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Contents

Abstracts

Editorial note

Clinical and Experimental Neurology, under that name or its earlier title of Proceedings of the Australian Association of Neurologists, has now appeared for 22 years. Over that time it has had only two editors, the late E. Graeme Robertson, who founded the publication and was responsible for its first 9 issues, and Professor John Tyrer, who edited the subsequent 12 annual volumes.

Since the publication of the most recent issue of Clinical and Experimental Neurology, Professor Tyrer has retired from the O'Neill Mayne Chair of Medicine in the University of Queensland, and has decided to relinquish the editorship. It is surely fitting that, at this time, some acknowledgement should be paid to Professor Tyrer for his years of devoted care in editing this publication of the Australian Association of Neurologists. As he embarks on his post-retirement career as Historian to the North Brisbane Hospitals Board, we would wish him much happiness and attempt to thank him for his great service to Australian neurology.

M.J. Eadie

Edrophonium Test in Myasthenia: Quantitative Oculography

I.M. Williams†‡, P. Dickinson* and A.C. Sum**

Every patient with diplopia, the cause of which is not obvious, should have an intravenous edrophonium test

Joel Glaser [1]

The effect of the anticholinesterase inhibitor, edrophonium, on eye movements can be measured easily, accurately and relatively quickly with infrared oculography. Previous authors have used infrared oculography to record the effect of edrophonium on opticokinetic nystagmus in patients suspected of having myasthenia gravis [2] and on refixational saccadic eye movements of patients known to have myasthenia gravis[3]. We recorded the effect of edrophonium on the saccades of 26 patients with diplopia or ptosis, the cause of which could not be explained unequivocally.

Methods

Each patient underwent a neurological and neuro-ophthalmological assessment prior to the edrophonium infrared oculography test. The signs recorded at the first interview are included in this report (Table 1). The eye movements were recorded in subdued lighting using infrared oculography (Figure 1) with a system band width of 100 Hz. The signal from each sensor was digitized, stored in the memory of the computer and displayed on the oscilloscope. Each of the 4 movements i.e. adduction and abduction of each eye, was calibrated. The computer was programmed to record separately a change in the movement of each eye and the velocities were derived by digital differentiation[4].

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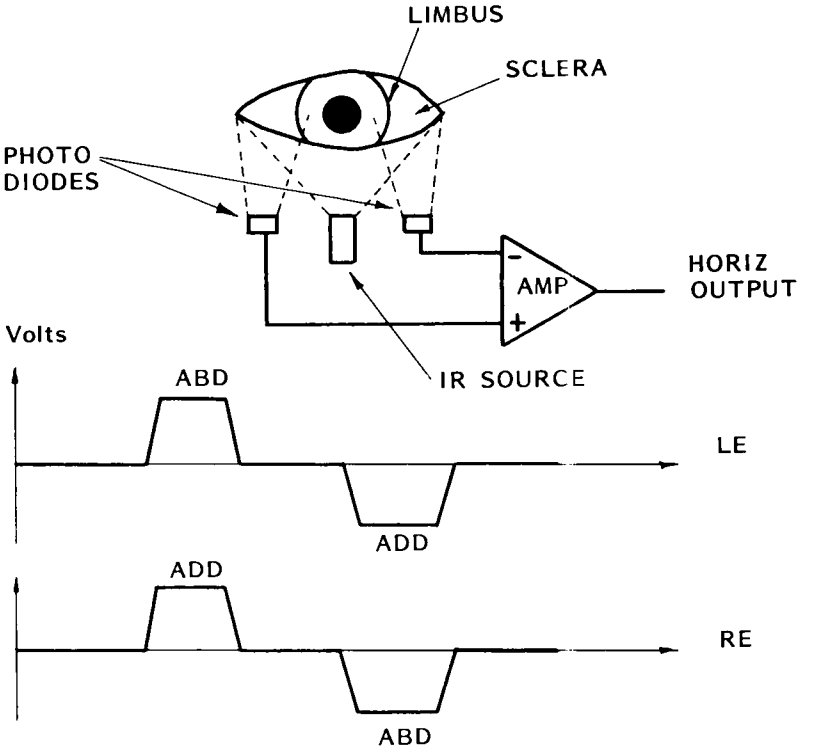

Figure 1. The infrared light (IR) source and two sensors (Photodiodes) sit on spectacle frames and the sensors pick up scattered reflection of infrared light from each corneal limbus. As the eye moves, the sensor in the direction of the movement receives less light since the infrared light is absorbed by the iris. The other sensor receives more light reflected by the sclera. The amount of light received by the sensors is proportional to the eye movement.

Each patient was seated in a chair with a head rest and brace at the centre of a 2 m arc containing red light-emitting diodes. Horizontal saccades from centre to eccentric targets (± 10°) were induced by instructing each patient to fixate alternating light-emitting diodes. Each 10° saccade was executed during a recording lasting two seconds. Binocular eye movements were recorded during each test and the fixating eye was defined by occluding one eye. Fatigue was induced by instructing the patient to gaze 30° to one side for 2 minutes immediately prior to recording a 10° saccade from centre to the same side. Fatigue tests were performed before and during anticholinesterase inhibition with edrophonium. The intravenous injection of edrophonium was preceded by saline and by atropine (600 mcg) to prevent the muscarinic effects of edrophonium. Ten mg of edrophonium were diluted to 10 ml with saline and injected in divided samples of which the first was 1 mg, the test dose. The protocol was then patient dependant. In most patients 3 injections, each of 3 mg, were then given and saccades were recorded 5 to 10 seconds after each injection and then repeatedly. Ten or more saccades were examined on the oscilloscope after each in-

jection. Examples were stored for future analysis, at which time the trajectory of each saccade was plotted on a digital plotter. When a response was obtained following an injection of 1 mg the same procedure was repeated with further injections each of 1 mg. This system accurately records the movement of each eye to 15 minutes of arc. The criterion for a positive response chosen in the present study was an increase in the amplitude of the saccades of the fixating eye by 10% or more after each of several injections of dilute edrophonium (Figures 2a, 2b). For the purpose of this study the criterion of fatigue was a decrease in the amplitude of the saccade of the fixating eye to the side of previous prolonged gaze of 10% or more.

Results

Infrared oculography edrophonium test

The edrophonium infrared oculography test was positive in 10 patients of whom 5 (Cases 1,2,3,12,13) had worn prisms for years to control diplopia. In 3 of the 5 patients the diplopia was becoming increasingly difficult to control. Case 1 subsequently developed severe generalized myasthenia gravis which was controlled with immunosupressive therapy. Examination of Case 2 revealed very mild weakness of peripheral muscles. The electromyography test was positive; the diplopia responded to pyridostigmine. In Case 3 the vertical diplopia was readily controlled with pyridostigmine. Prisms controlled the fixed ophthalmoplegia of Cases 12 and 13. The 12th patient preferred wearing prisms to taking pyridostigmine; the diplopia in Case 13 failed to respond to pyridostigmine.

Case 4 presented with fixed ophthalmoplegia for 4 weeks. The diagnosis of myasthenia gravis was supported by the positive response to pyridostigmine and by the positive test for antibodies to acetylcholine receptor.

Of the 10 patients in whom the response to edrophonium infrared oculography was positive, 4 presented with ptosis (Cases 5,6,7,11). Of these, 3 patients (Cases 5,6,7) had clinical signs of generalized myasthenia gravis which responded to pyridostigmine. The ptosis resolved spontaneously within one month in Case 11.

Case 8, a 75 year old farmer, had had recurrent attacks of diplopia but during previously recorded attacks the clinical signs were characteristic of an attack of an isolated palsy of one lateral rectus muscle. The recent attacks of momentary diplopia which had troubled him for one month resolved with pyridostigmine.

Case 9 presented with a 5 month history of intermittent diplopia which also responded to pyridostigmine. During the edrophonium infrared oculography test the saccades of the fixating eye in Case 9 responded to injections of 1 mg of dilute edrophonium.

Case 10 presented with 3 weeks of diplopia. The examination revealed ophthalmoplegia limited to the right eye, without ptosis. This patient had a past history of diplopia in childhood for which he had had strabismus surgery. Ptosis in childhood was recorded and was considered to be congenital. This patient had an abnormal level of antibodies to acetylcholine receptor. The ophthalmoplegia responded to prednisolone but not to pyridostigmine.

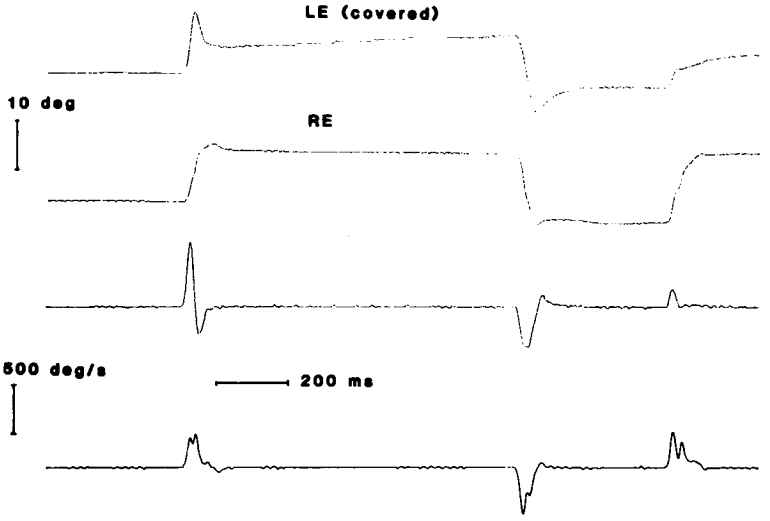

Figure 2a. Illustrates a 10° saccade from centre to left in Case 1. Note the left eye cannot fully abduct and cannot sustain the abduction achieved. The right eye overshoots the 10° mark to a minor extent. The movements are not conjugate. Note irregularities in the trajectory of the movement of the right eye, irregularities which are seen more clearly in the velocity tracing. These irregularities are common in patients with ocular myasthenia.

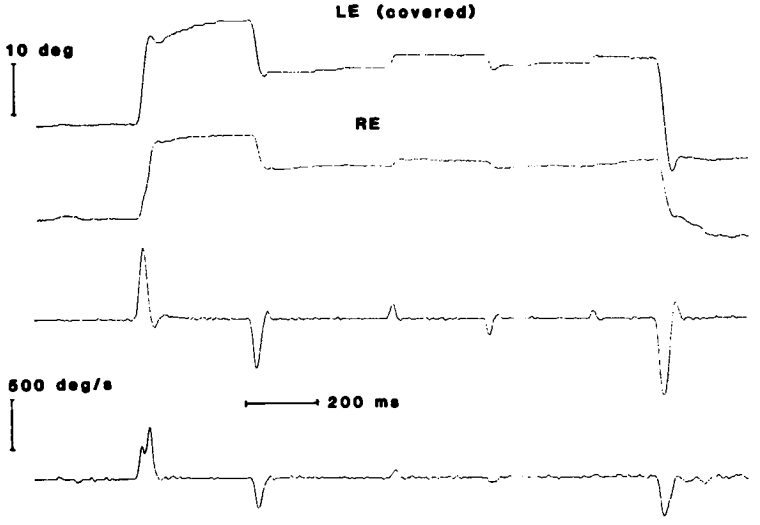

Figure 2b. Demonstrates 10° saccadic eye movements from centre to left in Case 1 5 seconds after the intravenous injection of edrophonium. Note an increase in the range of the movement of the right eye of 60%; the eye then returns to the 10° mark. The covered eye also increases its range of movement by 80%. This overshoot is the classic response to edrophonium in patients with ocular myasthenia.

In Figures 2a and 2b the top 2 tracings record the movements of the left eye and right eye respectively. Upward deflections on the page represent movements of each eye to the left and downward deflections, movements to the right. The bottom 2 tracings in each figure record the velocities of the left (above) and right (below) eyes respectively.

The edrophonium infrared oculography test was negative in 13 patients, in 10 of whom the basis of the diplopia or ptosis was explained by the diagnosis reached (Table 2) (Cases 14,15,16,17,18,19,20,21,22,23). None was considered to have myasthenia gravis (Figures 3a, 3b). In case 24 the diplopia resolved spontaneously before the test. In Case 25 a positive response to edrophonium was noted in the non-fixating eye — a response excluded by the criterion accepted as positive for the infrared oculography edrophonium test in this study. In Case 26 fatigue but no response to edrophonium was demonstrated.

Fatigue tests

Prolonged eccentric gaze to one side was followed by a hypometric saccade with a reduced amplitude of 10% or more to the same side in 8 patients who responded positively to intravenous edrophonium (Case 1,3,4,8,10,11,12,13). Of these 8 patients, edrophonium prevented fatigue in 4 (Cases 8,10,11,12).

Of the 13 patients with a negative response to edrophonium, fatigue was induced in 4 (Cases 19,20,21,25) and in these 4 patients edrophonium failed to prevent fatigue.

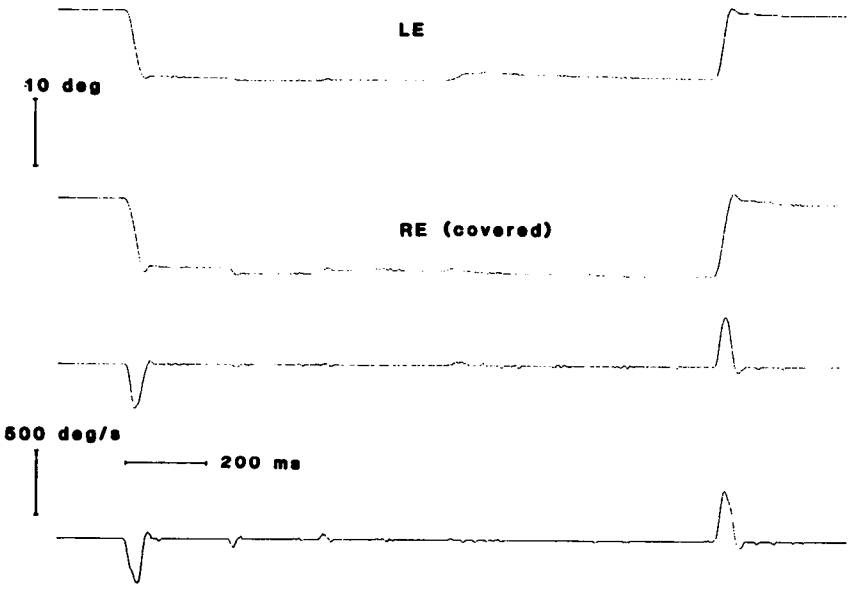

Figure 3(a). Illustrates a 10° saccade from centre to right in Case 21. Note the eyes move to the right conjugately.

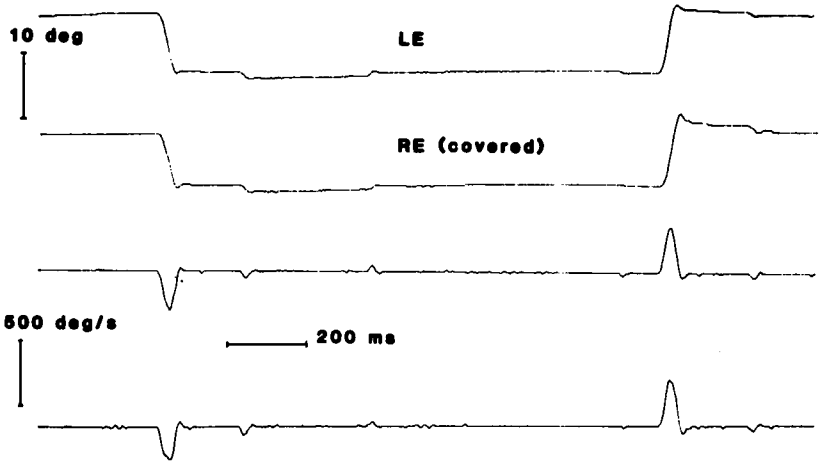

Figure 3(b). Demonstrates no change in the 10° saccadic eye movements from centre to right in Case 21 after the intravenous injection of edrophonium. Note the velocity tracing for each eye is virtually identical and without irregularities.

In Figures a and b the top 2 tracings record the movements of the left eye and right eye respectively. Upward deflections on the page represent movements of each eye to the left and downward deflections movements to the right. The bottom 2 tracings in each figure record the velocities of the left (above) and right (below) eyes respectively.

Discussion

Myasthenia gravis is an autoimmune disease which affects the neuromuscular junction and is defined in clinical, immunological, pharmacological and neurophysiological terms. The cause is unknown. Probably myasthenia gravis is more common than indicated by the estimated prevalence of 0.5-5/100,000[5].

The differential diagnosis of myasthenia gravis is broad. Many disorders cause diplopia, ptosis and muscle weakness. In the majority of patients the history and signs of muscle fatigability and the variation of muscle weakness leave the clinician in little doubt about the diagnosis. However some patients with myasthenia present with fixed ophthalmoplegia. The results of this study indicate myasthenia gravis may not be detected because the intravenous edrophonium test which relies on the clinical observation of the response of eye movements to tensilon may fail to demonstrate the response (Cases 1 and 4).

Again in this study the positive lid twitch characteristic of myasthenia gravis[6] (in the absence of fatigue induced by prolonged upward gaze) proved to be a valuable clinical sign of myasthenia gravis but was curiously absent in Case 1. Prolonged upward gaze readily induced a lid twitch, caused or aggravated ptosis and induced diplopia in patients in whom the diagnosis of myasthenia gravis was determined, but also in patients with ptosis and diplopia due to causes other than myasthenia gravis. Assessment of the weakness of the orbicularis oculi muscles was difficult because this test relies on the effort exerted by patients. A positive peek sign[7] was noted in Case 7 and surprisingly was absent at the first visit in other patients (Table 1).

Table 1. Diplopia and/or ptosis: edrophonium infrared oculography

Case No.	Age/Sex (yrs)	Clinical Presentation	LT	LTF	PF	DipF	OW	Edrophonium IRO test
1.	77M	3 yr ago RLR palsy; control of horizontal diplopia with prisms increasingly difficult. Previous edrophonium test negative. Exam L/R; bilateral LR palsy	-	-	-	-	-	+
2.	58/F	8 yr RLR palsy; control of diplopia with prisms increasingly difficult	+	+	+	-	-	+
3.	66/M	2 yr vertical diplopia; control with prisms increasingly difficult	+	+	-	-	-	+
4.	77/M	4 w vertical diplopia of sudden onset; R/L each position of gaze; unchanging. Previous edrophonium test negative	+	+	-	-	+	+
5.	48/F	12 mo bilateral variable ptosis. Palpebral fissures R 8mm L 6mm	+	+	-	+	+	+
6.	54/F	3 mo L ptosis. Palpebral fissures R 5mm L 3mm	+	+	+	-	-	+
7.	57/F	2 mo intermittent L ptosis. Palpebral fissures R 9mm L 9mm	-	+	+	-	+	+
8.	75/M	4 yr 6mo ago RLR palsy for 4 mo; 2 yr 3 mo ago diplopia for 2 w; 2 yr ago LLR palsy for 4 mo; for 1 mo attacks of momentary diplopia. Exam underaction RSR, LMR.	+	+	+	-	+	+
9.	59/M	5 mo intermittent vertical diplopia	-	+	-	-	+	+
10.	34/M	3 w widespread ophthalmoplegia of R eye only, no ptosis; 18 yr ago slight R ptosis RIR paresis treated with RSR recession	-	+	-	-	+	+
11.	74/F	2 yr R intermittent ptosis. Palpebral fissures R 5mm L 6mm	-	+	-	-	-	+
12.	71/F	3 yr vertical diplopia. L/R each position of gaze	-	+	+	-	-	+
13.	33/M	10 yr diplopia; tired chewing. R/L each position of gaze	-	-	-	-	+	+
14.	26/F	3 days bilateral weakness lower limbs, paraesthesiae of fingers, mild LLR palsy and R/L	-	-	+	-	+	-
15.	69/F	1 mo R ptosis, 8 yr muscles weakness; vertical diplopia L/R. Mild wasting of small muscles of L hand. Palpebral fissures R 9mm L 11mm	-	+	+	-	-	-
16.	60/F	1 mo bilateral SO weakness	-	-	-	-	-	-
17.	49/F	1 mo momentary attacks vertical diplopia. L internuclear ophthalmoplegia	-	-	-	-	-	-
18.	76/M	Mild bilateral intermittent ptosis. 9yr LSO palsy.	-	+	+	-	+	-

Table 1. continued.

Case No.	Age/Sex (yrs)	Clinical Presentation	LT	LTF	PF	DipF	OW	Edrophonium IRO test
19.	67/F	12 mo R ptosis. Severe head injury aged 12 yrs. R homonymous visual field defect,L third cranial nerve palsy, RSR palsy, bilateral partial ptosis. Palpebral fissures R 2mm L 4mm	-	-	-	-	+	-
20.	26/M	6 mo intermittent diplopia	-	+	-	-	-	-
21.	65/M	4 mo ago intermittent diplopia over 2 mo Palpebral fissures R 13mm L 10mm	-	-	-	-	-	-
22.	48/F	3 mo intermittent horizontal diplopia, 4 mo ago cervical sprain. Palpebral fissures R 9mm L 7mm	-	-	-	+	+	-
23.	69/M	15 mo diplopia horizontal & vertical R/L in evenings. 5 mo ago cervical sprain	-	+	+	-	+	-
24.	41/M	3 yr difficulty achieving binocular vision Palpebral fissures R 10mm L 9mm	-	-	+	+	-	-
25	63/F	2 mo difficulty achieving single binocular vision. 10 yr R ptosis Palpebral fissures R 5mm L 8mm	-	-	+	-	-	-
26	49/F	18 mo R ptosis. Palpebral fissures R 6mm L 8mm	-	+	+	-	+	-

LT = lid twitch; LTF = lid twitch after fatigue; PF = ptosis induced or aggravated by fatigue; DipF = diplopia induced by fatigue; OW = orbicularis oculi weakness; LR = lateral rectus; SR = superior rectus; MR = medial rectus; IRO = infrared oculography; SO = superior oblique.

The positive peek sign was noted subsequently in several patients.

In this study infrared oculography demonstrated the fine detail of saccades and identified the increased amplitude of saccades of the fixating eye after intravenous edrophonium in half the patients tested. Although the high bandwidth employed (100 Hz) allowed documentation of waveforms of the saccades characteristic of myasthenia gravis, neither the characteristic waveforms nor fatigability induced by prolonged gaze to one side were as helpful in identifying the neuromuscular junction defect as the response of the saccades of the fixating eye to intravenous edrophonium. The test demonstrated very clearly the uneven responses of eye movements to edrophonium — responses which often cannot be detected by clinical observation. In some patients the increased range of movement of one eye after edrophonium exceeded that in the second eye moving conjugately so that the apparent clinical result was an aggravation of the diplopia.

The infrared oculographic system used in this study accurately reveals eye movements as small as 0.25° and has very little noise. The linear range for horizontal eye movements recorded is ± 15°. Most saccadic eye movements are 15° or less.

Whereas the majority of 10° saccades are accurate in normal alert patients, the accuracy of saccades varies greatly in fatigued subjects. In this study repeated responses of the saccades of the fixating eye to edrophonium were used to decrease the possibility of isolated inaccurate saccades being misinterpreted as a positive response. To confirm that the neuromuscular junction defect (identified by the response to edrophonium) was due to myasthenia gravis, evidence was sought from the clinical picture which evolved, in particular a definite clinical response to oral pyridostigmine, from serum antibody levels to acetylcholine receptor and to striated muscle, and from electromyography. In many patients the ocular symptoms of myasthenia are not fully controlled with pyridostigmine. In this study of 7 patients who developed clinical signs of generalized myasthenia gravis 6 responded to pyridostigmine. The patient whose clinical symptoms and signs failed to respond to pyridostigmine did have an elevated level of serum antibodies to acetylcholine receptor and was considered to have myasthenia gravis (Tables 2 and 3).

In 3 patients (Cases 3,4,9) the symptoms and signs of myasthenia were strictly confined to the extra-ocular muscles and responded to pyridostigmine. In Case 4 the serum antibody level to acetylcholine receptor was raised and in Cases 3 and 9 the level was normal. The incidence of raised serum levels of antibody to acetylcholine receptor and to striated muscle is less in patients with ocular myasthenia than in patients with generalised myasthenia. The incidence reported varies [8][9]. We suspect ocular myasthenia and mild generalised myasthenia are commoner than realised and in these patients antibody levels may remain within normal limits.

The result of repetitive stimulation electromyography is positive in 30% of patients with ocular myasthenia[9] whereas in patients with generalised myasthenia the result is positive in 60%[9]. Single fibre electromyography (a less specific test for myasthenia) is positive in 84% of patients with ocular myasthenia and 94% of patients with generalised myasthenia[9]. In the 10 patients included in this report repetitive stimulation electromyography was positive in one patient (Case 2) and single fibre electromyography was positive in one patient (Case 1).

A decrease in the amplitude of the saccade of the fixating eye to the side of previous prolonged gaze of 10% or more was less reliable in identifying a neuromuscular junction defect than repeated increases in the amplitudes of saccades of the fixating eye following an intravenous injection of edrophonium. Similarly prevention of fatigue by intravenous edrophonium was an unreliable indicator of a neuromuscular junction defect. However we noted that a saccade with a reduced amplitude of 20% or more after prolonged gaze to the ipsilateral side occurred only in patients who subsequently had a positive response to edrophonium (Cases 1,4,8,10,12,13).

Although in this series computed tomography of the chest failed to reveal thymic enlargement in any one of the 10 patients found to have myasthenia gravis, the infrared oculographic test has led to the diagnosis of myasthenia gravis in 3 other patients in whom computer tomography of the chest identified thymic enlargement. Of these 3 patients 2 harboured a tumour — one a thymoma and the other a thymic seminoma[10]. The thymic enlargement in the third patient was due to thymic hyperplasia. More commonly myasthenia gravis has been identified in patients previously thought to have symptoms without an organic lesion.

