikes in 12 epileptic subjects with temporal or frontal cortical foci. Sixteen channels of monopolar EEG were recorded from 10–20 system electrode sites with a balanced sternoclavicular reference using a Grass EEG machine interfaced to a PDP 11/23 computer. The operator watched a conventional bipolar EEG trace and triggered the computer to store 1 s epochs of interest on disk. Reference-independent waveforms were computed off-line and colour-coded spatio-temporal maps of the spike and of immediate pre- and post-spike events were generated at 4 ms intervals and were displayed on a Tektronix 4105 colour terminal. Dipoles were modelled to give an origin and orientation in both the horizontal and sagittal planes. Results were correlated with cranial computed tomography and operative findings when available. Our findings indicate that the combination of spatio-temporal mapping and dipole modelling allows greater precision than that given by conventional EEG in localizing the source of epileptic discharges.

Abstract

Long Term Ambulatory EEG Monitoring with the Oxford 8-Channel System

H.D. Davies, F.L. Mastaglia, W.M. Carroll and J. Scopa†

Sixty 24-hour EEG recordings were obtained from 35 patients. In 27 patients with a diagnosis of possible epilepsy, conventional awake or sleep-deprived EEGs were normal (12) or showed non-diagnostic abnormalities (15), while in the 8 others (all epileptics) there was uncertainty regarding the seizure type (source) (4) or frequency (4). In 20 patients, the diagnosis of epilepsy was confirmed by the occurrence of spontaneous (6) or induced (1) seizures accompanied by focal (2) or

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focally initiated generalized (5) epileptiform discharges, or by the finding of focal (10) or generalized (5) inter-ictal discharges. In some patients such abnormalities were found solely (4) or principally (4) during nocturnal sleep. In 5 patients a diagnosis of pseudo-seizures was supported by the occurrence of typical attacks with no associated EEG changes. In 3 patients, the study allowed differentiation of transient ischaemic attacks (2) or syncopal episodes (1) from epilepsy by showing a normal EEG during attacks. The 8-channel system is particularly useful for the detection and localization of focal inter-ictal discharges or focal initiation of generalized discharges.

Abstract

Smoking and the Risk of Stroke or TIA: A Case Control Study. Background and Methodology

G.A. Donnan, J.J. McNeil† and A. E. Doyle**

Although chronic smoking has been strongly suggested to be a risk factor for coronary heart disease and occlusive peripheral vascular disease, evidence of a similar relationship between cigarette smoking and atherosclerotic cerebrovascular disease has been less convincing. Since smoking is one of the few potential risk factors whose effects can be eliminated, it is important that this information be determined in an Australian population. We have instigated a study using case control methods to assess smoking as a risk factor for cerebral infarction and transient ischaemic attacks (TIAs). Consecutive patients with first onset cerebral infarction or TIA entering the Stroke Unit, Austin Hospital are being studied. Patients are matched for age and sex with 2 separate control groups: (i) in-hospital patients *not* admitted for smoking-related conditions, (ii) 'neighbourhood' controls living in the same street as the subject. Questionnaires containing 90 enquiries are administered to both subjects and controls; these concentrate on smoking habits, but also investigate other potential risk factors such as dietary and exercise habits. Ultimately these factors will be correlated with stroke diagnostic subgroups while controlling for factors such as age and hypertension. The calculated sample size requirement, based on an estimate of 30% prevalence rate of smoking in the Australian community, is 406 subjects and 406 controls in each of 2 groups. This will give a power of 0.8 for an α of 0.05 thus allowing an 80% chance of detecting a relative risk of 1.5. This paper is primarily presented to outline background and methods, but early trends tend to support the hypothesis that smoking is a risk factor for stroke and transient ischaemic attack. Of the first 93 stroke or transient ischaemic attack patients, 65% were current or ex-smokers compared to 44% of neighbourhood control subjects.

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Abstract

Comparison of the Relative Sensitivity of Repetitive Stimulation of the Ulnar, Axillary and Accessory Nerves and Single Fibre Electromyography in Patients with Myasthenia

*P. King and C. Yiannikas**

It is generally accepted that the diagnostic yield from repetitive nerve stimulation in patients with myasthenia gravis is greater when proximal rather than distal muscles are studied. However, when stimulating the axillary nerve it is often difficult to avoid movement artifact which makes interpretation difficult. Recently it has been suggested that repetitive stimulation of the accessory nerve is less likely to cause movement artifact and is more tolerable, and that the diagnostic yield is similar to that from stimulating the axillary nerve. We have performed 13 repetitive nerve stimulation and 10 single fibre electromyography (EMG) studies of 9 patients with myasthenia gravis and 1 patient with the myasthenic syndrome to assess the relative sensitivity of these techniques. A significant decrement was observed after stimulation of the ulnar nerve in 27% (3 of 11), the axillary nerve in 85% (11 of 13) and the accessory nerve in 50% (6 of 12) of patients. Single fibre EMG was abnormal in 90% (9 of 10) of studies. The axillary study was abnormal and the accessory study was normal on 5 of 12 occasions whereas the converse was true on only one occasion. The accessory study was easier to perform than the axillary study and most patients preferred it. These results are consistent with a higher diagnostic yield from stimulation of proximal muscles and single fibre EMG. However, in view of the abnormalities in the axillary study when the accessory study was normal, we suggest that axillary nerve studies should not be abandoned in favour of accessory nerve studies. Rather, an accessory study should be performed and followed by an axillary study if no significant decrement is observed initially.

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Books and Other Monographs

Personal author(s)

Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974: 406.

Chapter in a book

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