Table 2. Investigations and follow-up

Case No.	Age/Sex Yr	AcChR AB	Str.Musc AB	EMG	CT scan chest	Follow-up
1.	77/M	+	+	+*	-	9 mo. Generalized myasthenia controlled with prednisolone, azathioprine and pyridostigmine
2.	58/F	-	-	+	-	12 mo. Mild generalized myasthenia controlled with pyridostigmine
3.	66/M	-	-	-	-	8 mo. Diplopia controlled with pyridostigmine
4.	77/M	+	-	-	-	12 mo. Diplopia controlled partially with pyridostigmine; spontaneous remission after 4 mo
5.	48/F	-	-	-	-	12mo. Mild generalized signs mainly controlled with pyridostigmine
6.	54/F	-	+	-	-	2 yr 5 mo. Mild generalized myasthenia controlled with pyridostigmine
7.	57/F	-	-	-	-	2 yr. Moderately severe generalized myasthenia controlled with pyridostigmine
8.	75/M	-	-	-	-	8 mo. Moderately severe generalized myasthenia controlled with pyridostigmine
9.	59/M	-	-	-	-	1 yr 2 mo. Diplopia controlled with pyridostigmine
10.	34/M	+	-	-	-	8 mo. Mild generalized myasthenia, no response to pyridostigmine, controlled with prednisolone
11.	74/F	-	-	-	-	12 mo. Ptosis resolved spontaneously
12.	71/F	-	-	-	-	10 mo. Diplopia controlled with prisms
13.	33/M	-	-	-	-	10 mo. Diplopia controlled with prisms

* = single fibre electromyography; CT = computer tomography; Excepting Case 1, all patients were tested with repetitive stimulation electromyography of proximal and ocular muscles.

Table 3. Follow-up and diagnosis

Case	Age/Sex	Follow-up	Diagnosis
14.	26/F	Diplopia resolved in 2 w	Guillain Barré syndrome; recovered in 2 mo
15.	69/F	Signs unchanged in 6 mo	Peripheral neuropathy
16.	60/F	Diplopia resolved in 4 mo	Probable ischaemic mononeuropathies
17.	49/F	Resolution in 2 mo	Left internuclear ophthalmoplegia; probable brainstem infarct
18.	76/M	Unchanged in 3 mo	Ptosis due to senescence with R pseudoptosis when left superior oblique paretic eye fixated
19.	67/F	Signs unchanged after 12 mo	Probable longstanding ptosis due to brain injury
20.	26/M	2 mo signs unchanged	Heterophoria at times becoming manifest
21.	65/M	2 mo diplopia resolved	Heterophoria at times becoming manifest
22.	48/F	Unchanged over 3 mo	Heterophoria at times becoming manifest
23.	69/F	Unchanged over 1 mo	Heterophoria at times becoming manifest
24.	41/M	Symptoms resolved over 2 mo	Cause uncertain
25.	63/F	13 mo. No change	Cause uncertain
26.	49/F	No change in 12 mo	Cause uncertain

We conclude that the infrared oculography edrophonium test is helpful in identifying a neuromuscular junction defect, the commonest cause of which is myasthenia gravis. As with the routine clinical edrophonium test the diagnosis of myasthenia must be confirmed by the clinical findings and, in some patients, by an assay of antibody to acetylcholine receptor or by electromyography. We are investigating the results of the test in normal subjects and in patients known to have mysathenia gravis (but who have not been treated) in order to establish the incidence of false positive and false negative results. At present the infrared oculography test is much more definite in identifying a positive response to edrophonium than the routine clinical edrophonium test.

Summary

The response of eye movements to edrophonium is easily missed by clinical observation alone. Binocular horizontal ten degree saccades were recorded by infrared oculography, whilst the vision of one eye was occluded, before and after (i) fatigue (ii) repeated intravenous injection of dilute edrophonium, and (iii) fatigue induced during anticholinesterase inhibition by intravenous edrophonium, in 26 patients with diplopia or ptosis of uncertain aetiology.

The most reliable criterion of a positive response was an increase in the amplitude of the saccades of the fixating eye by 10% or more after each of several injections of dilute edrophonium. The response was positive in 13 patients and was difficult to observe clinically (i) when the responses of the saccades of the eyes moving conjugately were unequal and (ii) when the patient presented with ptosis and no diplopia. Edrophonium infrared oculography proved to be a sensitive test for weakness due to the neuromuscular junction defect of myasthenia gravis affecting extraocular muscles.

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A Case of Invasive Thymoma associated with Myasthenia Gravis, Myositis and Demyelinating Neuropathy

H. Miller, B.D. Shenstone†, R. Joffe* and S. Kannangara†*

Thymoma has been associated with neurological syndromes[1], mostly myasthenia gravis and polymyositis. Involvement of peripheral nerve has also been described[2,3,4], but not characterised on biopsy as being of axonal or demyelinating types. We here describe a patient with locally invasive thymoma associated with the triad of polymyositis, myasthenia gravis and biopsy-proven demyelinating peripheral neuropathy.

Case Report

A 56 year old male auditor was admitted on 1.3.84 with a 2 month history of muscle stiffness and tenderness, initially near his ankles which later spread to the thighs and forearms. This was associated with weakness. He reported occasional rigors and night sweats but no weight loss. He had smoked till 1978. He drank 1 bottle of wine per day till 4 weeks prior to admission. His only medication was occasional paracetamol. He had had bleeding per rectum for 10 years; investigation had shown haemorrhoids only.

On examination his temperature was 37.4°C. Abnormalities were confined to his neuromuscular system. There was muscle tenderness of his thighs, calves and forearms with woody masses in right thigh and right forearm. Sensation appeared normal. No tendon jerks could be elicited except at his knees. Moderate weakness was noted in areas of muscle pain. His joints appeared normal.

Initial investigations were as follows: Creatine phosphokinase 45 IU/L (normal); no myoglobin in urine; erythrocyte sedimentation rate (Westergren) elevated at 53 mm/hr; alkaline phosphatase 160 IU/L (upper limit of normal 130); alanine transaminase 225 IU/L (upper limit 55); ECG normal. Initial nerve conduction studies: Left sural latency not obtained (amplitude of action potential too low). Left lateral popliteal nerve velocity 33 m/sec (normal is greater than 44). Left median nerve velocity 43 m/sec (normal is greater than 49).

EMG of left triceps humeri and left quadriceps femoris showed electrical silence at rest. On exertion there was a mildly disrupted low amplitude (1-2 mV) interference pattern, suggestive of myopathy. Muscle biopsy of a lump in right palmaris longus muscle revealed necrotic muscle.

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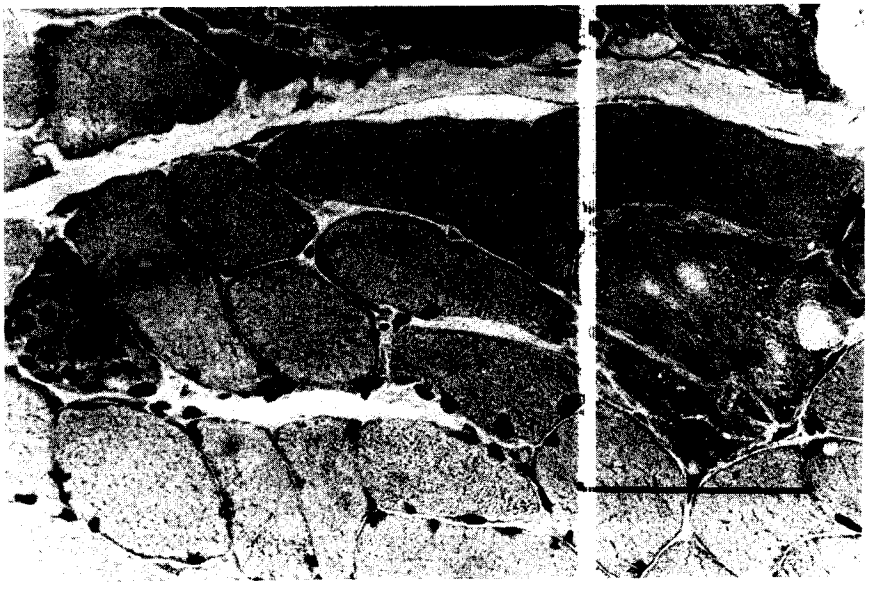

Figure 1. Normal sural nerve stained with osmium to show myelin. Scale equals 100 μm.

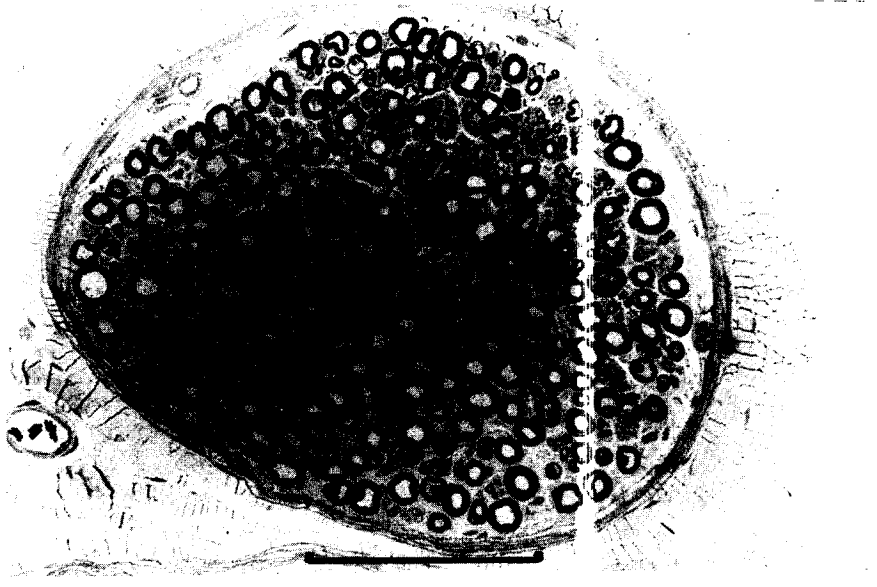

Figure 2. Right vastus lateralis muscle biopsy. At the left of the field is a muscle fibre undergoing phagocytosis. Above the scale is a fibre exhibiting vacuolation. Scale equals 100 μm. Frozen section, haematoxylin and eosin.

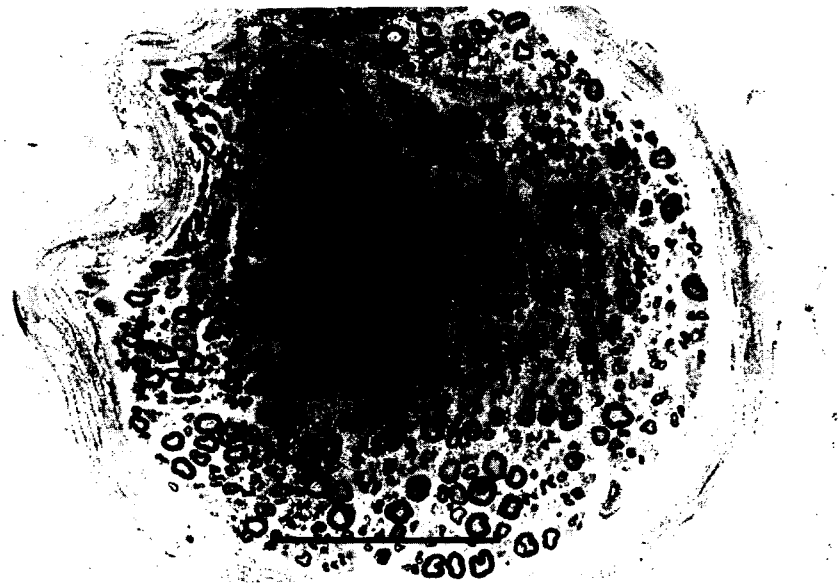

Figure 3. The patient's right sural nerve, stained under the same conditions as in Figure 2. Note the excessive proportion of unmyelinated and thinly myelinated fibres. Scale equals 100 μm.

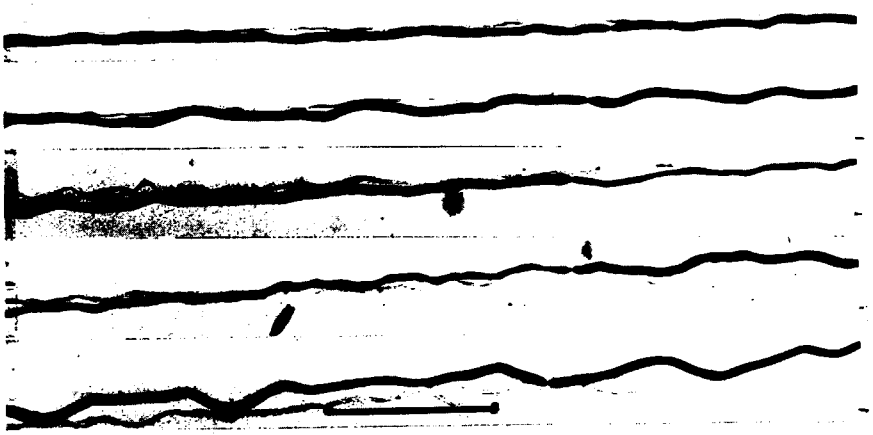

Figure 4. Teased sural nerve fibre showing demyelinated segment. Osmium tetroxide. Scale equals 200 μm.

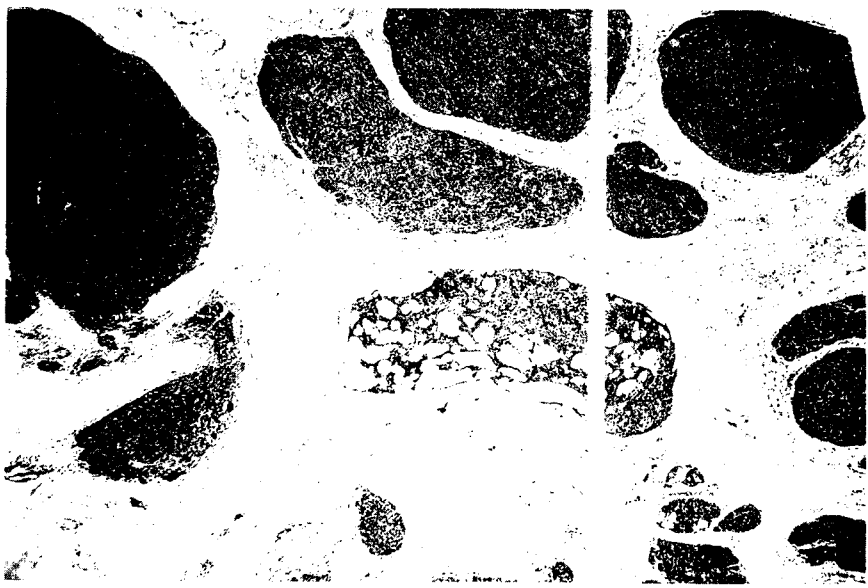

Figure 5. Section of thymoma removed from the patient. Note the multinodular appearance. The nodule in the centre shows a vacuolated gland-like appearance. Haematoxylin and eosin × 25.

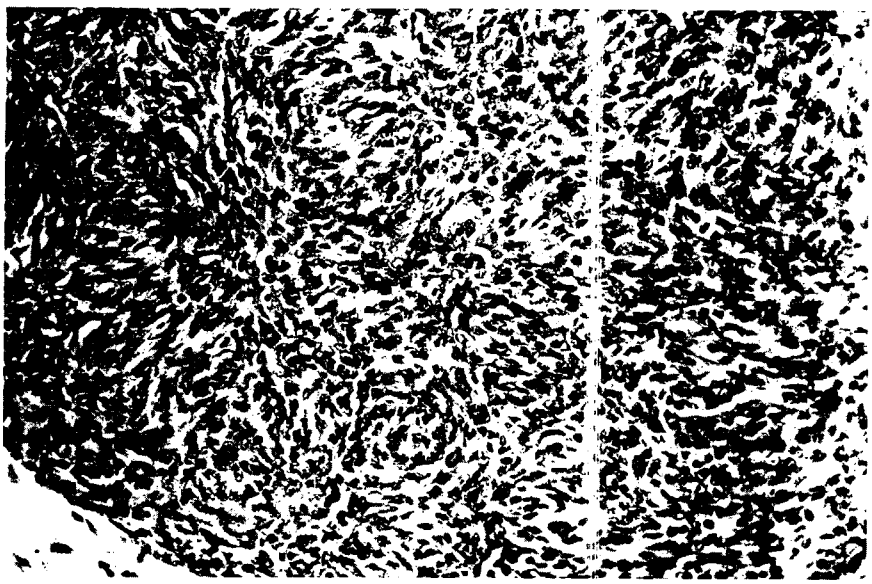

Figure 6. Higher power section of the tumour from the vacuolated nodule. Note the predominance of epithelioid spindle cells with scattered lymphocytes. Haematoxylin and eosin × 250.

Progress

Prednisolone therapy 100 mg per day was commenced on 8.3.84. 2 days later he noticed the onset of dyspnoea and nasal regurgitation of food and had an episode of diplopia. His muscle tenderness and masses resolved within 4 days of steroid therapy being started.

At examination on 12.3.84 he could not stand or lift his arms; his head was slumped forward onto his chest. The sensorium was clear. No bulbar or extraocular muscle weakness was demonstrated. He required endotracheal intubation and ventilatory support for 10 days. An initial edrophonium test (10 mg given intravenously) was negative but a later trial of edrophonium produced a doubling of his forced expiratory flow rate. Ptosis became evident later. It could be worsened by prolonged upward gaze and was markedly improved by intravenous edrophonium. An EMG on 15.3.84 suggested polyneuropathy with profuse fibrillation and a marked decrease in amplitude and number of motor units on contraction. A myasthenia protocol of repeated ulnar nerve stimulation (abductor digiti minimi, stimulation rate 5 Hertz) showed a decremental muscle response of 15 to 28% over 9 trials. After intravenous edrophonium this changed to a range of zero to 17% decrement over 17 trials. Acetylcholine receptor antibody was present at a high level of 50 nM (normal range less than 0.5 nM). Skeletal (striated) muscle antibody was strongly positive at a 1:160 titre. The CSF was clear with 2 white and 5 red cells per cubic millimetre. CSF protein was normal at 0.20 g/L. Antinuclear antibody, rheumatoid factor and hepatitis B surface antigen were negative. Thyroid function tests, blood sugar, serum electrophoretogram, serum complement levels and urinary heavy metal levels were all within normal limits. Computerised tomography of the thorax was reported as showing no evidence of thymoma.

On 22.3.84 a right vastus lateralis muscle biopsy was performed. It showed changes consistent with, but not diagnostic of, polymyositis (Figure 1). Right sural nerve biopsy showed segmental demyelination (Figures 2,3,4). He gradually improved on corticosteroids and pyridostigmine and was discharged. Outpatient follow-up showed return of lower limb tendon reflexes by mid April and upper limb reflexes some months later. The initial improvement was not sustained, difficulty in chewing being his main problem. He was given a course of plasmapheresis in July 1984 with marked clinical improvement and subsequently submitted to thymectomy. A thymoma was found invading the pleura and left phrenic nerve (Figures 5,6). 4000 Rads of radiotherapy was given to his mediastinum postoperatively. His subsequent course has been of steady improvement, with a return to gardening activities.

Discussion

The patient was ultimately found to have invasive thymoma at operation. Klein et al.[5] described 2 very similar cases, but without neuropathy; their patients' muscle pain and oedema had a similar dramatic response to corticosteroid therapy.

The initial differential diagnosis of this patient's illness included alcohol-induced myositis and neuropathy. His alcohol intake of about 90g per day had stopped completely a month before the onset of symptoms. Histological features of alcoholic neuropathy are generally those of axonal degeneration, though segments of nerve are seen where myelin is greatly thinned and the axis cylinders are preserved[6]. The clinical onset of myasthenia gravis occurred shortly after the introduction of corticosteroid therapy. Corticosteroids are well known to worsen myasthenia gravis[7]. We are not aware of any previous description of this combination of syndromes.

Summary

A 56 year old male presented after 2 months of muscle stiffness, pain and palpable lumps. Biopsy confirmed the presence of myositis. Myasthenia gravis and peripheral neuropathy became clinically apparent within days of commencing corticosteroid therapy. 4 months later, at operation, a locally invasive thymoma was found. This combination of features has not previously been described.

Acknowledgements

We wish to thank J. Baverstock, J. Walsh, J. Pollard, K. Kneale, R. Mackenzie, O. Peiris and G. Nicholson for help in preparing material used in this article, and D. Galey for the typing.

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Chronic Subdural Haematomas presenting with Parkinsonian Signs

R.F. Peppard, E. Byrne* and D. Nye†*

We wish to draw attention to a rare presentation of chronic subdural haematomas by describing 2 patients, each of whom developed a Parkinsonian syndrome which remitted after evacuation of a chronic subdural haematoma. The importance of recognition of chronic subdural haematomas rests on their favourable prognosis with timely operative intervention.

Diagnosis of chronic subdural haematoma in an elderly population may occasionally present difficulties for several reasons. These include the variability in symptoms and signs of this disorder, the chronic course with an insidious onset of symptoms, the frequent lack of a history of significant head trauma and the overlap of the symptoms with those of cerebral degenerative diseases. Focal signs typically occur late in the course of the disorder. Pyramidal signs are commonly seen but extrapyramidal system involvement is not stressed in the many large series of chronic subdural haematomas which have been reported[1,2].

Case Reports

Case 1

The first case was a 73 year old man who was assaulted in the street. He was struck heavily on the left forehead and briefly lost consciousness. At the time he was assessed in a casualty department and then discharged. 6 weeks later he started to develop a shuffling gait and a bilateral resting tremor in the hands. A diagnosis of Parkinson's disease was made initially but over the next week a further deterioration in his gait occurred and he was referred to a neurologist. As well as difficulty in walking he complained of bifrontal headaches from the time of the head injury.

On examination, he was unable to stand or walk unaided, but with assistance could take a few shuffling steps. He had a tendency to fall backwards. His face was expressionless and his speech soft. There were no other cranial nerve abnormalities. A resting tremor of both arms was present and moderate cog-wheel rigidity was noted in all limbs. Power in the limbs was normal. The deep

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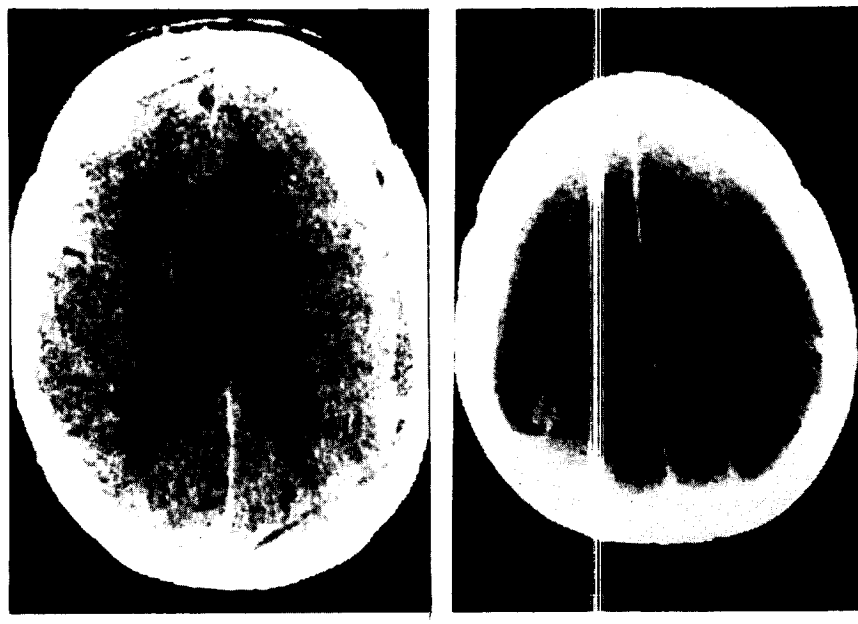

Figure 1A, 1B. Left temporo-parietal and right posterior parietal chronic subdural haematomas.

tendon reflexes were normal and symmetrical but the plantar responses were extensor bilaterally. There was a marked grasp response in both hands.

A CT head scan (Figure 1) was performed. It demonstrated a chronic subdural collection of moderate size over the left temporo-parietal region causing compression and displacement of the left lateral ventricle. There was also evidence of a moderate subdural collection in the right posterior parietal region. Craniotomy was performed and the left subdural haematoma, which extended over the temporal and frontal lobes, was evacuated.

Confusion and generalised cog-wheel rigidity persisted after this procedure and another CT scan showed a large air collection in the left subdural space. Further evacuation of both subdural spaces and ventricular cannulation to expand the left hemisphere was performed. Following this he made a steady recovery with return of muscle tone to normal, resolution of tremor and improved gait. It was possible to discharge him 10 days after operation. 2 months later there was no sign of Parkinsonian features.

Case 2

The second case was a 61 year old man who lost consciousness for half an hour as a result of a head injury sustained in a car accident. Over the next 4 months he noticed that his walking became increasingly unsteady. He had persistent headache, worse on the right side, from the time of the accident.

On examination he had a shuffling gait with a loss of postural reflexes and difficulty in turning. He had a mask-like facial expression but his cranial nerves were otherwise intact. There was no papil-

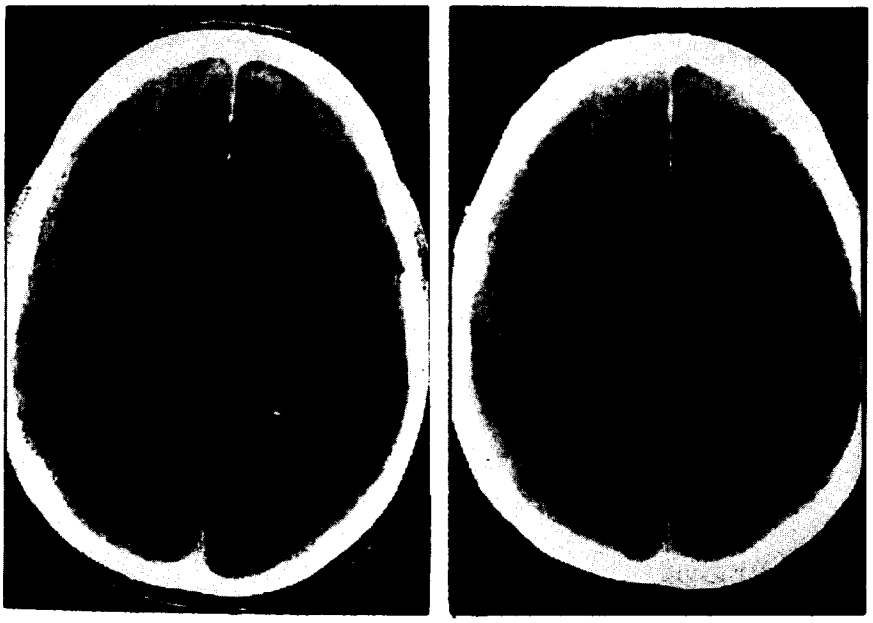

Figure 2A, 2B. Right chronic subdural haematoma.

loedema. He had mild cog-wheel rigidity around the left wrist, but tone was normal elsewhere in the limbs. The plantar responses were flexor.

CT head scan (Figure 2) demonstrated a right chronic subdural collection causing compression and displacement of the right lateral ventricle. Through a frontal burr hole a moderate-sized subdural haematoma was drained. One week after the operation he had made a good recovery. He was walking well and power and tone in all limbs was normal.

Discussion

Both patients presented with increasing difficulty in walking and also had persistent headache following head injuries with brief loss of consciousness. They had expressionless faces and shuffling gaits typical of Parkinson's disease. The first case also demonstrated a bilateral resting tremor in the hands and rigidity in all limbs, while the second case had cog-wheel rigidity around the left wrist. As well, the first case had bilateral extensor plantar responses and grasp reflexes — signs not usually seen early in the course of paralysis agitans. Both had initially been suspected of having idiopathic Parkinson's disease but their rapid deterioration led to neurological referral and further investigation. Evacuation of subdural collections was followed by resolution of the extrapyramidal signs.

One other patient with an atypical Parkinsonian presentation of a chronic subdural haematoma was reported by Sandyk[3]. This case was a 66 year old man who presented with headaches, confusional episodes, unsteady gait and tremor of the left arm developing over 4 months. Parkinson's disease was diagnosed and there was an initial improvement with L-Dopa therapy until increasing confusion developed. On examination there was a "frozen" facial expression, resting tremor of both upper limbs and cog-wheel rigidity of the left wrist as well as left hemiparesis. A left subdural haematoma was found on CT scan. Following removal of the haematoma, the extrapyramidal symptoms disappeared.

From these cases we consider that the following features should lead to suspicion that a Parkinsonian syndrome could be due to a chronic subdural haematoma: recent head injury, persistent headache, rapid progression of disability, associated non-Parkinsonian signs, and predominant gait disorder with axial involvement. Other causes of an atypical Parkinsonian syndrome which enter the differential diagnosis in such circumstances include drug-induced Parkinsonism, normal pressure hydrocephalus, vascular events, and brain tumour. It is of interest that acute onset Parkinsonism has recently been described by Tolosa and Santamaria[4] in 3 patients with CT scan evidence of bilateral basal ganglia infarcts. Their patients improved spontaneously, thus excluding a diagnosis of idiopathic Parkinson's disease

It is well established that brain tumours may rarely cause Parkinsonism. This has been described with gliomas involving the basal ganglia and thalamic region directly and with intracranial tumours at a distance from the substantia nigra or basal ganglia, including meningiomas in frontal, temporal, basal and parasagittal sites and deep tumours involving the pituitary region[5,6]. The following mechanisms which have been proposed to explain the development of Parkinsonism secondary to brain tumours may also apply to subdural haematomas. These include compression of the basal ganglia, compression of the midbrain by a transtentorial pressure cone or impairment of cortically-originating extra-pyramidal fibres. Resolution of Parkinsonian features has followed resection of meningiomas over the convexity of the cerebral hemispheres. Parkinsonian signs have also appeared in association with other clinical features of midbrain compression by a suspected transtentorial pressure cone and were improved with reduction in intracranial pressure[7].

A case of Parkinsonism in association with a large craniopharyngioma has been described[6] in which morphological examination revealed atrophy of the substantia nigra without Lewy bodies and biochemical studies showed reduced dopamine levels and reduced dopamine receptor sites in the putamen and caudate nuclei. In this case it was felt that the Parkinsonism was caused by basal ganglia compression which damaged both the presynaptic dopaminergic nigrostriatal neurons and the postsynaptic dopamine receptors. The extrapyramidal dysfunction described here with chronic subdural haematomas may be attributed to similar mechanisms to those which occur with brain tumours.

The majority of patients with a similar sized subdural collection do not develop a predominant Parkinsonian syndrome and we postulate that our patients may have a mild Parkinsonian tendency which has been unmasked by basal ganglia compression. This hypothesis will be confirmed if they subsequently develop idiopathic Park-

inson's disease. Subdural haematoma is a rare cause of an extrapyramidal syndrome. The patients presented add further support to the clinical impression that patients with rapidly progressive atypical Parkinsonism need further investigation.

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Global Stereopsis in Stroke Patients

B. Fenelon, K. Grant†, A. Delahunty*, R. Neill*, D. Dunlop*, P. Dunlop*, B. Frost* and A. Quayle**

A review by Brain[1] of case reports on visual disorientation revealed only a few instances in which a marked loss of stereoscopic vision had occurred in patients. The cited cases were originally reported by Riddoch in 1917 and Holmes and Horrax in 1919. The lesion in the single case reported by Holmes and Horrax involved both angular gyri.

The development of new techniques of assessing stereopsis led to the discovery of deficit in a large proportion of brain-lesioned subjects. Carmon and Bechtoldt[2] tested a group of right-hemisphere lesioned patients using static random-dot letter stereograms and found striking impairments of stereoscopic vision. The conclusion reached, that the right hemisphere plays a dominant role in stereopsis, began a controversy which has not been resolved to the present. A study by Benton and Hécaen[3] supported the Carmon and Bechtoldt position, although the more cautious interpretation of the data which they offered was that the right hemisphere plays an essential role in the realization of stereoscopic vision. Part support also came from Durnford and Kimura[4] who found that briefly exposed random dot stereogram forms were fused better by normal subjects when they were presented in the left visual field. (It should be noted that, in the view of Julesz[5], stereopsis is a more general function than fusion.)

Contradictory evidence was then presented by Rothstein and Sacks[6] who, using the Titmus Stereotest, found in a mixed group of right hemisphere vascular disease and tumour cases that damage to the left parietal lobe appeared to be related to a greater impairment of stereopsis than damage to the right parietal lobe.

Studies employing behavioural stereotests such as the Titmus are open to criticism on the grounds that the stimuli may provide monocular cues for the subject, as also may static random-dot stereogram tests, according to Breitmeyer et al.[7]. The studies cited above are open to this criticism and also that of Lehmann and Walchli[8] who used the Titmus test and found that they could not distinguish between

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patients with different locations of brain lesions, in the subgroup responses to graded disparities. The important question was also raised by these authors of the possible influence of dementia on the performance of patients tested by Carmon and Bechtoldt[2]. In a later study, Lehmann and Julesz[9] investigated a small group of normal adults using dynamic random-dot stereograms and recorded the lateralized evoked potentials. Their conclusion, that "stereopsis is not associated with preferential activity of the right hemisphere", brought the controversy to a head. In response, Hamsher[10] excluded dementia cases and controlled for age and education level in a study which came out in support of the interpretation that a right hemisphere mechanism was intimately involved in the stereoscopic resolution of random-pattern stereograms. Hamsher did not speculate about the nature of the mechanism but pointed to the evidence that it can be selectively impaired by lesions in the right cerebral hemisphere without necessarily affecting stereopsis. He went on to argue that the right hemisphere is dominant for global stereopsis, but not for local stereopsis, and speculated about an additional visuoperceptive mechanism, perhaps involved more widely in form recognition, for achieving global stereopsis. This same right-hemisphere mechanism, he considered, might be operable under monocular as well as stereoscopic binocular vision.

The aims of the present experiment were:

(i) to attempt to clarify, by empirical study, the question of a differential between the two hemispheres in evoked responses to dynamic random dot stereograms, in order to comment objectively on the standing controversy, and

(ii) to depict through multi-channel recording the stereoscopic evoked responses of stroke patients diagnosed clinically as having sustained unilateral brain damage.

In the presence of controversy and the absence of conclusive evidence in the literature, it is not prudent to go beyond a conservative general hypothesis: that interactions between side of lesion and field of stimulation may point up the differences between left and right hemisphere responses to the random-dot stimuli in the two lesion-lateralized groups. Neither hemisphere is an island unto itself and it may be expected that, whatever hemifield is stimulated, commissural transmission will ensure a bilateral response, at least outside the lesioned area.

Methods

Subjects

Prospective subjects were screened by ophthalmological and orthoptic tests with the aim of eliminating persons whose visual acuity or oculomotor balance was such as to preclude normal binocular function and stereopsis. Persons with the following conditions were thus saved the inconvenience of attending the laboratory for the electrophysiological tests: monocular or binocular cataracts or opacities in corneae or media; strabismus or ocular deviations of any type; gross nystagmus and fixation

difficulties; marked retinal disease or senile macular degeneration; glaucoma and significant field loss; and hemianopia which approached fixation. Refraction was noted so that tests could be performed with optimum correction for the visual targets to be used in the laboratory. These screening tests were carried out in hospital or in Stroke Club meeting places. The ocular tests screened out 13 patients. Two patients suffering dementia were excluded and 5 others with motivational or emotional problems brought the total number excluded to 20.

The remaining subjects included: 13 right-hemisphere lesion cases (mean age 62.5 years) and 13 left-sided lesion cases (mean age 65.9 years). Only vascular disease cases were included in the patient groups. The mean post-stroke interval was 112 weeks (range 5-520 weeks) in the right lesion group and 125 weeks (range 5-468 weeks) in the left lesion group.

Conventional behavioural tests of stereopsis preceded the random-dot stereogram (RDS) tests in the laboratory. Visual acuity inferior to 6/9 in one or both eyes was found in 6 patients, 3 in each group. The 3 patients in the right lesion group also failed to show a binocular advantage on the Stereo Wedge test[11].

Neuropsychological Assessment

Each subject underwent a series of neuropsychological tests which were carried out in familiar surroundings, at the rate required in the individual case. The Mini-Mental State Examination[12] was administered to screen for dementia. Colour perception, sensory-motor functioning and spatial perception and orientation were assessed by performance on a battery of short tests[13].

Random Dot Stereograms (RDS)

Dynamic RDS stimuli were displayed by a technique described in full elsewhere[14]. In brief, the system consisted of a hardwired random-dot generator controlled by a microcomputer, the output of which was presented through an optical system constructed around an amblyoscope. A square RDS stimulus was presented in left, right and centre visual fields at stimulus-to-field dot-density ratios of 0/8 and 8/8 (uniform stimulus and field; disparity-alone condition). The arc of disparity was 30 minutes and the stimulus was exposed for durations of 400 msec in the initial sets of trials and 250 msec thereafter (both of these exposures are longer than those used with normal subjects in the Newcastle laboratory and were implemented to assist stroke patients to perceive the stimuli). The stimulus was onset at 100 msec into a 1000 msec recording epoch. The interstimulus interval was 1143 msec and averages were taken of the event-related potentials over 64/32 trials in each condition. Shorter averaging runs were used in individual cases where the subject arousal level was variable.

Stick-on scalp electrodes were applied at International 10-20 system sites: 0_1, 0_2, T_5, T_6, P_3, P_4, T_3, T_4, with referential leading to linked ear lobes except in the first 2 sets of trials, where the reference was at a midline frontal site 10 cm above the nasion (for the purpose of comparing the stereoscopic evoked potentials of the stroke patients with those of normal subjects previously studied in the laboratory). Amplifier gain was set at 20 μV and filters at 0.26-30.0 Hz (—3dB).

Results

Neuropsychological Tests

One-way ANOVA and t-tests were performed on the data. The group performances may be characterized as follows:

Left-hemisphere damage patients were inferior to right lesion patients in mental status scores, in naming and identifying colours and verbal memory for colours (Ishihara results were normal in all cases in both groups) and in spelling. Sensory discrimination differences in the several modalities depended on the side stimulated, except for simultaneous, right face-left hand tactile stimulation, where the right-lesion patients were inferior. These patients were also poorer in response to binaural auditory stimuli and relatively more impaired than the left-lesion patients in respect of visual inattention measures.

Electrophysiological Results

The evoked potentials of the stroke patients were in general noisier and of lower amplitude than those of normal controls and of normal patients tested in earlier experiments in this laboratory. 8 patients in each of the clinical groups gave a valid description of the uniform density stimulus and the field in which it was presented. The other 5 patients in each group failed to perceive the stimulus. In all of the 16 perceiving subjects, an evoked response could be identified in the latency tolerance window of the waveform. In the majority of these subjects, the evoked response in the uniform density condition was of comparatively low amplitude and in many the definition was poor in comparison with the responses of normal healthy subjects. Only 2 left-lesion and 3 right-lesion patients produced evoked responses which might be considered normal in amplitude and morphology.

Figure 1 shows the superaveraged responses at 8 scalp sites of the 2 patient groups (n = 13 patients in each group) to centrefield stimuli in the uniform density condition. The averages for the 400 msec exposure data are illustrated because the longer duration stimuli maximized the possibility of the stroke patients to perceive the stimulus and emit a brain response. The main negative component occurred at a variable latency in each patient group, according to the imposed experimental condition. The highest amplitude response occurs at O_1, in the left-lesion group (1.7 μV).

Statistical Analyses of the 250 msec Stimulus Data

Following a three-point smoothing of the 256 data-point average waveforms of the individual subjects for all experimental conditions, peak and mean amplitudes were measured within the window extending from 180-250 msec after stimulus onset. Amplitudes were computed in relation to a normalization (baseline) period extending across the initial 100 msec prestimulus-onset portion of the 1000 msec averaging epoch. Latencies of the peak amplitudes were also computed. The data from the T_3 and T_4 sites were not included because responses were minimal or absent at these anterior positions.

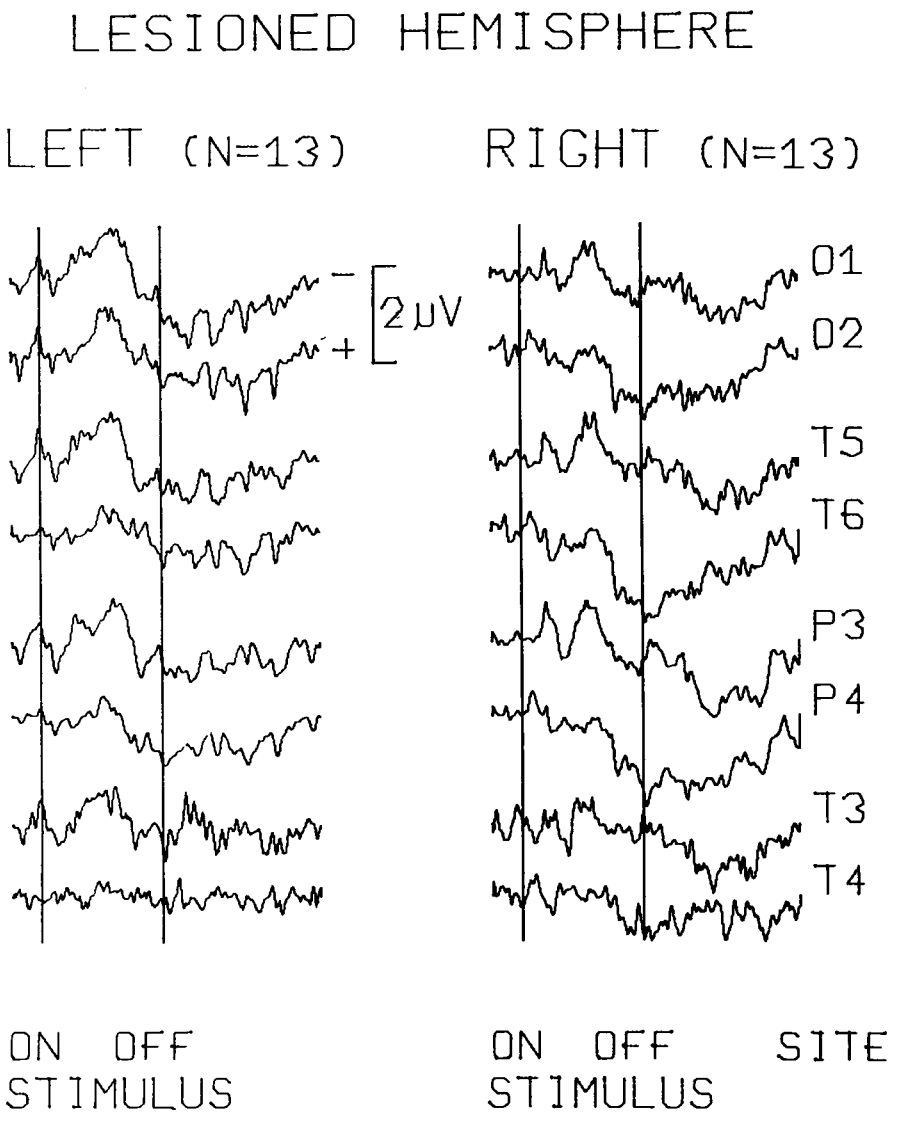

Figure 1. Average evoked responses of the two clinical groups to dynamic random-dot stereograms of uniform stimulus-field density exposed for 400 m sec in the centre field.

Between-group and within-group analyses of variance were then conducted on (i) the latency and amplitude data of the individual subjects in the two clinical groups and (ii) the data from the perceiving subjects (n=8 each group) and 8 normal controls. A sample of the complex results is shown in Table 1, which lists the patient group means for the combined occipital sites 0_1 and 0_2.

Table 1. Latencies (L) in msec, peak amplitudes (P) and mean amplitudes (M) in μV of the main negative component of the evoked response at occipital sites in the 2 stroke patient groups; maximum contrast (0/8) and no-contrast (8/8) stimuli presented in three visual fields.

Lesioned Hemisphere	Contrast		Field of Stimulation Left	Centre	Right
Left	0/8	L	220.6	217.7	211.4
		P	-2.7	-3.4	-3.4
		M	-0.6	-1.0	-1.3
	8/8	L	214.2	232.8	220.3
		P	-3.1	-2.7	No neg component
		M	-1.2	-0.7	+1.7
Right	0/8	L	215.5	213.2	215.2
		P	-2.6	-3.1	-3.0
		M	-1.1	-1.3	-1.2
	8/8	L	228.3	213.8	214.6
		P	-2.0	-1.8	-2.0
		M	-0.3	-0.9	-0.4

The analysis of variance results for the individual patient groups may be characterized briefly as follows. The only significant group main effect was for latency at occipital sites, to centre-field stimulation, where the mean for the left-lesion group (225.2 msec) exceeded that for the right-lesion group (213.5 msec). This result, however, combines the maximum contrast and uniform field conditions. A significant Group X Hemisphere interaction in the full data analysis of peak amplitudes revealed no more than a lower amplitude response, which is to be expected, in damaged hemispheres (3 sites combined). Confining attention to the disparity-only (8/8) stimulus condition, a Group X Field X Site interaction for both peak and mean amplitudes failed to meet the significance criterion and, in any event, did not indicate a trend for a differential between-hemispheres response to the left *v* right field stimulation.

Taking the perceiver subjects only in the patient groups (n=8 each group), the group means for latencies (222.2, 221.3 msec), peak amplitudes (2.4, 2.3 μV) and mean amplitudes (0.76, 0.76 μV), left- and right-lesion groups consecutively in parentheses, are obviously closely similar. The significant interactions in these analyses did not include Group X Field X Hemisphere and, again, there was nothing to indicate a Group X Field X (Hemisphere-Homotopic Sites) differential in any parameter of response. A number of other significant interactions emerging in the analyses are not of interest in relation to the questions under investigation.

Discussion

Answers to the questions of whether a controlling mechanism for stereopsis resides in the right hemisphere and whether the operation of such a mechanism is impaired by right-hemisphere lesions more than by left-hemisphere lesions in cerebral vascular disease patients can be sought at several levels. First, was there behavioural evidence of a difference in response between the 2 clinical groups to the binocular, uniform density, no-contrast stimulus? The clear answer is "No". The groups were nearly equal in the numbers of patients who were able to perceive and correctly locate the stimulus. Few patients in either group gave evoked responses of normal amplitude and morphology. These more superficial results can probably stand alone as evidence which fails to support the literature reports which proposed either a right- or left-hemisphere controlling mechanism for stereopsis. The results do show, however, that stereopsis is preserved, though probably with some degree of impairment, in a proportion of cerebral vascular disease patients. In fact, in the present samples, the proportion of perceivers was roughly equal to that found in normal subjects in studies previously carried out in this laboratory, though the stroke patients were more strongly cued. It is necessary to emphasise that the result on the patients in the present study should not be extended to bilateral lesion cases who were rejected from inclusion in the present study.

The waveforms in Figure 1 show that there are differences in the morphology of responses to RDS stimuli in the 2 patient groups. The main differences are notable at earlier latencies than the response to the stereo stimulus. Although it is only conjecture, it is possible that these differences may relate to different abilities in selective attention in the 2 groups and this may have been a variable which influenced results reported in the earlier literature.

The second answer concerning preferential hemispheric mechanisms comes from the results of the 250 msec-duration stimulus data analyses. No evidence was found in the results supporting the operation of a unilateral controlling mechanism for stereopsis. Such a mechanism would, presumably, operate to reveal a differential in the responses at homotopic sites in the 2 hemispheres to the left- and right-field stimulation, which differential would itself show up as a group difference. The crucial test for such an effect was seen as lying in the higher order interaction of Group X Field X Homotopic Site in the analyses carried out. No significant result emerged.

It is therefore concluded that no support can be adduced for the proposition that a generator which organizes or facilitates global stereopsis exists predominantly in a single cerebral hemisphere. This conclusion conflicts with that of other authors and it is suggested that the earlier findings may have resulted from the use of techniques not fully adequate for the study of the questions involved.

Summary

Contradictory evidence has been presented in the literature on the existence of a right-hemisphere mechanism subserving global stereopsis. In the present study evoked responses to dynamic random-dot stereograms were recorded from Interna-

tional 10-20 scalp sites O_2, P_4, T_6, T_4 and homotopic sites over the left hemisphere. Stroke patients with unilateral lesions were selected on the basis of satisfactory performance on ocular screening tests and on clinical or objective indications that dementia was absent. Control subjects were found among the relatives of patients.

The stereopsis test schedule included left, right and centre field presentations of 30 arc min. disparities. The dot density of the disparity, relative to that of the remainder of the random dot field, was manipulated to provide a full contrast stimulus and a no-contrast uniform field stimulus, thus varying the availability of monocular cues provided by the contrast factor.

Latency and amplitude of the evoked potentials were computed and submitted to analyses of variance. No significant results were found which supported the proposition of a lateralized mechanism for global stereopsis. This conclusion is in conflict with the findings of some earlier reports. It is suggested that the techniques used in the earlier experiments may not have been adequate for the study of the questions involved.

Acknowledgements

This study was supported by a grant from the National Health and Medical Research Council, Australia. Thanks are due to the patients and staff of William Lyne Hospital and other subjects who made their time available, and to the Toronto and Merewether Stroke Clubs who co-operated in the project. The authors thank Wendy Mead for her assistance in typing the manuscript.

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Extradural Malignancy Simulating Brachial Neuritis

*P.C. Gates, P.A. Kempster, D. Rischin and J.I. Balla**

The long thoracic nerve arises from the C5, 6 and 7 nerve roots. This nerve supplies the serratus anterior muscle and involvement of this muscle in an apparent brachial plexus lesion points to a lesion involving the nerve roots rather than the brachial plexus. A patient is described in whom the serratus anterior was spared despite the presence of an extradural tumour involving the C5-6 nerve roots.

Case Report

A 57 year old man awoke with a burning pain in the left side of the neck and shoulder radiating down the lateral aspect of the left arm. Over the ensuing week he rapidly developed weakness of his left arm. The pain and weakness persisted unchanged for a period of four weeks and was associated with anorexia and weight loss of 6 kg.

He was admitted to hospital, where examination revealed a thin unwell-looking man, pulse 70 and blood pressure 130/90 mmHg. There was no hepatomegaly or lymphadenopathy. The cranial nerves were normal, in particular there being no Horner's syndrome. Abnormalities were confined to the left upper limb and shoulder region. There were severe wasting and weakness of the left supra- and infraspinati, subscapularis, deltoid, biceps and brachioradialis. The left serratus anterior was spared. (Figure 1). The biceps and brachioradialis reflexes were absent but sensory examination was normal. The rhomboids were involved although the weakness was mild and there was minimal wasting.

Investigations revealed a haemoglobin of 11.4g per 100ml and an ESR of 102 mm per hour. Liver and renal function tests were normal. Multiple hot spots were present on a bone scan. On electromyography denervation was seen in the left biceps, deltoid, supra- and infraspinati but no denervation in the left serratus anterior. The scalenii and rhomboid muscles were not sampled. A CT scan (Figure 2) of the brachial plexus and spinal canal at the level of C5 and C6 demonstrated an irregular extradural mass at C5 and C6 with no evidence of tumour involving the brachial plexus. Extradural tumour deposits were seen at C5,C6,T8 and T12 on cisternal myelography (Figure 3). There was a complete block to the flow of metrizamide at T12.

Laminectomy was performed at the T12 level and histology revealed a poorly differentiated adenocarcinoma. No primary site could be found.

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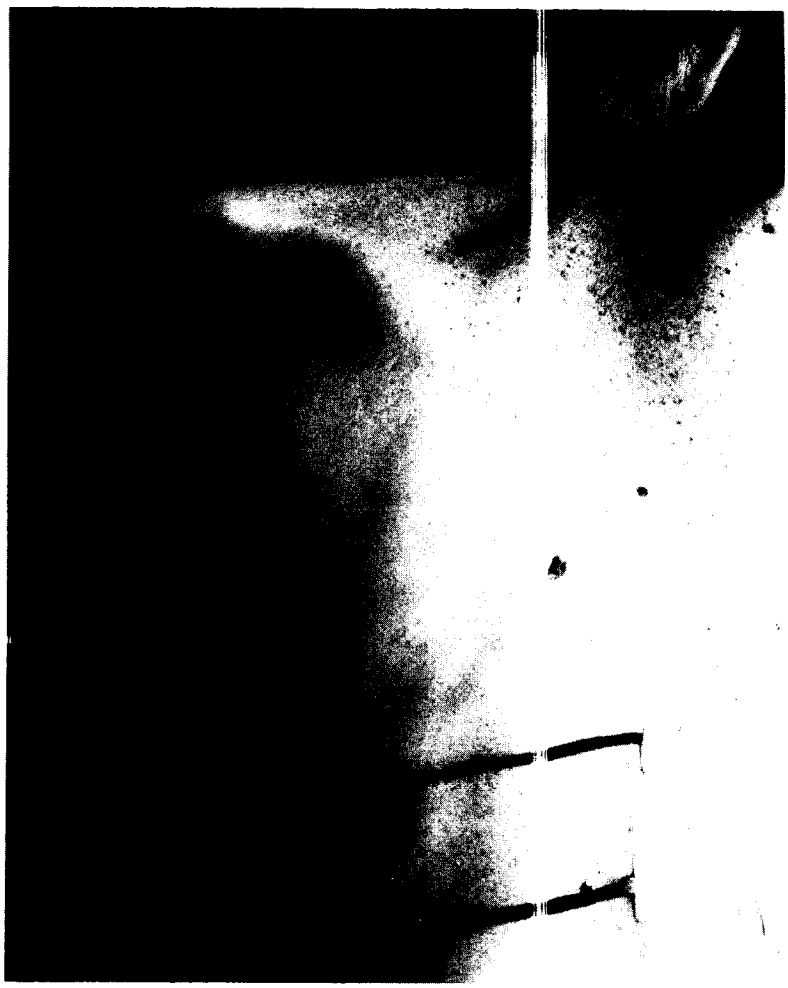

Figure 1. Wasting of scapular muscles, but absence of shoulder 'winging' on contraction of the serratus anterior.

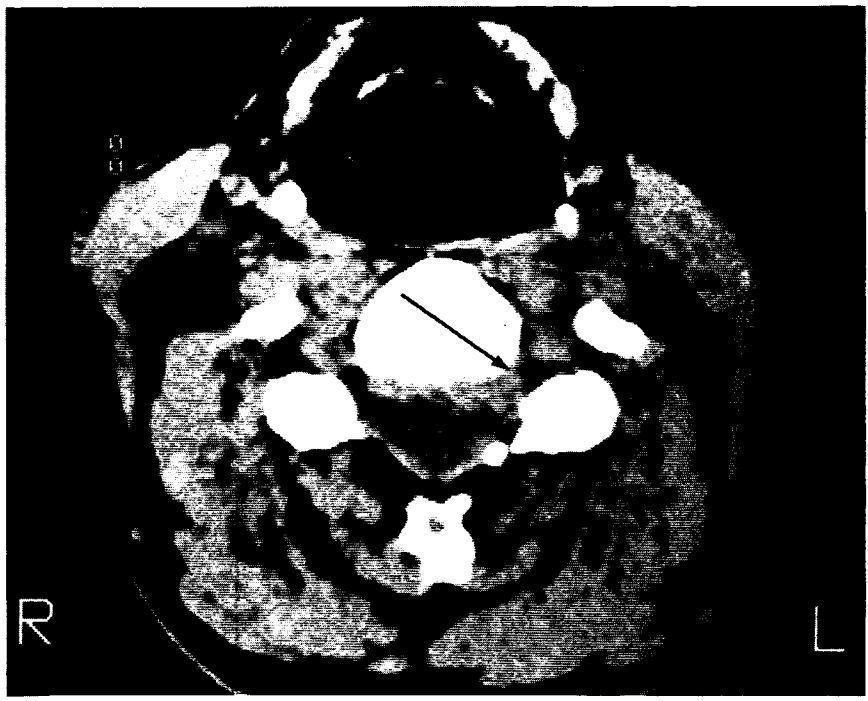

Figure 2. CT scan showing a soft-tissue mass occupying the root exit canal region on the left side between the C5 and C6 vertebrae (arrow).

Figure 3. Myelogram showing anterior indentations of the column of contrast medium at C5 level (arrow).

Discussion

The typical clinical picture of brachial neuritis consists of the acute onset of shoulder girdle pain (with or without an antecedent viral illness), followed by the rapid development of weakness of the shoulder girdle muscles and arms [1,2,3,4]. The history in the patient here described was suggestive of that diagnosis. The lack of involvement of the serratus anterior was interpreted as indicating that the lesion was distal to the C5-C6 nerve root. The rhomboids were involved to a lesser degree, with mild weakness and minimal wasting. These muscles are innervated by the dorsal scapular nerve which is derived from the 4th and 5th cervical nerve roots. The C5 and C6 innervated muscles (apart from the serratus anterior) were so weak that virtually no movement was present. It was considered in retrospect, incorrectly, that the serratus anterior would be unlikely to be spared in the presence of such marked involvement of other C5 and C6 innervated muscles in a nerve root lesion. One possible explanation is that the serratus anterior muscle in this man was innervated predominantly by the C7 root.

Although lack of tumour seen on a CT scan of the brachial plexus does not entirely exclude its presence, the upper brachial plexus is an unusual site of involvement by malignancy[5]. Furthermore, the extradural tumour at C5-C6 explains the clinical picture. Thus, although involvement of the serratus anterior muscle points to affection of the 5th, 6th and 7th cervical nerve roots, sparing of this muscle does not exclude a radicular lesion.

Summary

A 57 year old man is described who presented with symptoms and signs suggestive of brachial neuritis. Sparing of the serratus anterior both clinically and on electromyography suggested that the lesion was in the brachial plexus, thus supporting the diagnosis. Subsequent investigation showed an extradural tumour at C5-C6 level. Sparing of serratus anterior does not definitively localize the pathology as distal to the nerve roots.

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Peripheral Sympathetic Conduction Velocity Calculated from Surface Potentials

*T.J. Day, D. Offerman and S. Bajada**

A sympathetic skin potential (peripheral autonomic surface potential — PASP) can be recorded from the hands and feet and may be useful in assessing autonomic function. This report describes measurement of PASP from a proximal lower limb site as well, enabling a peripheral autonomic nerve conduction velocity (ANCV) to be calculated. The technique expands the range of non-invasive tests available for assessment of the autonomic nervous system.

Patients and Methods

Healthy volunteers were recruited who did not take regular medication or experience symptoms of autonomic dysfunction. There were 6 males and 4 females aged 24 to 39 with a mean age of 28 years. Surface electrodes were placed:

(i) on the second toe (active) and on the sole of the foot, and
(ii) in the lateral popliteal fossa (active) and on the patella.

The ground electrode was placed at the ankle (Figure 1). PASPs were recorded using 'DISA'—1500 Digital EMG apparatus with band pass 2 — 5,000 Hz, sensitivity 20 — 200 μV/cm and sweep speed 500 msec/cm. Random electrical median nerve stimuli were used with the subjects resting supine in a darkened room. At each site four reproducible responses were averaged following random, widely spaced stimuli. Latency to onset of the PASP was measured directly using the on-screen cursor. ANCV was calculated by dividing interrecording electrode distance by the difference in PASP latency at each site. Illustrative recordings are shown in Figures 2 and 3.

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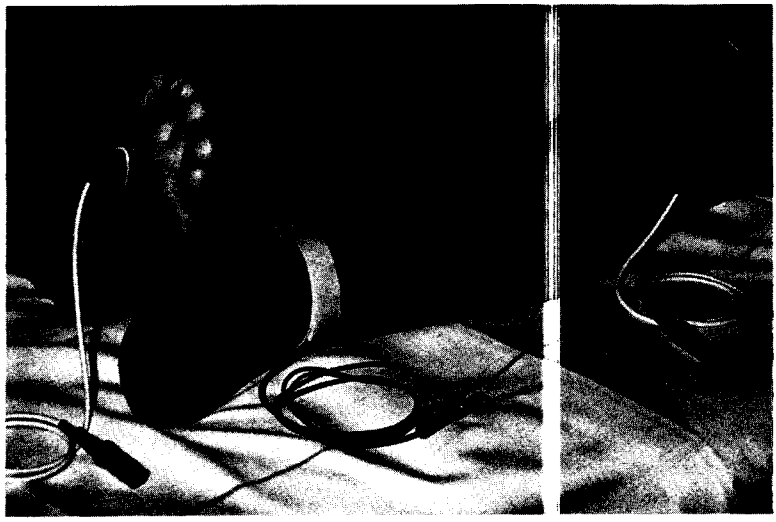

Figure 1. **Electrode placement for lower limb PASP recording.**

Results

Successful dual site lower limb recordings were made in 9 of 10 healthy subjects. The popliteal PASP was consistently of earlier onset and lower amplitude than the plantar PASP. For the popliteal PASP the mean latency to onset was 1.61 ± 0.14 seconds, and mean amplitude 62 μV. For the plantar PASP the mean latency to onset was 2.07 ± 0.21 seconds, and mean amplitude 218 μV. Conduction velocities ranged from 0.81 to 3.1 m/sec with a mean ANCV 1.49 ± 0.64 m/sec. The data from each subject are presented in Table 1.

Table 1. Subject details, conduction latency and velocity data.

Subject	Age	Sex	Latency (Secs) Plantar	Popliteal	Pl-Pop	Distance (cm)	ANCV (m/sec)
1	25	M	2.37	1.88	0.49	62	1.27
2	39	F	1.89	1.59	0.30	55	1.83
3	25	F	2.31	1.72	0.59	48	0.81
4	38	M	2.16	1.56	0.60	60	1.0
5	30	M	2.09	1.66	0.43	64	1.48
6	25	M	1.86	1.66	0.20	62	3.1
7	24	M	1.77	1.39	0.38	60	1.57
8	25	F	1.89	1.47	0.42	57	1.35
9	25	M	2.00	1.55	0.45	45	1.0
10	25	F	No Response Obtained				
		Mean	2.07	1.61			1.49
		SD	0.21	0.14			0.64

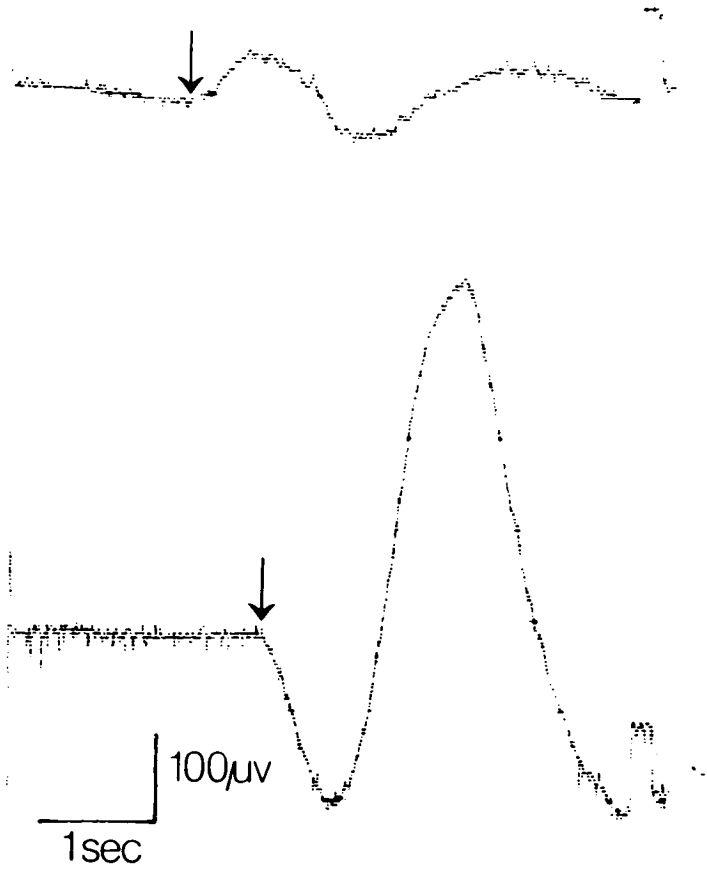

Figure 2. PASPs recorded from the popliteal fossa (upper) and plantar surface (lower). These traces represent the average of four separate responses. The onset of each response is marked (↓).

Discussion

Quantitation of autonomic function generally relies on measurement of cardiovascular reflex activity, and on qualitative assessment of sweating ability, pupillary responses, gut motility and bladder emptying. Previous workers have studied

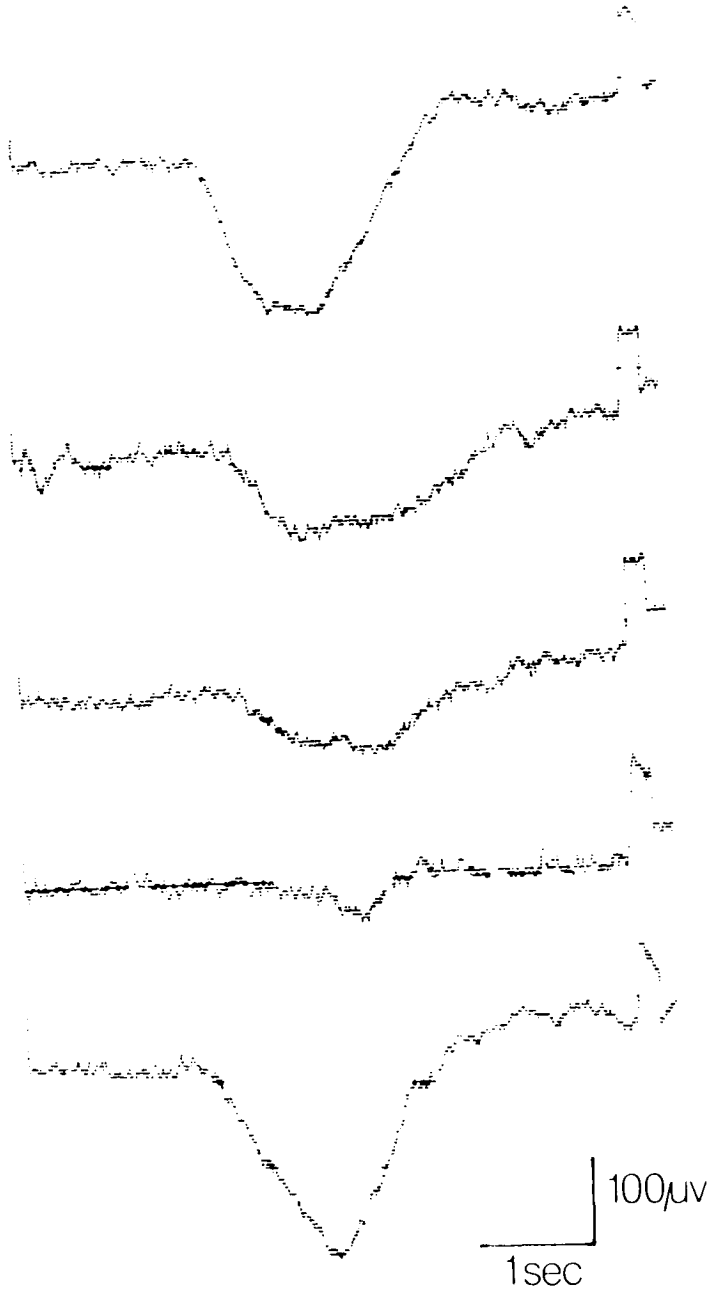

Figure 3. Four consecutive PASPs show fatigue of the response. After two minutes without stimulation, a good amplitude PASP is again recorded.

the galvanic skin response in patients with neuropathy and dysautonomia. Direct recording from autonomic nerves involves the difficult, time consuming and uncomfortable procedure of intraneural recording. We here describe a simple method of recording sympathetic nerve conduction which can be readily performed in a standard neurophysiology laboratory.

PASP recording techniques have previously been reported by Shahani et al.[1] and Knezevic and Bajada[2]. The PASP is closely related to the galvanic skin response and both are believed to represent the synchronized activation of sweat glands. Both are abolished by the application of atropine at the electrode site, and by chemical and surgical sympathectomy. Close correlation has been noted between these responses and phasic sympathetic nerve discharges recorded intraneurally[3]. The values of autonomic nerve conduction velocity obtained by our technique (mean ANCV = 1.49 m/sec.) are comparable to those obtained from skin sympathetic nerves by intraneural recording[3] and unmyelinated 'C' fibres in vitro[4].

Lower limb dual site recording was unsuccessful in 10% of our healthy subjects. Possible reasons for this include the rapid fatigue of the PASP which was observed after several stimuli and the relatively lower amplitude of the popliteal response. Hence, reproducible PASPs may not be obtained, especially if the initial PASP is of low amplitude. We postulate that a reliable popliteal PASP response is dependent on electrode position, the number of previous stimuli, the interstimulus interval, the local sweat gland density, and the degree of subject relaxation. Further studies using different electrode positions, allowing longer periods (40-60 seconds) between stimuli and maintaining subject alertness and concentration are currently in progress.

This technique may assist in the assessment of patients with autonomic neuropathy and is especially likely to be useful in identifying early disease and following its course. Further studies are indicated to investigate these applications.

Summary

A simple, non-invasive and well tolerated technique is described for measuring autonomic nerve conduction velocity (ANCV) using proximal and distal peripheral autonomic surface potential (PASP) recordings. ANCV were obtained in 90% of subjects, and are comparable to values measured by intraneural recording. This technique may have applications in the assessment of autonomic neuropathies and can be readily performed in a standard EMG laboratory.

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Myopathy with Fatiguability—Myositis or Myasthenia?

R. Peppard, E. Byrne* and X. Dennett†*

Human skeletal muscle is affected by 2 relatively discrete and well defined autoimmune diseases, (i) myasthenia gravis, where a humoral antibody is directed against a highly specialised area of sarcolemmal membrane, the post-junctional folds in the endplate zone, and (ii) polymyositis where a cell-mediated immunological process destroys whole muscle fibres.

In spite of their common basis in a disordered immunological response, there is surprisingly little clinical or pathological overlap between typical cases of polymyositis and myasthenia gravis. In occasional patients either clinical (prominent fatiguability in myositis) or pathological (fibre necrosis in myasthenia) findings in one condition may be more typical of the other, although this seldom causes diagnostic confusion. In this paper we present a patient with proximal weakness in whom the differentiation of polymyositis and myasthenia gravis presented some difficulties.

Case Report

A 47 year old woman developed increasing proximal arm weakness in November 1983, with difficulty in combing her hair and hanging up washing. Over the next 6 months she developed increasing weakness of neck extension. There was a marked diurnal fluctuation in the severity of weakness with a progressive increase towards the end of the day. Mild proximal leg weakness with difficulty in arising from a chair and mild dysphagia developed in May 1984.

The patient had a past history of nontoxic nodular goitre treated surgically 20 years before and of a polyarthritic illness 12 years earlier. On examination (4.5.84) the patient had mild lower facial weakness, severe weakness of neck extension with inability to lift her chin from the sternum, and moderate weakness of neck flexors, deltoids, biceps, triceps and finger extensors. The sternomastoids, upper trapezius and deltoid muscles were wasted. Moderate weakness of hip flexion was evident but distal leg power was normal. Marked fatiguability was evident in the weak muscles. For example, finger extension was 4/5 (MRC scale) on initial testing but sustained contraction against moderate

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resistance for 20-30 seconds caused fatiguability to the extent that the patient had difficulty straightening the fingers against gravity and minimal resistance. The reflexes were normally reactive and no muscle tenderness, myoedema or myotonia was present.

Table 1. Serological studies

Antibodies	
Nuclei (HE_p2 cells)	1:160 nucleolar 1:40 speckled
Striated Muscle	— VE
Acetylcholine receptor	— VE (RPH)
SM (Nuclei)	— VE
Lq	— VE
Anti Mi	— VE
Smooth muscle	— VE
Mitochondria	— VE
Gastric parietal cell	— VE
C_3	128(r70-160 mg/dl)
C_4	10(r16,3-44.7 mg/dl)
Ra	— VE
Rose Waaler	— VE

Investigations revealed an iron deficient anaemia (Hb 9.1g per dl, microcytic blood picture, serum iron 3.0 μmol/L : normal range 10.7-21.4) which subsequently responded to oral iron therapy. Serum creatine kinase level was 599 μ/L (normal range: 0-100). A positive ANF titre was detected (1:160 nucleolar, 1:40 speckled). Rheumatoid factor, Rose Waaler and comprehensive auto-antibody profile (including acetylcholine receptor antibodies) were negative (Table 1). The C4 level was depressed (10.0 mg/dl: normal range 16.3-44/7) with a normal C3 level (128 mg/dl: normal range 20-100). Electromyography (concentric needle electrode) revealed fibrillation potentials in the right deltoid, biceps, triceps and abductor pollicis brevis muscles with prominent low voltage short duration motor units on voluntary contraction. Repetitive stimulation of the right ulnar nerve at wrist level with recording over the hypothenar eminence revealed no decrement in the 5th response in the train with 3Hz stimulation before and after exercise. With 20Hz stimulation there was a 10% amplitude fall between the 1st and 5th response.

A biopsy of the left deltoid (Figure 1) revealed marked variation in fibre size (10-55 μm). All fascicles showed severe loss of muscle fibres with many atrophic and some split and coiled fibres. Many discrete collections of mononuclear cells were seen, mostly consisting of small lymphocytes but with occasional histiocytes, and there were some polymorphonuclear cells. Giant cells were not seen. Most of these collections were associated with necrotic fibres. Very little diffuse inflammatory infiltration was seen. The appearances suggested a nodular myositis.

The diagnosis of polymyositis was made and oral prednisolone 100 mg/day was commenced. The patient had no respiratory distress prior to steroid therapy. Over the next ten days there was a steady deterioration in the patient's clinical condition. 3 days after commencement of steroid therapy, increasing breathlessness became apparent after mild exertion (Figure 2) and the vital capacity (VC) was 1.81 litres (predicted value: 3.32 ± 0.7), with a forced expiratory volume (FEV) 1.0 sec/FVC ratio of 77% (predicted value: 70%). Over the next 4 days the vital capacity steadily declined to 800 ml. This was accompanied by increasing limb weakness. The patient was transferred to an intensive care ward and azathioprine added to the therapeutic regimen.

Clinical deterioration was accompanied by a restoration in creatine kinase levels to normal (Figure 2). The acetylcholine receptor antibody assay was repeated in another laboratory and was again normal. Single fibre EMG studies (Dr. L. Roberts) in the right extensor digitorum communis (a clinically fatiguable muscle) revealed a normal jitter (mean consecutive difference 31.8 μsec: normal range 6.4-40.4). CT scan of the mediastinum revealed no evidence of thymic hyperplasia or thymoma. The patient's condition stabilised with no further fall in vital capacity. There was no clinical improvement

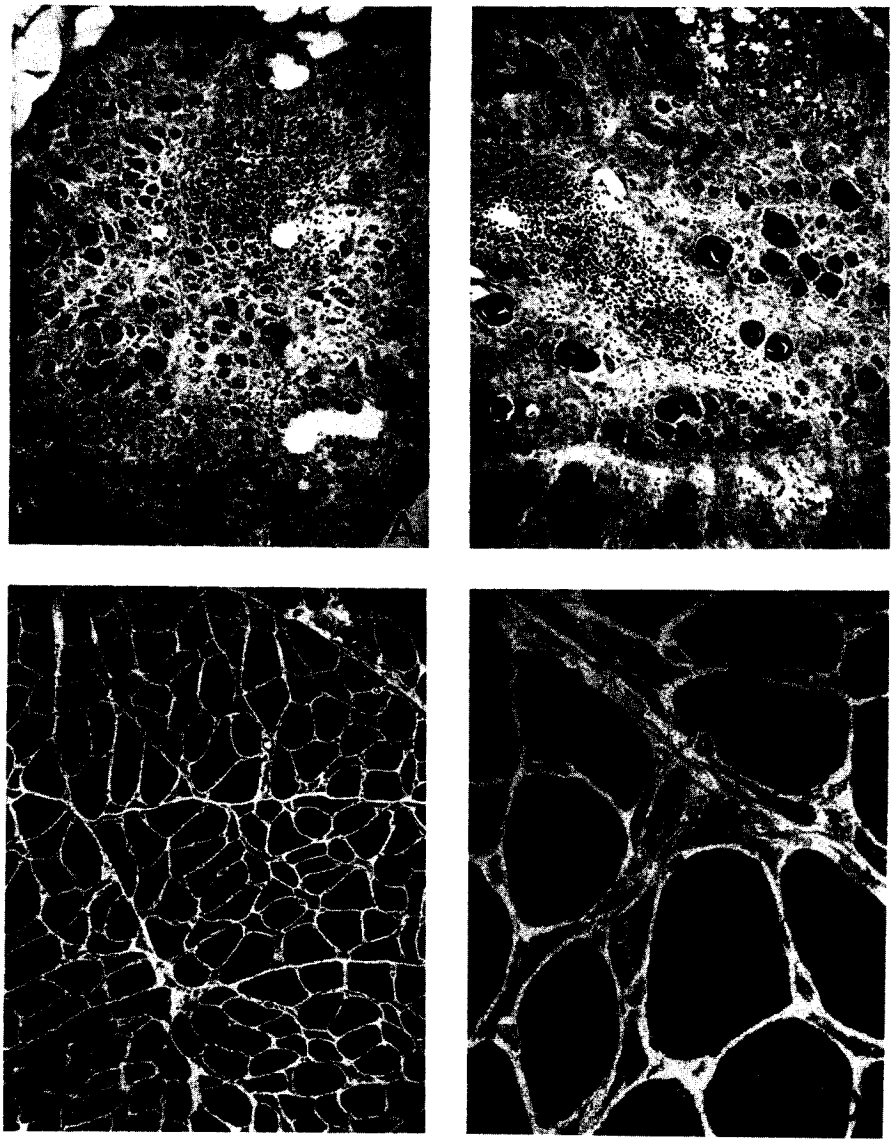

Figure 1. A,B: First biopsy from left deltoid muscle showing inflammatory cell aggregates, widespread fibre atrophy, fibrosis and a focal region of coiled and split fibres in B.

C.D: Second biopsy from left quadriceps muscle showing lack of cellular infiltrates, diffuse fibre atrophy — predominantly Type 2 with ATPase reactions and some attempted regeneration (arrows). (Transverse cryostat sections, H & E stains, A-C x 10, D x 40).

over the next 2 months whilst azathioprine was continued and prednisolone reduced to 40 mg/day. A repeat biopsy (Figure 1C, 1D) revealed no ongoing inflammation and significant fibre atrophy probably related to steroid therapy. Cyclophosphamide was substituted for azathioprine. A gradual improvement in muscle strength was seen which continued after cyclophosphamide was ceased because of a transient deterioration in liver function. Vital capacity improved over 6 months to reach 2.1 litres and resting strength returned almost to normal in girdle muscles, although the patient continued to have moderately severe fatiguability after exercise. Azathioprine 100 mg/day and prednisolone 30 mg on alternate days are currently being used.

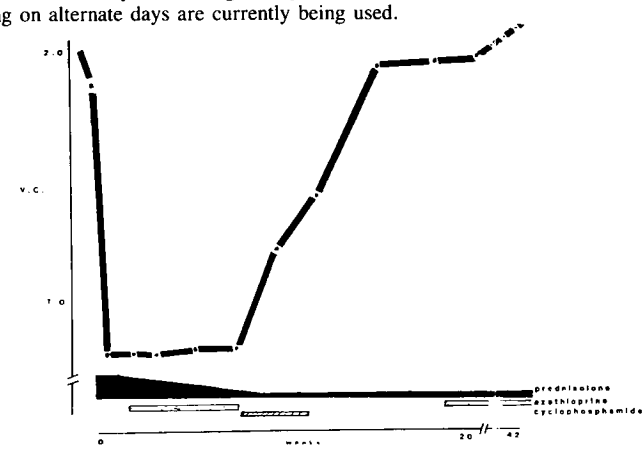

Figure 2. Vital capacity changes which occurred during the course of treatment.

Intensive investigation for a malignancy (abdominal and thoracic CT scan, upper GI endoscopy, colonoscopy, ERCP, gynaecological examination) revealed no abnormality. A year after presentation, the patient had returned to work but was still aware of fatiguability towards the end of the day.

Discussion

The patient here reported presented with progressive proximal limb weakness and severe weakness of posterior nuchal muscles with inability to lift the head from the chest, a pattern of weakness considered almost pathognomomic of polymyositis[1]. Severe fatiguability in many muscle groups was present on presentation and persisted throughout the illness even when fixed weakness had largely resolved. Some degree of fatiguability is commonly encountered in polymyositis[1] but its prominence, especially in distal muscles in this case, and the persistence of prominent fatiguability when fixed weakness had almost resolved is unusual. Muscle enzyme levels were elevated and EMG findings were typical of an inflammatory myopathy. Muscle biopsy revealed a picture of nodular myositis with prominent lymphorrhages and necrotic fibres. This appearance has been reported in myositis associated with drug-induced collagenosis[2], but similar findings may occur in association with organ specific autoimmune diseases such as Graves' disease. The histological findings in myasthenia gravis may also resemble a nodular myositis picture with lymphorrhages often accompanied by scattered degenerating or necrotic fibres occurring in about a third of cases[3]. The lymphorrhages may be perivenous in location but are more commonly

related to necrotic fibres as in the present patient[4]. The degree of muscle fibre necrosis in this patient was much more marked than is usual in myasthenia gravis but occasional cases of myasthenia with more marked myositis have been reported. Most of these patients have had associated thymomas[5,6]. 2 patients who presented with clinical features suggestive of polymyositis, which changed to a myasthenic picture after removal of a thymoma, have been reported[7] while Rowland and Schotland[5] reported a patient who developed polymyositis 5 years after experiencing myasthenia-like symptoms following removal of a thymoma. Clearly there are nosological problems in this group of patients and it is not clear whether they have myasthenia with an unusual degree of fibre necrosis of whether they have polymyositis and myasthenia simultaneously or sequentially. Rowland favours the first view in most cases[6].

A diagnosis of polymyositis (nodular) was made in the present case and high dose steroid therapy was commenced. A moderate impairment of vital capacity was noted soon afterwards and progressive respiratory failure developed rapidly as the serum creatine kinase level returned to normal. Respiratory failure is uncommon in polymyositis[8]. Although the correlation between serum enzyme levels and clinical weakness is far from exact, especially in the early stages of treatment where biochemical improvement may antedate clinical improvement, marked clinical deterioration with rapidly progressive respiratory failure at a time when the creatine kinase level is rapidly returning to normal in response to treatment, is a most unusual finding in polymyositis. Paradoxical early deterioration with steroid therapy is characteristic of myasthenia gravis[9,10] and this finding re-opened the question of diagnosis.

The serological abnormalities in this case favoured a diagnosis of polymyositis. The ANF titre was moderately elevated with a reduction in C_4 complement levels. A high ANF titre has been reported by some authors in a substantial percentage of cases of polymyositis[11] but in a more critical analysis, anti-RNP (ANF) is uncommon in patients with myositis without evidence of a more widespread connective tissue involvement[12]. Acetylcholine receptor antibodies were not identified on several occasions early in the hospital course, a finding against a diagnosis of myasthenia[13]. The patient eventually made a satisfactory response to immunosuppressive therapy. The final diagnosis is not absolutely clear. The most likely diagnosis is polymyositis. The evidence for an inflammatory myopathy is indisputable with a raised creatine kinase level, typical EMG findings and inflammatory and necrotic changes in a muscle biopsy. The key question is whether these myositic changes were of the type occasionally associated with myasthenia gravis. This variant of myasthenia usually arises in association with thymoma, and the normal mediastinal CT scan and absence of striatal antibodies[14] made thymoma unlikely. The histological findings in skeletal muscle, however, were consistent with those reported in myasthenics with inflammatory change and 2 clinical findings, the persistence of severe fatiguability after both the fixed weakness and the inflammatory changes in the biopsy had largely resolved, and the parodoxical early deterioration in respiratory status with steroid therapy favour a myasthenic illness. Acetylcholine receptor antibodies were not detected and "jitter" in single fibre EMG studies was not increased, findings which are against but which do not totally exclude myasthenia.

The balance of evidence in this patient favours a diagnosis of polymyositis but several atypical findings raise the possibility of myasthenia gravis with associated myositic change. A grey area exists between polymyositis with undue fatiguability and unusual cases of myasthenia with pronounced inflammatory changes. The purpose of this report is to present a patient in whom clinical opinion about the nature of the auto-immune disease attacking striated muscle may be divided.

Acknowledgements

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A Clinical Study of Convulsive Syncope

*P.A. Kempster and J.I. Balla**

Patients who have vasodepressor or posture-related syncopal attacks which culminate in convulsive phenomena may present for evaluation of possible epilepsy. Neurologists generally regard this entity as benign and tend not to prescribe anticonvulsant medication. However, the condition is less well recognised by non-neurologists. The purpose of this study is to document the range of clinical features of convulsive syncope and to define its prognosis.

Methods

This study is based on a review of the case notes of 52 patients seen by a single neurologist (J.B.) between 1969 and 1984. All patients had been referred because of possible epilepsy and in each case a clinical diagnosis of convulsive syncope had been made. The results of electroencephalography, where performed, were also reviewed. Follow up was attempted by contacting the referring doctor and/or the patient.

The diagnosis was based on evidence that a convulsive phenomenon had occurred and that it had been preceded by a syncopal onset to the episode. The convulsive element to a presenting attack was suggested by eyewitness account in all but one case. The syncopal onset was established by considering two aspects of the history, as follows:

(i) the description of a prodrome of symptoms suggestive of global cerebral hypoperfusion, and

(ii) that an episode had occurred in circumstances likely to have precipitated a faint.

A typical case is described as an illustration. A 31 year old man was seated while watching a film about microsurgery. He began to feel light-headed and sweaty and thought that he was about to faint. He put his head between his knees but shortly afterwards lost consciousness. An eyewitness reported that his limbs and body went stiff and that a few limb muscular twitches occurred. He was pale and sweating profusely. When followed up eight years later he had experienced no further attacks.

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Results

The mean age of presentation was 23 years: ages ranged from 5 years to 45 years. The series included 21 males and 31 females. The majority of patients presented with one episode only. Only 4 gave a history of more than 2 attacks.

The range of precipitating circumstances for attacks is set out in Table 1.

Table 1. Circumstances associated with the onset of convulsive syncope.

Emotional	
Medical or dental procedure	11
Pain	6
"Sight of blood"	7
Posture	17
Intercurrent illness	6
Not identified	5

The medical or dental procedure was most frequently a venepuncture. "Sight-of-blood" type of attacks included also attacks due to similar emotional stimuli such as visiting a hospital. Posture-related syncope was inferred if there was an immediate relationship of the episode to change to the upright posture or to a prolonged period of standing upright. Several patients had premonitory symptoms of syncope while unwell because of another illness, often a gastrointestinal upset associated with nausea. In 5 cases a single clear precipitating factor was not apparent. Symptoms of global cerebral hypoperfusion were reported in 44 cases. This symptom complex usually consisted of some combination of light-headedness, feeling of impending fainting, vision blacking-out, ringing in the ears and nausea. Eyewitnesses reported skin pallor with attacks in 23 cases.

With regard to the convulsive element of the attacks, eyewitness accounts were mostly of pure tonic or tonic-clonic convulsive phenomena. However, 3 patients had asymmetrical convulsive motor activity. 12 patients were incontinent of urine during attacks. According to eyewitnesses, post-ictal recovery to full alertness was delayed for at least some minutes in the majority of patients. Electroencephalography (EEG) was performed in 40 patients. 24 of the records were normal and 8 had minor abnormalities only. In 4 patients there were paroxysmal slow or sharp waves seen bilaterally and a further 4 EEG records contained focal sharp and slow wave activity.

Of the series of 52 patients, 43 were followed up after a mean period of 5.5 years. The remainder were lost to follow-up. 38 patients had no further episodes and simple syncope had occurred in 2. Subsequent convulsive attacks were reported in 3 cases — these attacks all occurred in circumstances similar to those identified at the times of presentation. No patient had subsequent seizures without such provocation. Only 2 patients took anticonvulsants for a short time in the follow up period. This therapy had been initiated prior to neurological consultation in both cases.

Discussion

Previous reports on convulsive syncope in the neurological literature give some information about the frequency of such episodes and about their pathophysiology. In a study of 250,000 blood donors in the United States, syncopal reactions were witnessed in 0.03%. As many as 12% of these were observed to involve convulsive movements[1]. Convulsive syncope has also been studied under laboratory conditions, with syncope induced by venepuncture in susceptible subjects, or by manoeuvres which increase vagal tone such as eyeball pressure. When haemodynamic parameters are measured, these are shown to be not significantly different in convulsive and non-convulsive syncope[2]. Observation of such episodes with recording of the ictal EEG shows two patterns. More commonly EEG slowing and then loss of amplitude occurs as the patient lost consciousness. An extensor tonic spasm and a few clonic jerks are seen while the cortical EEG appears flat, perhaps suggesting that the observed convulsion is a brainstem release phenomenon. Sometimes the tonic phase may be asymmetrical with head deviation or asymmetrical limb posturing[3]. One report however, documents a laboratory convulsive syncopal episode where the EEG showed spike and wave discharge concurrent with the observed convulsive activity. The patient had previously had typical syncopal responses to venepuncture[4].

Summary

An analysis of the clinical features of patients having evidence of a syncopal onset to convulsive episodes is reported. The range of convulsive phenomena was quite wide and did not appear to differentiate the syndrome from primary epilepsy in terms of seizure morphology, occurrence of incontinence or pattern of post-ictal recovery. It is therefore suggested that the premonitory and precipitating features are more specific in the diagnosis of convulsive syncope. Skin pallor was often reported during attacks. Although EEG abnormalities were seen in some cases, the follow-up results indicate a low incidence of unprovoked convulsions in patients with this condition without anticonvulsant treatment.

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Effects of Age on the Axon Reflex Response to Noxious Chemical Stimulation

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Capsaicin applied to the skin causes vasodilatation beyond the area of application. This response occurs only in the presence of an intact sensory innervation. The response to capsaicin and some other chemicals has been termed neurogenic inflammation[1,2] and is similar to the flare and plasma extravasation seen after nerve stimulation and intradermal histamine injection[3]. As part of a larger study on the effects of capsaicin-induced red reaction and flare[4], we examined the effects of age on the response.

As substance P is generally considered an important mediator of the neurogenic flare response[5], and is contained within small afferent nerve fibres in the skin[6] we also examined the substance P content of skin samples from comparable regions obtained at autopsy from patients without known disease of the peripheral nervous system. This parameter was used to assess the contribution of neural elements to the observed decrease in flare response with age. Epidermal thickness was also measured to assess the contribution of skin components in the response.

Methods

In the study of the effects of application of topical capsaicin, 220 subjects were tested; 50 were student volunteers and the rest comprised hospital inpatients and unpaid volunteers. Informed consent was obtained and the project had been approved by the Hospital/Medical School Ethics Committee.

The concentration of capsaicin solution used for the investigation of the induced flare response was 1.0g/L in 70% alcohol. The time period of application was 30 minutes. The capsaicin (Sigma) was applied to one or several of a set of standard anatomical sites. In addition to the flare size, information on the subject's age, sex, intake of medication and the presence of any medical condition was collected.

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For post-mortem studies, a 3 mm punch was used to obtain biopsy samples of skin from 14 subjects at autopsy. The age range was 37 to 88 years. The patients were not known to have had disease of the peripheral nervous system.

For the estimation of substance P content, samples from one side of the body of each of the subjects were weighed and frozen to -70°C until the time of assay. Before assay the samples were homogenised and extracted into acetic acid and acetone. The extracted tissue was then subjected to a sensitive and specific radio-immunoassay for substance P[7]. The results were analysed after conversion to substance P content per mg wet weight of tissue. The flare response was outlined with a marking pen and then traced. A Leitz ASM was used to measure the area enclosed by the tracing. For the estimation of epidermal thickness, samples from the other side of the body from 10 of the subjects were fixed in formalin, paraffin-embedded, sectioned, mounted on slides and stained with toluidine blue. For each slide a projection microscope and mirror were used to transmit the image of the section being investigated onto the measuring grid of a Zeiss MOP image analyser connected to a Z80 dedicated microprocessor. The probe pen of the MOP was run along the image of the basement membrane on the grid and around the outline of the image of the keratinized and non-keratinized portions of the epidermis for each section. The MOP calculated the area enclosed by the path of the pen in square micrometres. By

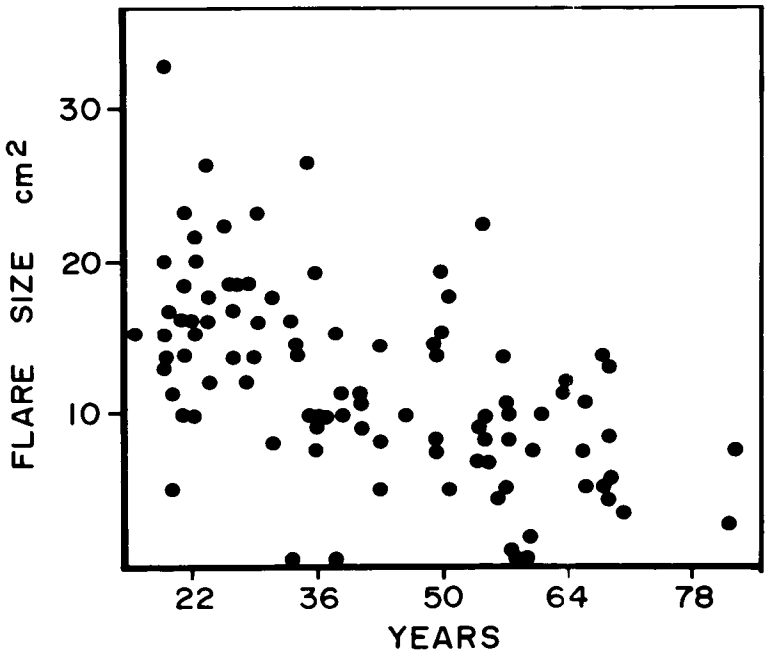

Figure 1. Scatter diagram of flare size plotted against age of the left trapezoid ridge.

dividing the area of the keratinized and non-keratinized portions of the epidermis by the length of the basement membrane along the section, a measure of the mean thickness of the 2 layers was obtained.

Flare relationships with age were analysed using the Kendall tau correlation. Substance P content and epidermal thickness were analysed by Spearman correlations.

Results

The relationship between flare size and age is illustrated for the trapezoid ridge in the scatter diagram (Figure 1). It is clear that flare size elicited by capsaicin decreases with increasing age ($r=-0.41$; $p<0.001$). This relationship was true only for the trunk and proximal extremities including the cubital and popliteal fossae.

The substance P content of skin ranged between 0.8 and 1.3 fmol/mg wet weight for the sites examined. There was a negative correlation between substance P content and age at all sites examined. This reached statistical significance at the cubital fossa ($r=-0.57$; $p<0.05$; $n=12$). Sex and autopsy delay were not important variables. There was no relationship between flare size and skin thickness.

Discussion

The major observation of this study is that neurogenic flare, in response to topical application of capsaicin, markedly decreases with advancing age, especially on the upper trunk and proximal parts of the limbs. Topically applied capsaicin must diffuse through the epidermis to act on epidermal and subepidermal nerve fibres. Thus any effect of age on the flare response must take into account properties of the skin as well as those of the chemical nociceptive fibres. Since capsaicin is lipid soluble, the epidermis should provide little barrier to its passage. Time must still be taken, however, for the capsaicin to diffuse far enough to reach the receptor terminals of sufficient nerve fibres to precipitate the flare response. One explanation for the inverse correlation of flare with age is that the epidermis might become thicker with advancing age and thus prolong the optimum time for observing flare. This is not supported by the results of our epidermis measurements, which suggest that, if anything, the epidermis over much of the body gets thinner with advancing years. In addition, Tan, Stattham, Marks and Payne[8], using an ultrasound technique, also found whole skin thickness to decrease with age. Conversely it is possible that the peak flare size occurs sooner with the thinner skin of older people and be on the decline when the measurements were taken. This was not observed in our previous study[4]. It should also be noted that flare responses are greater on the trunk than the limbs[4], yet skin thickness is greater on the trunk[8], arguing against skin thickness as an important factor in modifying the response.

We suggest there may be loss of substance P containing nerve fibre terminals with age. Although the substance P content of the skin was not reduced significantly at all sites, the trend was consistent for all regions examined. It should be noted that

the substance P content is also dependent on the volume of the whole specimen and we could not measure this variable in the samples studied. However, as skin thickness is reduced with age, we expected an increased rather than decreased concentration of substance P with increasing age. If there was a loss of nerve terminals with age, the size of collateral spread for axon reflexes could be reduced and thus flare size would decrease. The substance P changes are consistent with this view.

What may be the pathophysiological significance of diminished neurogenic inflammatory responses in the elderly? Currently there is no clinical evidence to support the view that the afferent nervous system is important in the inflammatory response to injury. Nevertheless recent observations in animal studies[9,10] suggest that substance P containing afferent nerves may modulate inflammatory responses to chemical and immunological injury, and that this may be relevant to clinical syndromes such as migraine[11]. Other studies[12,13] also suggest that substance P may be important in activating neutrophils and macrophages attracted to the site of injury. Certainly the effects on the maintenance of normal skin structure and function by nerves is amply illustrated by the effects of chronic denervation. It remains to be seen whether the changes in the structure and function of the skin seen in the elderly may be partly attributed to loss of substance P containing afferent nerve fibres with advancing age.

Summary

The axon reflex flare response to noxious stimulation of the skin is mediated by polymodal nociceptors of "C" fibre primary afferent nerves. Topical application of capsaicin initiates such a flare. The mediator of the response is presumed to be substance P.

In this study we examined the flare response to topical capsaicin (1g/L in 70% alcohol for 30 minutes; n=220) and the substance P content of autopsied skin (3mm punch biopsy; n=14). The area of the flare response was measured by tracing a Leitz ASM probe onto traced flare outlines. Skin was extracted in acetic acid and acetone and substance P measured by radio-immunoassay. Skin thickness was also measured in parallel biopsy specimens. The flare response decreased with increasing age at sites examined on the trunk and proximal extremities (for the trapezoid ridge $r = -0.41$; $p < 0.001$). The substance P content of skin also decreased with age at those sites examined (for the cubital fossa $r = -0.57$; $p < 0.05$). There was no relationship between age and skin thickness. The results demonstrate decreased activity of the axon reflex mechanism with increasing age. This may be due to changes in substance P containing nerve terminal density. The importance of a reduced neurogenic inflammatory response in the pathology of ageing is unknown.

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The Use of Lisuride in severe Parkinson's Disease

D. Chin, Y.L. Yu† and C.Y. Huang†*

Although most patients with Parkinson's disease respond to levodopa, the response ultimately diminishes. The diminished response may result from continued degeneration of nigrostriatal neurons. In time, the remaining neurons may be incapable of making dopamine in sufficient quantities to stimulate striatal dopamine receptors. Patients with such a diminishing response to levodopa might benefit from drugs that bypass the degenerating nigrostriatal dopaminergic neurons and stimulate dopamine receptors directly, e.g. agonists such as bromocriptine, lergotrile and lisuride.

Lisuride hydrogen maleate [N-(D-6-methyl-8-isoergolenyl)-N', N'-diethylcarbamide] is a semisynthetic ergot alkaloid that is effective in experimental models of Parkinson's disease. It resembles bromocriptine in tetracyclic configuration but differs in several respects, such as the absence of a peptide moiety and a halogen. Lisuride is many times more potent on a milligram-per-milligram basis than bromocriptine or lergotrile. Its effects are independent of presynaptic synthesis or storage as it probably acts directly on dopamine receptors. Lisuride suppresses the release of prolactin from the anterior pituitary and also blocks the release of alpha-MSH from the intermediate lobe, suggesting stimulation of D_2 receptors. We therefore evaluated lisuride clinically.

Patients and Methods

4 patients with severe Parkinson's disease who could not be well controlled with levodopa-carbidopa (Sinemet), bromocriptine or anticholinergics were selected for a trial of lisuride. 2 patients had the "on and off" phenomenon, one patient had mobility problems despite a high dose of benzhexol, and the other patient had troublesome dyskinesia despite low dosage of "Sinemet". Lisuride was started in small amounts (0.1mg b.d.) and the dosage was slowly increased to a therapeutic dosage. "Sinemet" and/or bromocriptine were usually ceased before starting lisuride

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but anticholinergic intake was usually maintained. The patients were assessed clinically before starting lisuride and then weekly using the Hoehn and Yahr classification (H & Y)[1], the New York University Disability Scale (NYUDS)[2], and the North Western University Disability Scale (NUDS)[3].

Results

Case 1

A 35 year old female factory worker was first admitted into the Hong Kong University Neurological Unit at Tung Wah Hospital in October, 1983 with 4 years history of progressive stiffness of her limbs and difficulty in walking with frequent falls. On admission, she had marked cog-wheel rigidity and bradykinesia of all limbs. She was able only to take a couple of steps with the assistance of 2 nurses. Her mental state was normal and no Kayser-Fleischer rings were detected. There was no history of encephalitis, brain injury or drug abuse. Her serum copper studies and liver biopsy showed no evidence of Wilson's disease. Computerized tomography of the brain was normal. Treatment was started with a small dose of 'Sinemet' but she developed marked dyskinesia and this therapy was ceased. She was then given benzhexol and its dosage was slowly increased to 40 mg per day. Initially her response was reasonable, as she became able to walk independently, though with a shuffling gait. However, she deteriorated again after a few months and bromocriptine was then tried for several months with no good response. Lisuride was started and she showed a significant improvement clinically at the end of 6 weeks. She was taking 0.8 mg lisuride per day and had improved from stage 3 of H & Y staging to stage 2, on the NYUDS scale from 9 to 4, and on the NUDS from 39 to 45 (Figure 1). She was able to maintain these scores when reassessed after 38 weeks of treatment and could then walk independently and go shopping with her mother.

Case 2

A 60 year old electric welder had noticed a left hand tremor with progressing stiffness of his limbs and marked slowness in daily activity since 1978. He was given L-dopa and anticholingerics, producing good mobility initially. However in December 1983 he started to develop a severe "on-off" problem and became almost bed-ridden in the "off" periods. He was initially given bromocriptine with some improvement of his mobility. 2 months later he deteriorated again and became bed-ridden. After bromocriptine had been stopped, lisuride was started and he improved with a marked reduction in the "on-off" phenomena. However, when the dose reached 3.6 mg per day, he became confused and started to hallucinate. The medication was then ceased, with recovery of his mental state. Lisuride was then reintroduced with the maximum dose limited to 0.8 mg per day, supplemented by small amounts of 'Sinemet' between the doses of lisuride. He was well maintained with this combination and after 39 weeks of continuous therapy had improved from stage 3 on H & Y staging to stage 2. On NYUDS, he had improved from a score of 8 to a score of 4, and on NUDS he had improved from a score of 22 to a score of 39 (Figure 2).

Case 3

A 52 year old clerk had Parkinson's disease for 8 years and was initially treated with 'Sinemet' and benzhexol with a reasonable response. In March, 1984, he developed dyskinesia and an "on-off" problem. 'Sinemet' was then ceased and bromocriptine was tried. However, this was stopped because of gastrointestinal intolerance. L-deprenyl was added without any significant improvement. Lisuride was then started with significant clinical improvement initially. He had improved from stage 4 of H & Y staging to stage 3, from a score of 16 to one of 11 on NYUDS and from 16 to a score of 38 on NUDS (Figure 3). Unfortunately he became paranoid and had troublesome hallucinations when the lisuride dose was increased to 3 mg per day. The drug was stopped and subsequently was reintroduced twice but each time resulted in a similar psychiatric disturbance despite the use of only a small dosage. Therefore lisuride was finally ceased after a trial of 12 weeks.

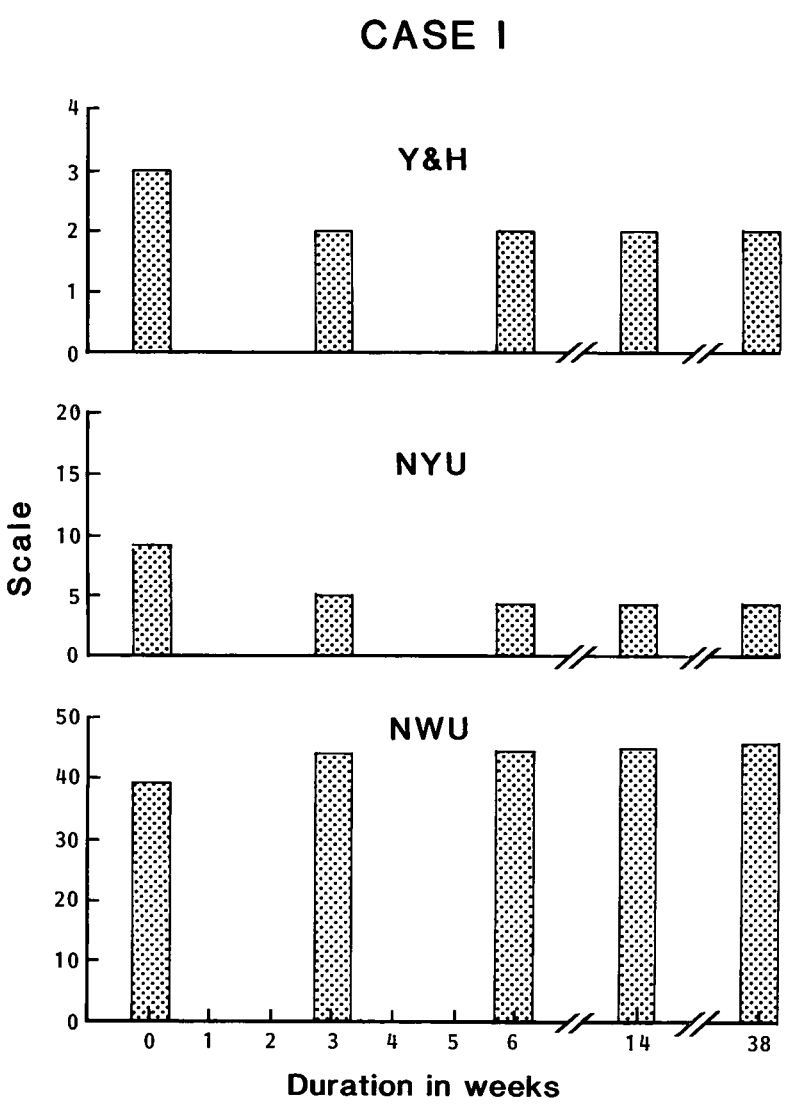

Figure 1. The Hoehn and Yahr Staging, New York University Disability Score and North Western University Disability Score of Case 1 while she was on lisuride and benzhexol.

Y&H Yahr & Hoehn Staging
NYU New York University Disability Scale
NWU North Western University Disability Scale

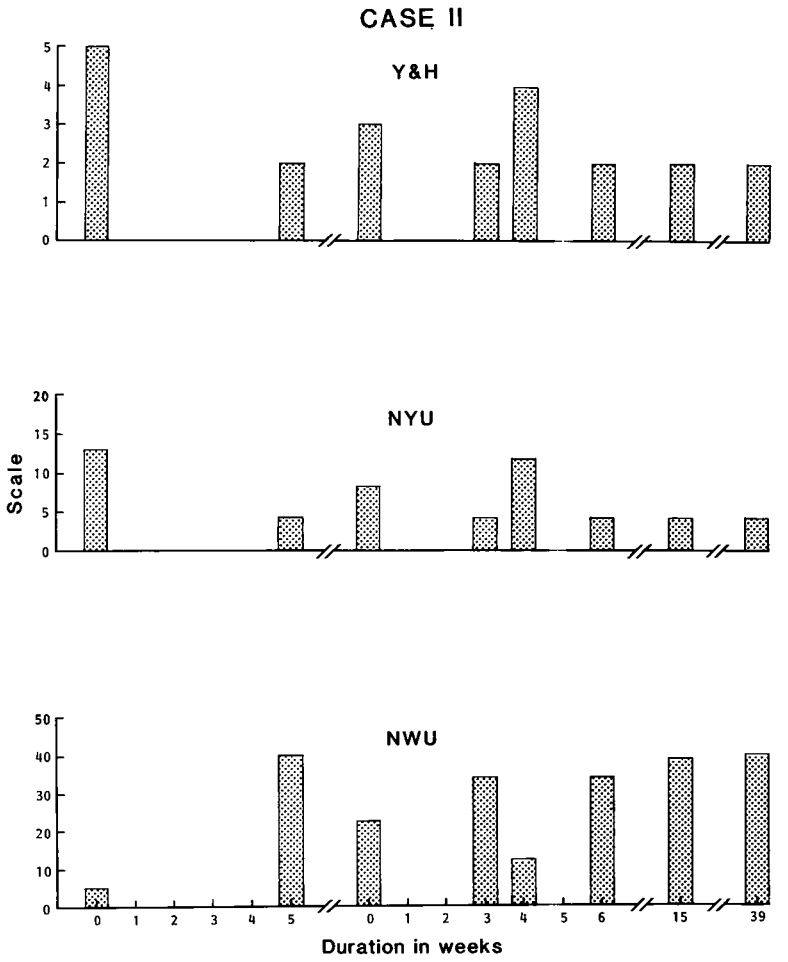

Figure 2. The Hoehn and Yahr Staging, New York University Disability Score and North Western University Score of Case 2 while he was taking lisuride. He was also given 'Sinemet' after the 4th week of the second trial period.

Y&H Yahr & Hoehn Staging
NYU New York University Disability Scale
NWU North Western University Disability Scale

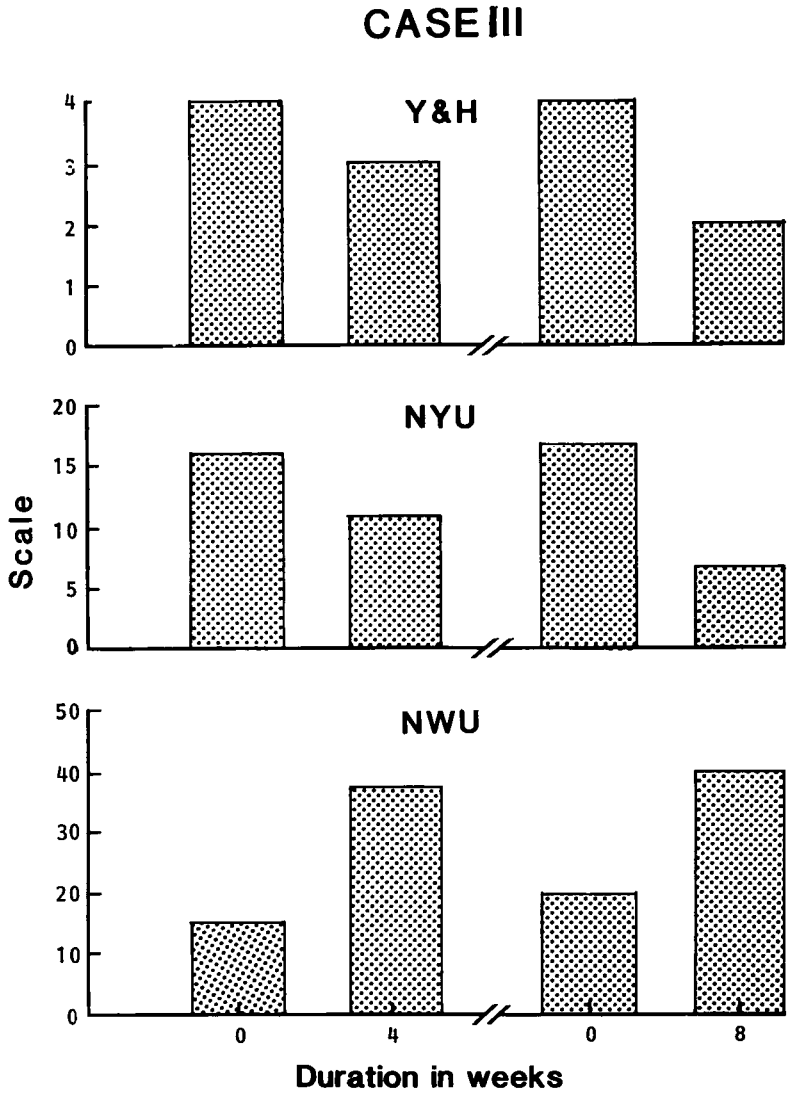

Figure 3. The Hoehn and Yahr Staging, New York University Disability Score and North Western University Disability Score of Case 3 while receiving lisuride and benzhexol. Lisuride was finally ceased because of psychiatric complications.

Y&H Yahr & Hoehn Staging
NYU New York University Disability Scale
NWU North Western University Disability Scale

Case 4

A 60 year old housewife had Parkinson's disease since 1974 and was given 'Sinemet' and benzhexol. However in 1984 she started to develop troublesome dyskinesia despite low and frequent doses of 'Sinemet.' A trial of lisuride was commenced but she developed hallucinations and confusion at a dose of 0.8 mg per day. The drug was ceased. On reintroduction of lisuride, she developed dystonic spasm of her legs and severe hand tremor even at very low dosage (0.2 mg per day). The drug was abandoned.

Discussion

Lisuride alone had a definite anti-Parkinsonian effect that was manifest by improvement in 3 of our patients. This has also been reported in other studies[4,5,6,7,8]. In one of our successfully treated patients, the drug was finally ceased because of psychiatric complications. In our fourth patient, a therapeutic dosage of lisuride could never be attained because of side effects comprising tremor, dystonic spasms, and hallucinations. It appears that psychiatric complications are a major limiting factor in using lisuride.

One of our patients (Case 2) had previously responded to bromocriptine but later lost the response. However, when he was given lisuride he responded quite well. Both lisuride and bromocriptine are dopamine agonists and both preferentially stimulate a population of dopamine receptors that are not linked to enzyme adenylate cyclase[9,10]. Lisuride also has properties of a central serotonin agonist[11,12,13]. Stimulation of these receptors could have been responsible for the anti-Parkinsonian effect of lisuride in this patient.

A "drug holiday" has been reported as useful in managing Parkinson's disease with an "on-off" phenomenon[14,15]. While levodopa may be discontinued in patients who experience decreased responsiveness to the drug, it would be quite feasible to treat them for several months with lisuride. If the response to lisuride then decreased, they might, after a "levodopa holiday", be treated with levodopa again and might then have an enhanced response to levodopa. Because dopamine predominantly stimulates a population of receptors that are linked to adenylate cyclase, whereas lisuride stimulates a population that is not linked to adenylate cyclase[11,13], the combination of the two drugs could be synergistic. The initial cessation of 'Sinemet' and the later combination of lisuride with 'Sinemet' in our Case II, might illustrate this possibility.

Since lisuride is water-soluble, it may be useful in the management of Parkinsonian patients who cannot take drugs orally, e.g. during the peri-operative period or in the reversal of drug-induced acute dystonia. Following a report on control of "on-off" phenomena by continuous intravenous infusion of levodopa[16], it may be useful to evaluate the use of intravenous lisuride in the future.

Summary

Four patients with severe Parkinson's disease were given a trial of lisuride. Two patients responded well, but the other 2 developed psychiatric complications which seemed to be a major limiting factor in the use of the drug. Otherwise, lisuride could be useful in difficult Parkinsonian patients who have a diminished response to levodopa.

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The Natural History of Syringomyelia

*N.E. Anderson, E.W. Willoughby and P. Wrightson**

The surgical treatment of syringomyelia is controversial. Several factors have contributed to the difficulty of assessing the value of surgery in this condition. Many different surgical procedures have been used. These include decompressive laminectomy[1,2], simple drainage of the syrinx by aspiration or incision of the spinal cord[1,2], drainage of the syrinx via a tube into the subarachnoid space[3] or into the peritoneal cavity[4], and various operations at the cervicomedullary junction, ranging from a relatively simple decompression of the foramen magnum[5] to a more formidable procedure involving dissection of the cerebellar tonsils away from the underlying structures, opening of the foramen of Magendie and plugging of the potential communication between the lower end of the fourth ventricle and the central canal of the spinal cord[6]. More recently, terminal ventriculostomy[7] and percutaneous aspiration of the syrinx[8] have been proposed as useful procedures. Radiotherapy is a popular choice of treatment in some parts of the world[9]. Some authors have advocated the use of multiple surgical procedures, applied according to the pathophysiology of the patient's symptoms[10].

An uncertainty about the pathogenesis of syringomyelia underlies this proliferation of surgical approaches[6,11,12,13,14]. Not all cases can be attributed to abnormal fourth ventricular drainage or to severe spinal cord trauma.

There is a lack of information on the long-term results of surgery. Encouraging early results often have been followed by a recurrence of symptoms or the development of new ones after longer follow-up[7,10,15,16,17,18]. In recent years little attention has been given to the natural history of untreated syringomyelia, yet the long duration and variable rate of progression of the untreated disease[19,20,21,22] are important factors contributing to the difficulty in interpreting the results of surgical treatment.

At Auckland Hospital we have had the opportunity to follow 24 patients with syringomyelia who have not had an operation. This report is a retrospective review of the clinical and radiological features, and the natural history in these patients. Twenty of these patients have been described in a previous report[23].

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Methods

The Auckland Hospital medical records and records kept within the Departments of Neurology and Neurosurgery at Auckland Hospital from 1963 to 1983 were reviewed. 52 patients with syringomyelia were seen by the Neurology and Neurosurgery Departments during those years. Some of these patients first presented prior to 1963. Patients with intramedullary spinal cord tumours or syringomyelia resulting from severe spinal cord trauma are excluded. Of the 52 patients with syringomyelia, 24 did not have surgery and are the subject of this report. 20 of the non-surgical patients and 24 of the patients treated surgically have been described in a previous report[23].

Information on progress following initial presentation was obtained by interview and examination of the patient in 16 cases and from the patient's general practitioner and other hospital notes in the other 8. During follow-up, 5 patients died 0.3 to 24 years (median 6 years) after diagnosis. The surviving patients were followed for 1 to 37 (median 9) years after diagnosis.

The severity of disability at long term follow-up was graded as mild if symptoms were not associated with loss of function, and moderate if there was impairment of function without loss of independence. Patients with a moderate disability usually had marked weakness in the arms with upper motor neurone signs in the legs and significant sensory loss over the arms and trunk. However, they were able to dress and feed themselves, were able to walk with little difficulty and, in most cases, were able to continue with their employment or were able to perform normal household duties. Disability was severe if the patient depended on others for assistance in activities of daily living and was unable to walk, either unaided or with a walking stick.

Table 1. Frequency of symptoms at onset and at presentation in 24 patients with syringomyelia

	Initial Symptoms		Presenting Symptoms	
	N	%	N	%
Pain	11	46	18	75
Sensory symptoms (arms/trunk)	9	37	18	75
Upper limb weakness	8	33	17	71
Leg weakness/gait disorder	3	12	9	37
Cranial nerve symptoms*	0	0	7	29
Sensory symptoms in legs	3	12	4	17
Urinary symptoms	0	0	3	12
Altered facial sweating	2	8	2	8
Fasciculation in arms	1	4	1	4

* The cranial nerve symptoms were facial numbness (2 patients), oscillopsia (2 patients), diplopia (2), dysarthria (1), dysphagia (1).

Table 2. Frequency of examination abnormalities at presentation in 24 patients with syringomyelia.

	N	%
Reduced tendon reflexes in arm(s)	24	100
Reduced pain, temperature sensation	21	87
Wasting, weakness in arms	20	83
Upper motor neurone signs in legs	14	58
Kyphosocliosis	14	58
Reduced joint position, vibration sensation	11	46
Cranial nerve signs*	11	46
Fasciculation in arms	7	29
Reduced tendon reflexes in leg(s)	3	12
Horner's syndrome	3	12
Fixed flexion deformity of hand	3	12
Trophic skin lesions of the hand	2	8
Neurogenic arthropathy	2	8
Upper motor neurone signs in arm(s)	2	8

The cranial nerve signs were an abnormality of facial sensation (7 patients), nystagmus (5), wasting and weakness of the sternomastoid and trapezius (3), palatal and pharyngeal weakness (3), masseter weakness (2), wasting, weakness and fasciculation of the tongue (2).

It was not always made clear in the hospital records which reasons were most important in leading to a decision to undertake conservative treatment rather than surgery in these patients. In 9 cases the pathological anatomy was unsuitable (either a normal cervicomedullary junction or a small cervical spinal cord) and in 9 patients the neurological deficit was stable or progressing only very slowly. One patient died suddenly while awaiting operation and 3 patients refused to have an operation. In 2 cases with progressive disease, the reason for conservative treatment was not clear from the hospital records.

Results

Clinical features

24 patients, 11 men and 13 women, with syringomyelia were not treated surgically. The age at onset of symptoms ranged from 8 to 60 (mean 26) years. In 87% of cases, the age of onset lay between 10 and 40 years. The onset of symptoms apparently was precipitated by minor trauma in 5 patients. The precipitating event often appeared to be trivial. For example, one patient first noticed the abrupt onset of symptoms when he sneezed while carrying a bucket of water in each hand.

The frequency of symptoms, at the onset and at presentation is shown in Table 1 and the abnormalities found at initial examination are listed in Table 2. The most common initial symptom was pain and ¾ of the patients had developed pain by the time of presentation. Of the 18 patients who developed pain, 13 complained of neck pain, which radiated into one or both arms in 6 and into the occipital area in 2. Another 3 patients did not have neck pain but noticed pain in the arms. Pain usually was intermittent and often was described as "shooting" in character. It was exacerbated by exertion, coughing, straining, sneezing and neck movements. An unusual distribution of pain was observed in 2 patients. One patient presented with pain in the left leg during exertion, and another described intermittent pain over the left anterior aspects of the thighs during neck flexion. Pain tended to be a prominent clinical feature during the early course, but later it often spontaneously improved. Leg weakness, unsteady gait and cranial nerve and urinary symptoms were unusual initial manifestations but occurred more commonly later in the course of the illness.

The neurological deficit was unilateral in 4 patients (17%) and bilateral but asymmetrical in 17 (71%) cases. Atypical presentations were common. In 3 patients there was loss of tendon reflexes in the legs, unilateral in one and bilateral in 2, in addition to loss of reflexes in the arms. 2 patients had upper motor neurone signs in one arm and lower motor neurone weakness in the other. In 2 cases there was loss of the biceps and supinator jerks, with abnormally brisk triceps and finger jerks. 4 patients (patients 10,12,16,18) had minor neurological findings with normal cranial nerve examination, mild reduction in pain and temperature sensation in cervical and thoracic dermatomes, loss of upper limb tendon reflexes but little or no arm weakness.

Investigations

Skull radiographs were abnormal in 3 of 12 cases. The abnormalities included basilar invagination (one case), atlanto-axial fusion (one case) and platybasia (one case). Cervical spine radiographs showed widening of the cervical spinal canal in 2 of 24 cases (8%) and dysmorphic cervical vertebrae in one patient. In the other 21 patients, spine radiographs were either normal or showed other abnormalities such as cervical spondylosis.

The following special radiological investigations were performed: positive contrast myelography (19 cases), which was followed by computerised tomography (CT) of the cervicomedullary junction and spinal cord in 9 patients; air myelography (4 cases); metrizamide ventriculography (one case) and vertebrobasilar angiography (one case). 4 patients did not have these investigations but a confident diagnosis was made on the clinical features and a prolonged course typical of syringomyelia. In 19 of the other 20 patients radiological findings were characteristic of syringomyelia[9,24]. One patient had a normal myelogram in 1948 but supine views of the cervicomedullary junction were not obtained. However, the clinical features and prolonged course over 43 years were typical of syringomyelia. Spinal cord size, as assessed by these radiological investigations, was normal in 6 patients (30%), increased in 10 cases (50%) and smaller than normal in 4 (20%). A posterior fossa abnormality was seen in

11 of the 20 patients (55%) who had special radiological investigations. The cerebrospinal fluid (CSF) was normal except for a mildly elevated protein in some cases. The median CSF protein in the 19 patients in whom this was recorded in the notes was 0.39 g/L (range 0.10-0.84 g/L).

Table 3. Natural history in 24 patients with syringomyelia

A. Surviving Patients (n = 19)

Patient	Age at Onset	Spinal Cord Dilatation*	Abnormal CMJ†	Duration Symptoms (years)	Duration Follow-up (years)	Age at Follow-up	Clinical Course	Current Disability
1	34	?	?	27	27	61	Chronic progressive	Moderate
2	22	0	?	43	37	65	Chronic progressive	Severe
3	48	+	+	24	5.5	72	Chronic progressive	Severe
4	38	0	0	11	1	49	Chronic progressive	Moderate
5	30	0	+	29	25	59	Chronic progressive	Moderate
6	14	?	?	46	36	60	Chronic progressive	Severe
7	21	?	?	35	5	56	Chronic progressive	Moderate
8	14	+	+	4	2	18	Chronic progressive	Mild
9	37	+	0	15	5	52	Intermittently progressive	Moderate
10	11	0	+	17	16	28	Intermittently progressive	Mild
11	20	0	+	31	31	51	Intermittently progressive	Moderate
12	8	0	0	22	9	30	Non-progressive	Mild
13	30	+	0	13	4	43	Non-progressive	Mild
14	31	0	+	13	6	44	Non-progressive	Mild
15	18	+	0	5	3	23	Non-progressive	Mild
16	16	+	?	17	16	33	Non-progressive	Mild
17	17	+	?	22	21	39	Non-progressive	Mild
18	33	+	+	3	1	36	Non-progressive	Mild
19	18	0	+	28	26	46	Non-progressive	Mild

B. Deceased Patients (n = 5)

20	25	0	+	38	24	63	Chronic progressive	Moderate
21	60	?	?	16	12	76	Chronic progressive	Severe
22	32	+	+	5	2	37	Chronic progressive	Mild
23	23	+	?	23	6	46	Chronic progressive	Severe
24	21	0	+	26	0.3	47	Chronic progressive	Severe

* Spinal cord dilatation: 0 = absent, + = present, ? = not known.
† Abnormal CMJ (cervicomedullary junction): 0 = absent, + = present, ? = not known.

Clinical Course

Details of the clinical course are given in Table 3. Since presentation 5 patients had died. In 2 patients (patients 20,21) aged 63 and 76, the cause of death was unrelated to syringomyelia. Both patients had had slowly progressive disease for 38 and 16 years respectively and, prior to death, were moderately or severely disabled. 3 patients (patients 22, 23, 24) died as a result of the syringomyelia. 2 of them died suddenly, patient 22 after several episodes of transient brainstem dysfunction and patient 23 after several episodes of sudden loss of consciousness associated with a rapid progression in the neurological deficit over several days. In the latter patient, post-mortem examination showed a dilated central cavity in the thoracic and cervical spinal cord without haemorrhage. The medulla was normal and no cause of death was identified. One patient (patient 24), with slowly progressive disease over 26 years, died of respiratory failure. Post-mortem examination in this patient revealed an enlarged central canal extending throughout the cervical and thoracic spinal cord. This was associated with gliosis, demyelination and loss of anterior horn cells in the surrounding tissue.

Of the 19 survivors, 8 followed a slowly progressive course for intervals ranging from 4 to 46 years (median 27) and for intervals of one to 37 years (median 5.5) after initial presentation. At most recent follow-up, these patients were aged 18 to 72 years (mean 55). Neurological disability was mild in one patient, moderate in 4 cases and severe in the other 3. Although the patients with a moderate disability had severe wasting and weakness of the arms, often with spasticity in the legs, they were able to walk unaided or with a walking stick and were able to care for themselves. In all but one case (patient 7) they were able either to continue working or to perform all but the most arduous household tasks. Increasing difficulty with walking and urinary problems were the major cause of a late increase in disability. Of the 3 severely disabled patients, 2 were just able to walk with walking frames and the other was confined to a wheelchair. All 3 required considerable assistance with feeding and self-care. Despite this, they continued to live at home, cared for by relatives. The duration of symptoms before the onset of severe disability in patients 2, 3 and 6 was 25, 24 and 10 years, respectively.

Three patients had an intermittent progression of symptoms. Periods of stability lasting 8 or more years were followed by further progression. At latest follow-up, 2 were moderately disabled and one had a mild disability. Patient 11 first developed symptoms at the age of 20 years but there was no progression in the neurological deficit until 30 years later. After the initial onset of symptoms, patient 10 enjoyed a period of 10 years during which there was no further progression of the neurological deficit. She then noticed an abrupt increase in the sensory deficit, combined with an exacerbation of neck and arm pain following labour and delivery in 2 pregnancies.

Eight patients had no further progression in their symptoms following presentation. These patients were followed for 1 to 26 (median 6 years and had symptoms for 3 to 28 (median 13) years. Their ages at latest follow-up ranged between 23 and 46 years (mean 37 years). In all cases, disability was mild, usually with some sensory

loss over the arms and trunk, trivial or mild weakness in the arms and intermittent neck pain. All these patients remained employed or were able to perform full household duties. Several participated in strenuous sport.

Discussion

The clinical features in these patients were similar to those reported in the literature[25] and were similar to those in patients in Auckland Hospital who had surgery for syringomyelia[23]. Approximately equal numbers of males and females were affected. Symptoms usually began between 10 and 40 years but, in some, the onset occurred in earlier childhood or was delayed to late middle age. The majority of patients presented with classical signs of an intrinsic cervical spinal cord lesion. However, the clinical presentation was variable and numerous atypical presentations were recognised. The neurological signs sometimes were unilateral and, when bilateral, were usually asymmetrical. Pain was the most common symptom and, although a well recognised clinical feature of syringomyelia[5,16,20,26,27], its frequency is often not emphasised.

Adequate assessment of the results of surgical treatment requires a knowledge of the natural history of the untreated disease. However, compared with the proliferation of reports on surgical treatment, relatively little attention has been given to the natural history of syringomyelia. The most extensive report on this issue is that of Boman and Iivanainen[19] who reported on 55 patients with syringomyelia observed for 2 to 45 years. 6 of these patients had an exploratory laminectomy but no other surgical procedure and 22 received radiotherapy. In most patients the progression of the neurological involvement was slow and in 27 patients the condition was stationary for periods of 10 years or more. In reviewing the results of surgical treatment in 127 patients with syringomyelia, Levy et al.[20] commented that the preoperative clinical course was variable and patients often had months or years of stability followed by a period of worsening deficit. Similar, variable clinical courses have been described, with slightly more than half the patients following a slowly but steadily downhill course and the remainder showing little or intermittent progression of symptoms[21,22]. A partial remission of signs[22] or a rapid downhill course[21] rarely may be observed.

In the present series, ⅓ of the patients had no further progression of the neurological deficit after their initial presentation and none of this subgroup developed severe or disabling neurological signs. It is uncertain whether the neurological deficit in these patients will remain stable indefinitely. The possibility of late deterioration is highlighted by the 3 patients who had further progression of symptoms after periods of stability lasting as long as 30 years. In these cases, late progression developed gradually rather than abruptly. Another group had a slowly progressive course. Even among these patients, prolonged survival was usual and they did not become severely disabled until 10 years or more after the onset. In some cases, when the patient died after many years of progressive disease, the cause of death was unrelated to syringomyelia. In some of these patients with slowly progressive disease, sudden de-

terioration in neurological state was seen, usually without subsequent recovery and often leading to death shortly afterwards. Such sudden development of new symptoms has been described by previous authors[21]. The mechanism underlying the sudden deterioration is speculative but haemorrhage into the syrinx[21] and occlusion of small spinal arteries are the most likely causes. Mild trauma may be an important precipitating factor but a history of injury is not always obtained.

The patients described in the present report cannot be compared directly with other patients who have been treated surgically because a number of factors affected the decision to carry out surgery. Patients who were more rapidly deteriorating or who had more severe neurological signs were more likely to be offered surgery. The patients described in this report, therefore, may well be a selected group with a better long-term prognosis than the average. Our findings do show that there is a group of patients with syringomyelia in whom symptoms may not progress over many years, that severe disability is often only a late feature of progressive disease and that prolonged survival is usual. The results show that the clinical course is variable and unpredictable. The variable rate of progression and uncertain clinical course present difficulties in the timing of surgical intervention and the interpretation of the results of operations.

In our experience, the use of CT scanning in the assessment of spinal cord disease has led to the detection of patients with a cystic cavity within a spinal cord of normal or reduced size. In many of these patients the clinical presentation was not typical of syringomyelia and the diagnosis would not have been made with myelography alone. This suggests that the clinical spectrum of the disease may be wider than previously suspected. There may be difficulty, however, on CT scanning with intrathecal soluble contrast medium in distinguishing a syrinx from other lesions that lead to late uptake of contrast in the spinal cord. Exploratory surgery with intraoperative ultrasound scanning of the cord may be necessary in doubtful cases, although it now seems likely that magnetic resonance imaging will become the scanning technique of choice in the diagnosis of syringomyelia and in following the long-term course of patients.

Summary

A retrospective analysis was made of the clinical course in 24 patients with syringomyelia who had not been treated surgically. 5 patients died during follow-up, and the survivors were followed for 1 to 37 (median 9) years after diagnosis. 8 of the 19 survivors followed a slowly progressive course over 4 to 46 (median 27) years but only 3 were severely disabled. 3 patients had an intermittent progression of symptoms, often with long intervening periods of stability. 8 patients had no progression in symptoms after presentation; none of these patients was severely disabled at last follow-up. It is concluded that the natural history of syringomyelia is unpredictable. Some patients have no further progression in symptoms for many years after onset. Prolonged survival is usual even among those patients with a slowly progressive deficit.

The uncertain progression of the clinical course presents considerable difficulties in the timing of surgical intervention and in interpretation of the results.

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Thoracic Intervertebral Disc Protrusion with Spinal Cord Compression

*B. Gilligan and J. Frayne**

Protrusion of intervertebral disc material in the thoracic spine is very uncommon. Dreyfus et al.[1] found fewer than 250 reported cases in the world literature, whilst Love and Schorn[2] postulated an incidence of five cases of protruded thoracic disc per one thousand cases of protruded lumbar disc. Calcification of intervertebral discs is usually confined to the annulus fibrosus and is regarded as a chronic degenerative process of limited clinical importance. Calcification occurring in the nucleus pulposus is far less common and is of greater clinical importance, at least in the thoracic region. Of 11 cases of ruptured thoracic discs, with compression of the spinal cord, reported by Logue[3] 7 showed calcification of the protruded nucleus and another of a calcified nucleus four segments above the rupture. Logue concluded that "Nuclear calcification in the thoracic region is indicative of a degenerative change of such a nature as to render the disc liable to prolapse". Most authors agree that to make a purely clinical diagnosis of the condition is difficult as thoracic disc protrusion may mimic other disorders including spinal cord neoplasms and multiple sclerosis.

Radiographic diagnosis may be achieved pre-operatively with remarkable accuracy using plain films, tomography, myelography and particularly CT scanning. Prolapse of a thoracic intervertebral disc has acquired a somewhat sinister reputation due to the significant hazards associated with surgical removal.

It is our purpose to describe four cases of prolapsed thoracic intervertebral discs, all proven at operation, which to some extent confirm the serious nature of the disorder.

Case Reports

Case 1

A fifty year old physician was referred on the 2nd November, 1978 with a 20 year history of intermittent pain in the right lower chest and back area. For 2 years pain had been severe in the right iliac fossa, radiating through to the back. For 2 weeks the intensity and frequency of the pain had

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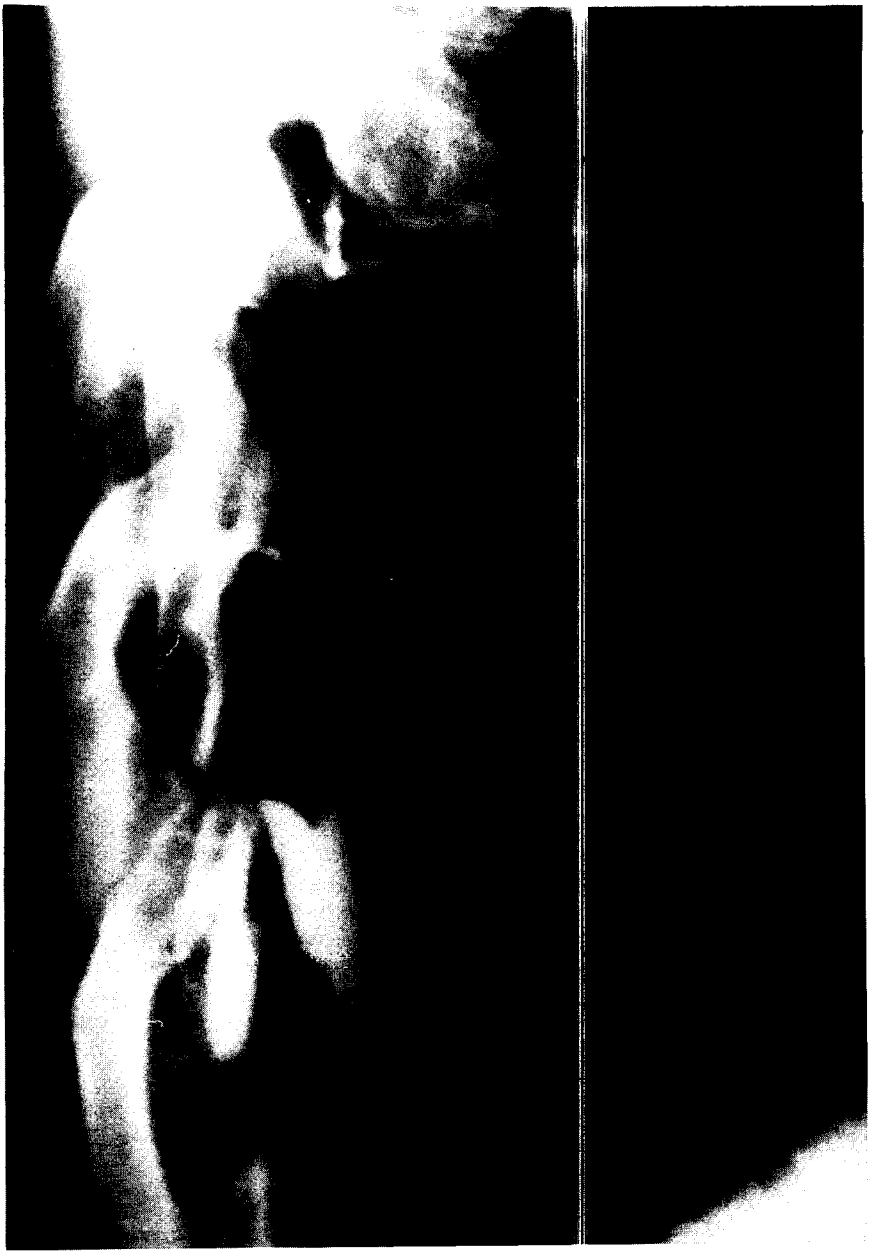

Figure 1. Case 1. Lateral view of myelogram showing thecal obstruction at T10-11 disc space. Note calcification of corresponding disc nucleus.

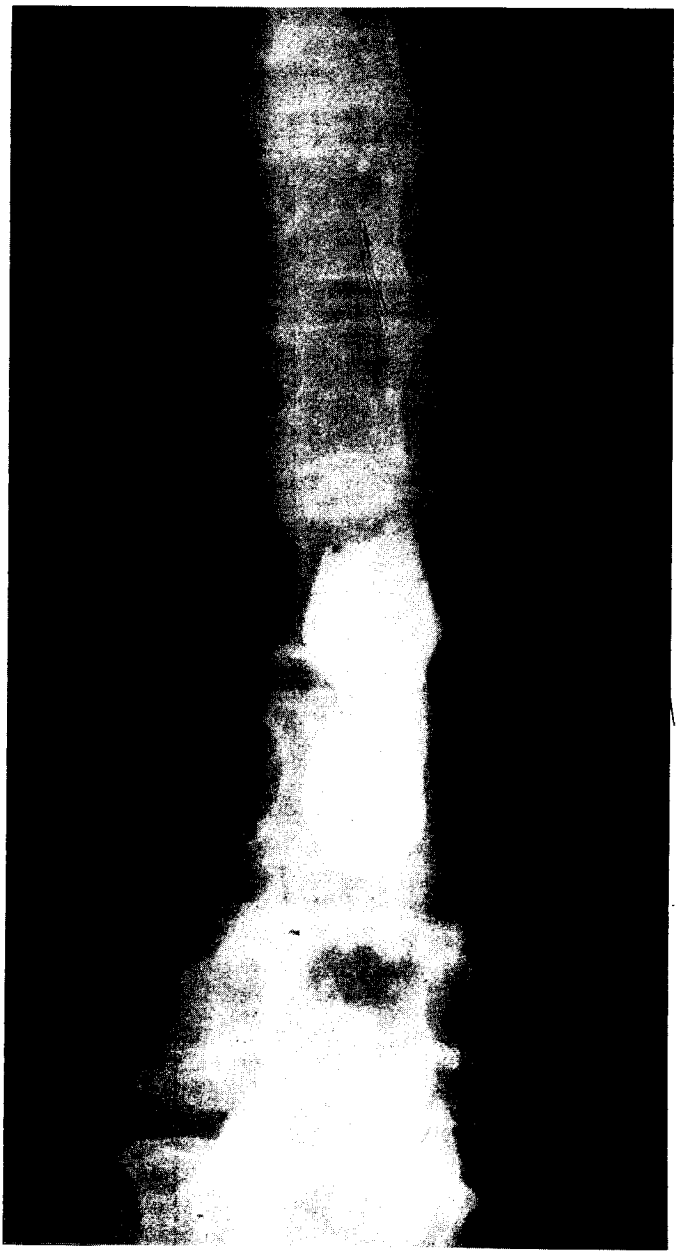

Figure 2. Case 1. A-P view of myelogram showing spinal cord displaced to the left by indentation from right side.

been much more severe, waking him 3 or 4 times each night. There were no accompanying urinary symptoms. However there had been a tendency towards constipation. The pain had been associated with 19kg weight loss over 2 years. Prior to referral full blood examination, erythrocyte sedimentation rate, chest radiographs, plain abdominal radiographs, intravenous pyelogram, barium enema, urine microscopy and culture and renal and liver function tests were all normal.

Physical examination revealed a middle aged man who looked thin and unwell and was in obvious discomfort. There was deep local tenderness in the right iliac fossa and in the corresponding region posteriorly. Neurological examination revealed increased muscular tone in the lower limbs with hyperactive reflexes at knee and ankle, and sustained clonus at both ankles. The plantar responses were extensor. Sensory testing disclosed a band of hyperaesthesia at T9-11 with impaired appreciation of pain and temperature bilaterally to the same level. Vibration sense was minimally impaired at the ankles, but proprioception was normal. Plain radiographs of the thoracic spine showed minor degenerative beaking of the lower thoracic vertebral bodies with a small intrusion of calcified disc substance at the T10-11 interspace. CT scan of the dorsal spine revealed an intraspinal mass of calcium due to extrusion of the intervertebral disc at this level. Myelography showed thecal obstruction at the T10-11 disc space (Figure 1). The corresponding disc nucleus was heavily calcified and a rounded calcified collection measuring approximately 1.5 cm in diameter lay within the spinal canal to the right of the spinal cord. The spinal cord was displaced to the left and the right side of the theca was deeply indented (Figure 2).

On the 13th November, 1978 a dorsal laminectomy was performed from T8 to T11 by Mr. W. Elrick. Intraspinal calcified disc was noted at the T10-11 interspace protruding backwards into the spinal cord which was in turn compressed against the lamina. The dura was incised longitudinally and the spinal cord retracted to the left and laterally. Calcified disc material was curetted out until the disc was level with the posterior aspect of the vertebral bodies. Post-operatively the patient was unable to move his right lower limb and complained of paraesthesia in it. The left leg was also weak but movement was possible both at the foot and hip. Urinary retention was noted. Improvement occurred over the next few days, and the patient was admitted to a rehabilitation unit. He made good progress returning to his practice within three months. At review on the 11th March, 1980, he walked with a spastic gait using a four point stick, and had a significant scoliosis concave to the right. Both legs showed spasticity with extensor plantar responses. Pain and temperature sensation were impaired on the left side to T12 level. On the right side of the body he had reasonably normal sensation but a patch of numbness in the right T10-11 dematome. CT scan of the thoracic spine on the 16th April, 1980 showed a small calcific nodule in the right side of the spinal canal at the T10 level with a large amount of calcific material in the anterior aspect of the spinal canal at the T11 level. In view of the static neurological situation no further surgery appeared indicated.

Case 2

A 51 year old lady presented in May, 1980 with a 5 to 6 year history of intermittent tingling feelings in the feet and lower legs, not extending as high as the knee. She had previously been seen in 1978 with no objective physical findings, and then had normal nerve conduction studies of the lower limbs. For 18 months she had fallen several times and stated that as she walked she had a feeling of a throb in the left knee which might radiate down to the foot or left ankle. She stated that sensation about the right ankle was not as good as it was elsewhere and that if she continued to walk she felt that her left knee would give way. On sleeping at night she tended to wake and then lacked awareness of her legs. If she turned over in bed she had an uncomfortable feeling in the left knee. Sphincter function was normal but her balance had become unsteady.

Examination revealed a young looking woman who walked with a mildly stiff-legged gait, but could walk on her toes and her heels. There were no abnormalities in the cranial nerves or upper limbs but increased tone was present in both lower limbs, with clonus at the ankles and knees, hyperactive reflexes in the legs and bilateral extensor plantar responses. Sensory examination was normal and Romberg's sign negative. She was hospitalized a week later and myelography revealed an incomplete block at the T7-T8 level due to an extradural mass measuring approximately 1 cm wide and 2 cm long (Figure 3). The block was opposite the T7-T8 disc space and was partly calcified

Figure 3. Case 2. A-P view of myelogram revealing incomplete block at T7-8 due to calcified disc material.

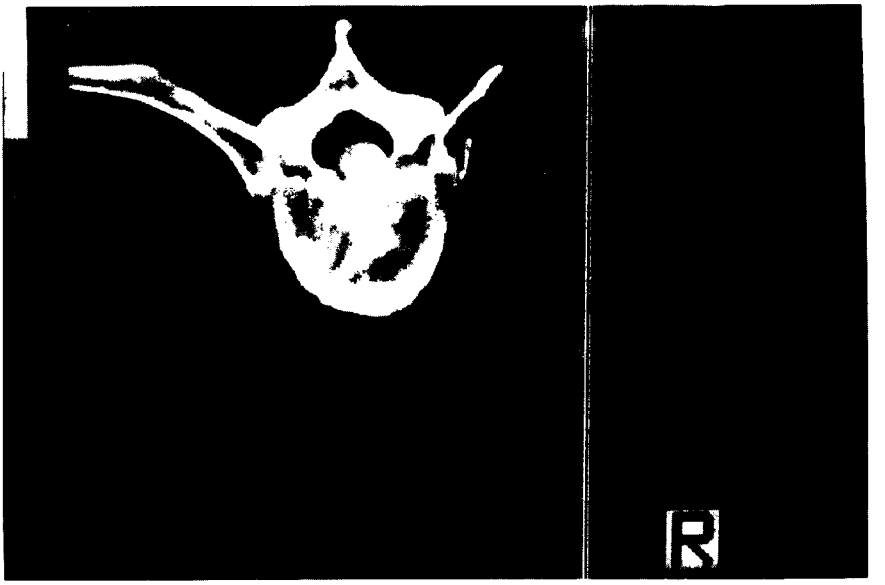

Figure 4. **Case 2. CT scan of dorsal spine showing rounded calcified mass occupying much of spinal canal and associated calcification within disc material.**

with calcification appearing to extend into the disc itself. The corresponding disc space was narrowed. It was concluded that the lesion at the T7-T8 level was an extruded calcified intervertebral disc but the possibility of a meningioma could not be excluded. It was also noted that there was evidence of right postero-lateral herniation of the L1-L2 intervertebral disc with associated calcification. The CSF protein was 540 mg/L and no cells were seen. The CSF WR was negative and the serum vitamin B12 level was 423 pgm/ml (normal range 150-800). CT scan of the thoracic spine showed a rounded calcified mass at the T7-T8 level measuring 2 cm long and 1 cm wide. The mass occupied the greater part of the spinal canal. There was calcification within the T7-T8 intervertebral disc (Figure 4). She was referred to Mr. R. Southby for surgery. The myelogram had been interpreted as suggesting a largely central lesion, although the CT scan suggested that the calcified lesion was largely to the right of the spinal cord. This was one of the first spinal scans done in Melbourne and it was decided to be guided by the myelogram. Therefore a left lateral approach was carried out, approaching the antero-lateral aspect of the bodies of T7 and T8 through the extra-pleural space. After dividing the anterior longitudinal ligament some disc material was removed, but working gradually around the antero-lateral aspect of the dura no significant disc prolapse on the left side, as had been suggested by the myelogram, was found. Laminectomy at T7 and T8 was then performed at the same operation. On opening the dura the spinal cord was grossly displaced posteriorly and to the left and it was apparent that there was a largely right-sided disc prolapse. It was decided to close the wound and steroid therapy was commenced. On recovering from the anaesthetic the patient had signs of a complete cord lesion at the T8 level affecting both motor and sensory functions. She was transferred to a major teaching hospital. On the following day a right-sided extra-pleural lateral approach was made. On entering the antero-lateral aspect of the disc space, a significant calcified lesion indenting the anterior aspect of the dura was found. This material was removed, giving adequate decompression. Post-operatively steroids were continued for a few days, but unfortunately her paraplegia remained complete. She was transferred to a spinal unit several weeks later where she underwent a course of rehabilitation. Unfortunately there was no improvement in her neurological deficit.

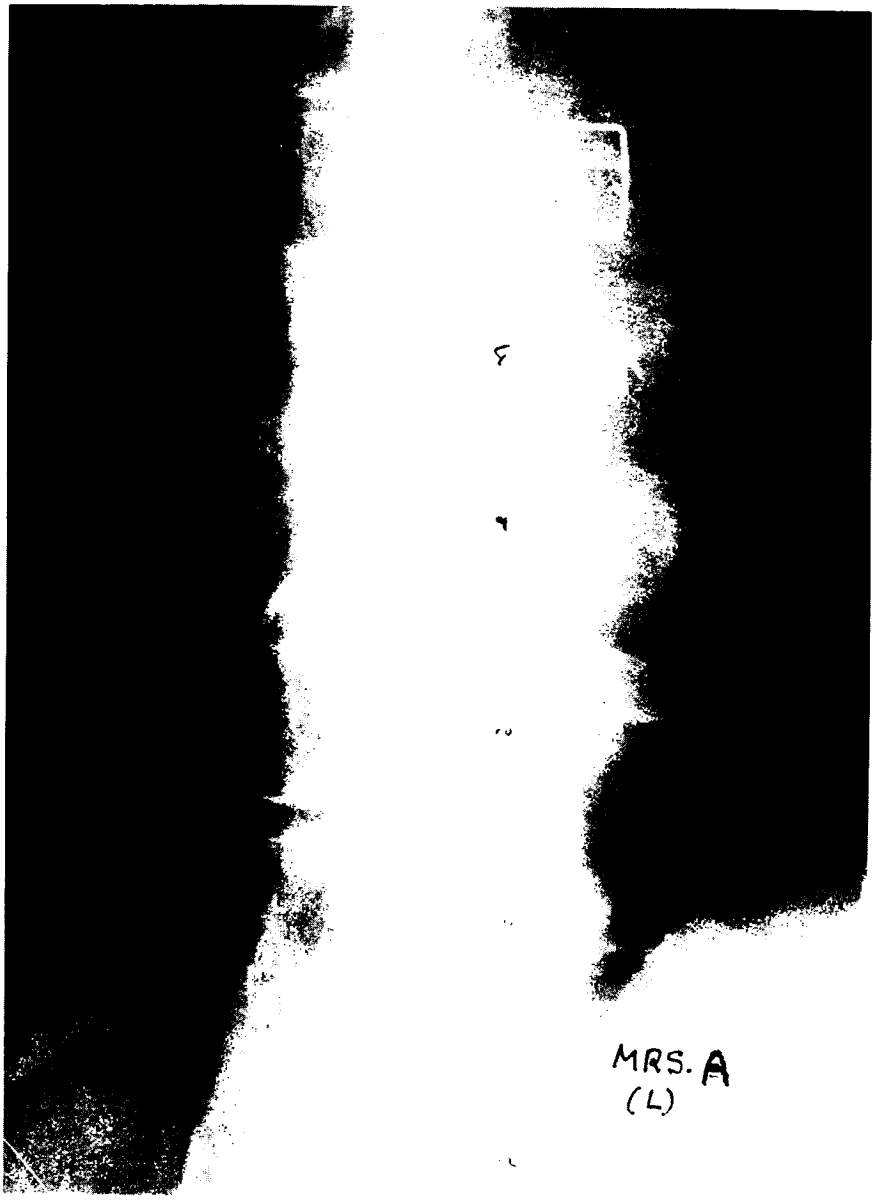

Figure 5. Case 3. A-P view of myelogram showing centrally situated anterior indentation at T8-9 disc space, and calcified disc material.

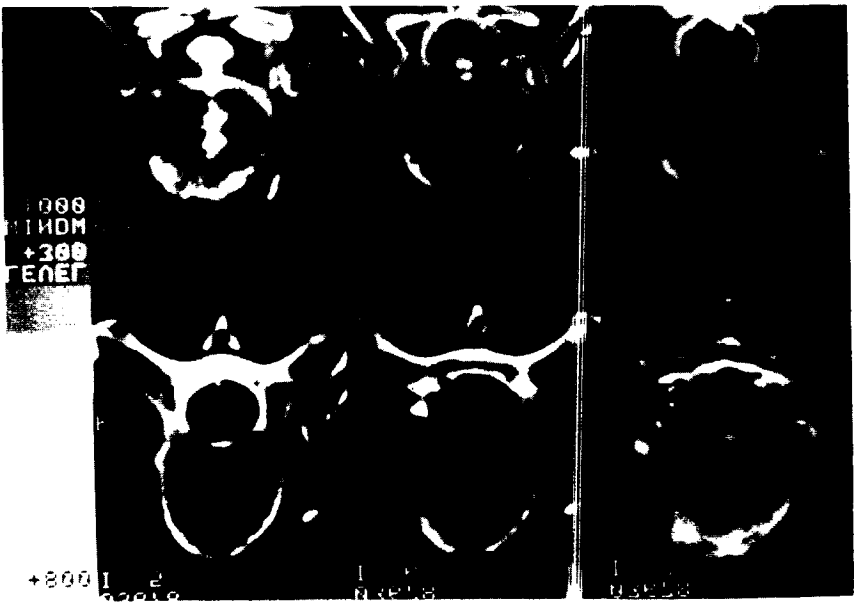

Figure 6 Case 3. CT scan of dorsal spine showing calcified disc material extending deeply into the spinal canal as a large "button" (CT cuts 1-7, 1-8, 1-9, 1-10).

Case 3

A 68 year old lady presented in August, 1983 with an 18 month history of difficulty standing up after delivering a bowling ball. A month before presentation she was at dinner and her right foot went to sleep but recovered quickly. For 10 days she stated her feet felt like lumps of lead, and this seemed to follow an 8 hour drive in a car. At the time of consultation her feet felt warm and tingling. She denied motor or sensory disturbance in her hands.

Examination revealed a rather large woman who had no abnormality in her cranial nerves or upper limbs but who walked with a very spastic gait with some distal weakness and increased reflexes at the knees and ankles. On active neck flexion in the supine position, her umbilicus moved towards her head, indicating weakness of the lower abdominal muscles (Beavor's sign). The plantar reflexes were extensor, vibration sense was impaired as high as the rib cage but the rest of the sensory examination was normal. Myelography was performed on the 1st September, 1983 and revealed a significant anterior thecal indentation at T8-9 approximately 15 mm long and 5 mm deep (Figure 5). The indentation was centrally situated and was associated with extrathecal calcification in this region. CT scan of the thoracic spine the following day confirmed the presence of heavy calcification in the nucleus of T8-9 disc, with an associated large calcified disc sequestrum measuring approximately 1 cm in diameter projecting into the spinal canal, deeply indenting the theca (Figure 6). The CSF protein was 0.58 g/L, with no increase in cells. Multiple disc degeneration was also seen in the lumbar region with significant canal stenosis at L3-4 and L4-5 levels. In addition multiple disc degeneration in the cervical region was noted, with a moderate anterior thecal impression at C5-6.

She was referred for surgical decompression to Mr. R. Southby who made an antero-lateral approach to the T8-9 level through the extra-pleural space. The disc space was entered, removing a central calcified prolapsed disc, without disturbing the dura of the spinal cord. The patient was reviewed

on the 9th January, 1984 and had done extremely well. She walked with a slightly wide based gait but the spasticity, which was previously very obvious, had largely disappeared. Muscle strength and co-ordination were normal, and the sensory symptoms had resolved.

Case 4

A 43 year old medical technologist presented with a 6 month history of increasing weakness in both legs, the right more than the left. For 2 months there had been a strange feeling in the sole of the right foot and calf and a constant feeling of stiffness of the right second toe, with some numbness extending to the right buttock. A sensation of freezing cold on the anterior aspect of the left shin, moving up towards the left buttock, had also been noted. No pain was experienced and sphincter function was normal. Spontaneous jumping of the right leg in bed had been present for 2 weeks.

Table 1. Summary of clinical and radiological findings

	Case 1	Case 2	Case 3	Case 4
Age	50	51	68	43
Sex	M	F	F	F
Duration of Symptoms	20 Yrs	5-6 Yrs	18 Months	6 Months
Symptoms				
Pain	+	–	–	–
Sensory	+	+	+	+
Motor	–	+	–	+
Sphincter disturbance	–	–	–	–
Signs				
Corticospinal	+	+	+	+
Spinothalamic	+	–	–	+
Posterior Column	–	–	+	+
Nerve Root	+	–	–	–
CSF Protein	0.81g/L	0.54g/L	0.58g/L	0.54g/L
Radiographic findings				
Plain Film				
Calcification of Disc	+	+	+	+
CT Intraspinal				
Calcification	+	+	+	+
Myelographic				
Obstruction	+	+	+	+
Operative findings				
Situation of disc	Centrolateral T10-11	Centrolateral T7-8	Central T8-9	Centrolateral T10-11
Postoperative state	Incomplete Spinal Cord Lesion	Paraplegia	Improved	Improved

+ indicates feature present.
– indicates feature absent.

Examination showed no abnormality in the cranial nerves or arms but she had a mildly spastic gait affecting the right leg more than the left. Strength in the right lower limb was grade 4, on a scale of 5, for all groups. Tendon reflexes in the lower limbs were hyperactive and both plantar responses were extensor. Sensory examination revealed impaired appreciation of pain and temperature on the left leg as high as L1 with some impairment of proprioception and vibration sense bilaterally. Plain films of the thoracic spine revealed marked calcification in the intervertebral discs at T9-10 and T10-11 levels (Figure 7). Metrizamide myelography displayed an extra-dural filling defect opposite the body of T10, pushing the spinal cord to the left (Figure 8). The appearance was that of a calcified disc

Figure 7. Case 4. Plain film of dorsal spine showing marked calcification in intervertebral disc at T9-10, and more obviously at T10-11.

Figure 8. Case 4. CT scan of dorsal spine showing densely calcified lesion displacing spinal cord posteriorly and to the left.

protrusion at T10-11 level. CT scan of the thoracic spine confirmed a dense calcific lesion displacing the spinal cord posteriorly and to the left. The patient was referred to Mr. K. Siu for surgical decompression of the spinal cord. A right-sided approach using costotransversectomy was used. The T10-11 disc space was entered laterally and portions of the contiguous vertebral bodies resected. The disc was calcified and proved extremely difficult to extract. Because of the difficulty encountered it was decided to close the wound and review the situation later. Postoperatively there was a small right pneumothorax requiring drainage for 24 hours. Post-operative CT scan of the region suggested residual disc material medially occupying the spinal canal at T10-11. After considerable reflection it was agreed to perform a further operation a month later.

On the 7th October, 1982 the T10-11 disc space was approached by a combined transthoracic transvertebral approach (Mr. K. Siu, Mr. G. Shardey). A right lateral thoracotomy was performed allowing access through the inferior pleural cavity. The T10-11 disc space was approached laterally and bone from the lower half of T10 and the upper half of T11 was drilled out to expose the ventral boundary of the spinal canal. Dense scar tissue made dissection difficult and cheesy material representing the calcified disc prolapse oozed from the canal when the cavity was entered. Disc removal was completed and the bone defect filled with a Kiel plug and rib chips. The post-operative course was uncomplicated and the patient experienced rapid and marked relief of sensory symptoms and a gradual improvement in power. When reviewed on the 21st December, 1982 she was walking extremely well with a minor limp of her left leg. She had hyperactive reflexes in both lower limbs, the left more than the right, with some hypoaesthesia to pinprick over the left leg below the knee.

Discussion

The salient clinical and radiological features of the cases are summarised in Table 1.

Symptoms

Duration

One patient had symptoms over 20 years and the other 3 patients had histories ranging from 6 months to 6 years. In all 4 patients the symptoms became worse gradually. There was no significant history of trauma in any of the patients.

Sensory

Sensory symptoms occurred in all 4 patients. Pain was the dominant symptom in Case 1 and the pain which had been present for some 20 years reached such proportions and was associated with such weight loss that a visceral malignancy had been suspected by his physicians. Tingling, numbness, heaviness and paraesthesia of the lower limbs occurred in 3 of the 4 patients and were bilateral.

Motor

Two of the patients complained of weakness in the lower limbs, causing a disturbance of gait of minor degree.

Sphincter Disturbance

This was not evident in any patient.

Physical Findings

Motor

All 4 patients had involvement of the pyramidal tracts with increased muscular tone, hyperreflexia and extensor plantar responses. 3 patients showed evidence of a spastic ataxic gait. There was no evidence of muscle weakness.

Sensory

One patient had segmental hyperaesthesia corresponding with the level of disc protrusion and in addition had involvement of the spinothalamic tracts bilaterally. Patient 4 had evidence of spinothalamic dysfunction and 2 patients had impairment of vibration sense.

Diagnostic studies

Cerebrospinal fluid examination

The cerebrospinal fluid protein concentration was mildly elevated in 3 patients, of the order of 0.54 g/L, and in Case 1 the protein was 0.81 g/L. There was no increase in cells in any patient.

Radiology

Plain films of the thoracic spine revealed significant calcification within the relevant intervertebral disc. This calcification was seen to extend into the spinal canal in all 4 patients. Myelography revealed an extradural filling defect opposite the calcified disc in all patients. This was associated with partial thecal obstruction in 2 patients. The average size of the extradural mass was approximately 1.5 cm. CT scan of the dorsal spine in each case revealed an intraspinal mass of calcium due to extrusion of the intervertebral disc at the same level. The investigation also accurately revealed the direction of displacement of the spinal cord and the relationship of the calcified material to the anterior aspect of the cord.

Surgical Procedures

Surgery was recommended for all 4 patients. A dorsal laminectomy was carried out at the appropriate level in one patient and in the second case dorsal laminectomy was performed when a lateral approach proved to be unrewarding. This same patient subsequently had a further lateral approach from the opposite side, at which stage the calcified disc material was removed. Case 3 was operated using the lateral approach and Case 4 had 2 separate surgical procedures using a lateral approach. On the second occasion a transthoracic transvertebral approach proved necessary to obtain adequate access to the anteriorly situated disc material. Two of the patients responded well to surgical decompression with improvement in pre-operative physical signs and symptoms. One patient has remained completely paraplegic following the first surgical procedure while Case 1 had residual neurological dysfunction of significant degree although the pre-operative symptom of pain was dramatically relieved.

Comment

The human intervertebral disc consists of two different anatomical structures, viz. a nucleus pulposus which is an avascular mucoid substance lying on the border be-

tween the medial and posterior third of the disc and a firm annulus fibrosus made up of fibrocartilage which encloses the nucleus and is demarcated from it by a transitional zone of collagenous fibres. Changes appear in the disc with advancing age: the annulus undergoes hyaline change and the nucleus is replaced by fibrocartilage elements that initially contain fluid but progressively become coarsened and desiccated. Several diseases are known to be associated with intervertebral disc calcification. These include ochronosis, a metabolic disorder in which an excess of homogentisic acid occurs due to homogentisic acid oxidase deficiency. Disc calcification has also been reported in patients with haemochromatosis, chondrocalcinosis, hyperparathyroidism (where the calcification has been shown to be due to calcium pyrophosphate deposition) and in patients following severe poliomyelitis. Intervertebral disc calcification has been observed in acromegaly and amyloidosis. None of the patients described here suffered from these conditions and in these patients it would appear that the nuclear calcification is simply the result of severe degenerative change. Unlike disc degeneration in the cervical and lumbar regions, trauma does not appear to be a significant aetiological factor. Although not common as a cause of physical signs or symptoms, thoracic intervertebral disc calcification is seen in 5% of chest x-rays in the general adult population[4].

Various mechanisms have been put forward to explain the involvement of the long tracts of the spinal cord. In some cases there is obviously a true compression as a result of the large size of the protrusion which may occupy the greater part of the diameter of the spinal canal, thus compressing the cord backwards against the lamina, and ligamentum flavum. Kahn[5] suggested that the dentate ligaments resisted the backward displacement of the spinal cord and produced traction on, and distortion of, the nerve fibres in the vicinity of the attachment of these ligaments to the transverse meridian of the spinal cord. In some cases it is likely that interference with the blood supply is the basis of a pathological change, in particular as a result of obstruction or occlusion of the main arterial trunk — the anterior spinal artery. This would certainly explain the neurological picture resulting from necrosis of the cord substance and the severe spinal cord damage in those cases where the size of the protrusion is not great, and also the poor recovery that may result despite complete removal of the prolapse. It is of interest that in Logue's Case 6[3], necropsy did not reveal demonstrable changes in the main vessel which could have been invoked as the cause of the neurological picture and of the subsequent postoperative transverse cord lesion. There was demonstrated, however, extreme distortion of the fibre tracts due to the close apposition of the prolapsed calcified disc to the cord. Extraordinarily close apposition of the prolapsed calcified disc is demonstrated very clearly on the CT scans of the spinal column. Previous reports on this subject have agreed that it is impossible to formulate a distinctive clinical syndrome of thoracic intervertebral disc protrusion as the condition may mimic other disorders such as spinal cord neoplasm and multiple sclerosis very closely.

Examination of the cerebrospinal fluid has again been unhelpful in any specific diagnostic way. McAllister and Sage[6] reported that 75% of their 20 surgically proven thoracic disc protrusions had significant changes on plain radiographs. They stated that disc space calcification in a patient with symptoms suggestive of spinal cord compression should alert one to the possibility of thoracic disc protrusion. These

findings correspond very well with Logue's series[3]. However, disc-space calcification was present in only 18 of 61 cases reported by Love and Schorn[2]. In this latter series the calcified disc proved to be the offending one in every case. Calcified material within the spinal canal is an important radiological feature and was present in all of our 4 cases. It was clearly demonstrated by CT scanning, which in all 4 cases gave an accurate pre-operative diagnosis as well as providing an accurate display of the nature and extent of the disc protrusion and its relationship to the spinal cord. In particular CT scanning revealed that the calcified disc material may virtually invaginate the ventral aspect of the spinal cord to a significant degree in severe prolapse. Myelography was performed in all 4 of our cases and confirmed the presence of an extra-dural mass, in each case of approximately 1.5 cm in diameter indenting the anterior aspect of the spinal theca. This finding has been reported in most previous series. Love and Schorn[2], in reviewing their 61 cases of surgically verified thoracic disc protrusions, stated that the natural course of this disorder is one of progression and that for this reason surgical exploration and decompression is necessary. Furthermore they indicated that the surgical procedure of choice in patients with cord dysfunction appeared to be a wide complete laminectomy of 2 or more vertebrae. They recommended that the disc should be removed extradurally, but stated that it was sometimes wiser to open the dura and to remove the disc transdurally as this may prove to be less traumatic, particularly in the case of a firm mid-line disc protrusion which is adherent to the dura. Division of the dentate ligaments may be necessary to facilitate rotation of the spinal cord or to allow it more freedom of movement. In their 61 patients they found 7 instances in which the disc had eroded through the anterior dura. In one of these a spicule of extruded disc fragment had actually penetrated the spinal cord. Of Logue's 11 patients[3] 3 developed total transections of the cord postoperatively and 2 patients had increased neurological deficit following surgery. The remaining 6 patients did well. Because the compressive lesion lies anterior to the spinal cord and is commonly median in position, laminectomy provides the least favourable access. Further, because the protrusion is often a hard, calcified excrescence with a bulbous extremity adhering tightly to the dura, with a jeopardized blood supply to the spinal cord, a lateral approach to calcified prolapsed thoracic discs has been developed using an extension of costotransversectomy. This technique was used successfully in 2 of the 4 patients described here, but was associated with paraplegia in one of the patients.

Summary

Four patients presenting with spinal cord compression and spinal nerve root irritation are described. The clinical and radiological features are described and the contribution of CT scanning to accurate diagnosis of this condition is highlighted. Review of the literature indicates that the natural history of this disorder is one of steadily progressive neurological dysfunction. Surgical decompression of the lesion, although hazardous, is the only therapeutic option. Brief comment is made on the neurosurgical approaches currently in vogue.

Acknowledgements

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Substance P in Human Hypothalamus

*R.D. Helme and K. Thomas**

Substance P (SP) is an undecapeptide found widely distributed in the brain. It has been localized, using immunohistochemical studies, in the hypothalamus of experimental animals[1,2] but appears to be relatively sparse in the tuberal region. One study indicated that SP was localized in the median eminence of the primate neurohypophysis[3], but no details were provided. Radioimmunoassay data have suggested that SP is found in higher concentration in the basal tuberal region in man[4] but the pituitary stalk was not examined. No study has examined the immunohistochemical localization of SP in the hypothalamus and pituitary stalk of man, although regional studies of brainstem[5] and basal ganglia[6] have been reported.

More recently SP has been implicated in endocrine function in animals[7,8,9]. It has been suggested that this might occur at the level of the hypothalamo-pituitary axis. If such a role for SP is postulated in man, it should be established that the peptide is distributed in appropriate areas of the human hypothalamus and neurohypophysis. In this study the distribution of SP has been examined in human hypothalamus and pituitary stalk using radio-immunoassay and indirect immunohistochemistry.

Methods

Samples of hypothalamus and pituitary stalk were collected from 28 human autopsy cases without known pathology of the region. Twenty-one were used for biochemical examination and 7 for histochemical studies. The samples were frozen and details of the subject's sex, age, disease processes and duration from death to freezing were recorded. Samples were obtained from 12 males and 9 females. The age range of the subjects was 42 to 77 years, and the duration to freezing ranged from 2 to 48 hours. The disease states considered as variables were cancer, alcoholism,

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vascular disease and others, and the terminal causes of death as respiratory infection, vascular, metabolic and others. The samples were trimmed whilst frozen by vertical cuts at a level just rostral to the optic chiasm, caudal and lateral to the mammillary bodies. A horizontal cut at the anterior commissure determined the vertical extent of the samples. They were then divided into regions as follows : the pituitary stalk was cut at the junction with the tuber cinereum; 2 vertical cuts separated supraoptic, tuberal and mammillary regions; the latter 2 were divided into superior and inferior parts; the inferior tuberal region was further subdivided into medial and lateral components.

Details of the radio-immunoassay have been published previously[10]. The tracer used was Tyr^8-Substance P (Peninsular Laboratories) iodinated with ^{125}I, using the chloramine-T method. Initial antibody dilution is 1:15,000. A Dextran 10-coated charcoal separation method was used. Assay sensitivity was 6pg/tube. Inter-assay and intra-assay variation was 12% and 10%, respectively. Cross reactivity occurred with the C-terminal peptide analogues of SP. Recovery of synthetic SP added to the tissues was 93%. Tissues were homogenized in 2M acetic acid. An aliquot was taken for protein estimation using the Bradford method. Results were expressed as ng SP per mg protein. The effects of age, sex, disease state and duration to freezing were examined by analysis of variance using the Statistical Package for the Social Sciences. Differences between areas were also examined by analysis of variance.

For immunohistochemistry, 5 samples were fixed in cold 10% buffered formalin (pH7) and then immersed in 15% sucrose in phosphate buffered saline and frozen in a mixture of chloroform and dry ice. Ten micron cryostat sections were used, antisera were diluted 1:250 and used in 50 μL aliquots under coverslips with an initial overnight incubation time. Controls included phosphate-buffered saline, normal rabbit serum and BSA/Triton X-100 diluent. Some antisera were preincubated with Substance P (1.5×10^{-3} μmoles/50 μL) to neutralize specific staining. Sections were mounted in veronal glycerol and viewed in a Leitz Orthoplax fluorescence microscope with an epi-illumination system.

Both radio-immunoassay and immunohistochemistry lack complete specificity for peptide identification. Thus all the results must be interpreted as representing SP-like immunoreactivity.

Results

The concentration of SP in each region examined is shown in Table 1. The SP content was greatest in the pituitary stalk, followed by the mediobasal hypothalamus immediately above. All other regions had lower concentrations. No effect of age, sex, disease state or duration to freezing was shown.

The immunohistochemical experiments showed perikarya of neurons containing SP in the pituitary stalk with a few in the lateral and periventricular hypothalamus. These had a diameter of approximately 20 μm and the staining was finely granular around an eccentric nucleus. Fibres were widespread in the hypothalamus and pituitary stalk with the highest density in the periventricular region parallel to, but slightly

Table 1. Substance P content of human hypothalamus

Area	Substance P content (ng/mg protein) $\bar{x} \pm SE\ \bar{x}$
Pituitary Stalk	16.7 ± 2.9*
Suprachiasmatic hypothalamus	3.7 ± 0.4
tuberal hypothalamus	
superior	6.0 ± 1.2
mediobasal	8.3 ± 1.1**
laterobasal	5.3 ± 0.8
Mammillary hypothalamus	
superior	5.5 ± 0.7
inferior	5.1 ± 0.9

* Significantly different from all other values $p < 0.01$
** Significantly different from 1 and 2, $p < 0.05$

separated from, the third ventricle. Black and white photographs could not be used to demonstrate the fluorescence because of large amounts of yellow autofluorescence due to lipofuscin. However, specific staining could easily be identified under the microscope.

Discussion

SP has been suggested as a neuromodulator or neurotransmitter in a number of regions of the central[11] and peripheral;[12] nervous systems. A role for SP as a modulator of hypothalamo-pituitary endocrine function has been suggested in studies on experimental animals. The radio-immunoassay data for the regional distribution of SP reported here are in agreement with previous results[4] showing that very high concentrations are found in the mediobasal hypothalamus. In addition we have shown even higher concentrations in the pituitary stalk. Therefore SP is well placed to serve such a modulatory role in man. The distribution of SP as shown by immunohistochemistry was similar to that previously described in the rat[1,2], except for the higher concentration of fibres and perikarya in the tuberal region and pituitary stalk. Furthermore it has been shown that, as in other studies in man[6,13], there is no effect of age, terminal disease state or time to freezing of tissue on the measurement of SP content. It is therefore possible to examine SP content of human hypothalamus and pituitary stalk in conditions where there are pathological changes in this region, to establish further the role of SP in endocrine function.

Summary

The undecapeptide substance P (SP) is found in widely dispersed areas of the brain. Recently, in experimental animals, a role for SP as a presumptive neuromodulator of endocrine responses has been described. Part of this role appears to be expressed at the level of the hypothalamo-pituitary axis. The distribution of SP in human hypothalamus and pituitary stalk has rarely been examined.

In this study the distribution of SP was determined using radio-immunoassay and immunohistochemical methods in 7 regions of hypothalamus and the pituitary stalk in 21 autopsy samples. The SP content was greatest in the pituitary stalk (16.7 $\pm$ 2.9 ng/mg protein) and the mediobasal hypothalamus at the level of the tuber cinereum (8.3 $\pm$ 1.1 ng/mg protein) compared with all other regions (range 3.7 to 6.0 ng/mg protein). Histochemical studies in 7 cases showed a dense innervation of the pituitary stalk portal vessels by substance P-containing nerve terminals. The pituitary stalk, mediobasal and lateral hypothalamus had the highest number of SP-containing neuronal perikarya. The SP content was not affected by age, sex or delay from death to freezing of tissue. The distribution of SP supports the view that the peptide is a neuromodulator of hypothalamo-pituitary endocrine function in man.

Acknowledgements

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The Neuropathology of Progressive Autonomic Failure of Central Origin (the Shy-Drager Syndrome)

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The neuropathology of progressive autonomic failure of central origin has become better established in the light of recent experience. These advances are briefly reviewed and a classification based on the neuropathological findings assembled by Oppenheimer[1] is presented below.

Primary orthostatic hypotension may be due to 2 quite distinct disease processes[2]. The first, described by Bradbury and Eggleston[13], is caused by postganglionic sympathetic failure. In such patients the parasympathetic system is relatively spared. In the second, described by Shy and Drager[4], sympathetic paralysis is preganglionic, resulting from degeneration of the neurons of the lateral horn of the thoracic spinal cord. In this type the parasympathetic system is usually also involved.

The preganglionic and postganglionic types can be readily differentiated by use of serum noradrenaline levels. In the peripheral postganglionic type, noradrenaline is found to be decreased in the recumbent posture. These patients also show noradrenaline hypersensitivity. In the central, preganglionic type, resting noradrenaline levels are normal and hypersensitivity to injected noradrenaline does not occur. In both disorders there is postural hypotension, which may be associated with anhidrosis, impotence and sphincteric disturbances. However, it is only the central type which is linked with wider neurological involvement. In the central type such associated neurological syndromes assume two main forms, either Parkinson's disease or "multiple system atrophy" of ponto-cerebellar-striato-nigral type. Because of the common occurrence of other neurological disturbances the unqualified use of the term

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"Shy-Drager syndrome" is not an adequate description for progressive autonomic failure of central origin. The neuropathological substratum, in addition to degeneration of the lateral neurons of the thoracic cord, often includes atrophy of brain stem and corpus striatum. Clinically, orthostatic hypotension usually antecedes the appearance of Parkinsonian or other neurological signs.

In 1983 Oppenheimer[1] reviewed the 51 case reports he was able to find in the literature, in which neuropathological findings were given. As a result he grouped central progressive autonomic failure into 2 main types. In about 20% of the patients, changes similar to those of Parkinson's disease were present in the substantia nigra and locus caeruleus. In these cases the pigmented nerve cells were lost, degenerate or contained Lewy bodies. Approximately half of these patients had Parkinsonian signs during life. The remainder had shown only autonomic failure even though the neuropathological lesions, including Lewy bodies, were present in the pigmented nuclei of the brain stem. The remaining 80% of patients, in Oppenheimer's[1] review, had suffered ataxic syndromes during life, in association with progressive autonomic failure. At autopsy these patients were found to have combined striato-nigral degeneration and ponto-cerebellar atrophy. A classification based on Oppenheimer's[1] report is given in Table 1.

To illustrate these nosological concepts the necropsy findings of 3 patients who had progressive autonomic failure during life, obtained from the files of the Department of Neuropathology, Royal Perth Hospital, will be described.

Table 1. Progressive Central Autonomic Failure (Based on Oppenheimer[1])

Oppenheimer Type I
Patients with brain stem lesions containing Lewy bodies.
A Autonomic dysfunction associated with Parkinsonism (Shy-Drager syndrome)
B Progressive autonomic failure without neurological signs
Oppenheimer Type II
Progressive autonomic failure with multiple system atrophy
Degeneration of preganglionic sympathetic neurons of thoracic cord occurs in all types.

Case 1

Clinical Features

An 84 year old male patient had suffered Parkinsonian symptoms and episodes of postural hypotension for 14 years. His disabilities consisted of bradykinesia, postural tremor and rigidity. He was treated with anti-Parkinsonian medication without effect and in the last few years of his life was virtually immobile. He later became bedridden and died of bronchopneumonia.

General Necropsy Findings

The general necropsy revealed healed infarcts of the heart and right kidney, and terminal bronchopneumonia.

Neuropathological findings

The brain weighed 1160 g and showed a moderate degree of cerebral cortical atrophy. There were signs of past ischaemic necrosis with cavities in the right occipital and right frontal lobes, each approximately 1 cm in diameter. In the brain stem, both the substantia nigra of the midbrain and the locus caeruleus of the upper pons were pale, having lost their normal pigmented appearance. The pons, medulla and cerebellum were macroscopically normal.

Microscopic sections of the substantia nigra and locus caeruleus showed loss of pigmented neurons with numbers of melanin containing macrophages. Surviving neurons contained classical Lewy bodies which, in some neurons, were multiple. There were no lesions in the basal ganglia. In the thoracic spinal cord a decrease in the number of neurons of the intermediolateral grey matter was evident. Neurofibrillary tangles were found in an occasional neuron of the hippocampus, which also contained senile plaques. The areas of ischaemic necrosis found in the cerebral hemispheres contained macrophages and glial trabeculae and were unremarkable.

Case 2

Clinical Features

A 70 year old female patient had found it difficult to walk and climb stairs for the past 6 years. She later had problems negotiating slightly uneven surfaces and walking in a straight line. Her walking difficulty was much worse in hot weather and she suffered a number of falls. Several months later she required an oesophagoscopy because of food caught in her throat. This swallowing difficulty became gradually worse as time progressed. Lingual movements were poor. She had been an accomplished piano player and noticed that her proficiency was being affected by her poor motor control. Later her performance markedly deteriorated. She often complained of the heat. Postural hypotension was also an early feature of her illness. Her blood pressure was 90/60 mm Hg when she was first examined. It remained at about this level throughout the 6 years of her progressive disorder. Over the ensuing years she developed slight proximal weakness of the lower limbs and worsening coordination. The main difficulty in the limbs was her inability to perform rapid repeated movements. Romberg's sign was present. As the illness progressed over the years truncal ataxia made her almost unable to stand or walk. Other neurological signs consisted of cerebellar dysarthria and hyperflexia. In the few months before death she developed urinary and faecal incontinence.

General Necropsy Findings

There was widespread wasting in the general organs, acute diverticulitis with pericolic abscesses of the descending colon together with suppurative pyelonephritis.

Neuropathological findings

The brain weighed 1010 g. Advanced pontocerebellar atrophy was obvious externally (Figure 1). Examination following fixation revealed a small 2.0 cm meningioma attached to the flax. The blood vessels at the base of the brain were normal and the leptomeninges were thin and translucent. Externally the cerebral hemispheres were symmetrical, the gyral pattern normal and the insula fully opercularized. However, the cerebral sulci were slightly wider than normal. The subarachnoid cisternae were all much increased in size in relationship to advanced atrophy of the brain stem and cerebellum.

The cerebellum and brain stem together weighed 84 g. The pons showed an extreme degree of symmetrical atrophy, being almost totally absent. The middle cerebellar peduncles were reduced to narrow bridges arising from the remnants of the pons. The midbrain appeared slightly less shrunken. The interpeduncular fossa was enlarged. In the medulla the olives were barely discernable to the naked eye. The pyramids of the medulla appeared normal.

Figure 1. Case 2. There is extreme atrophy of the pons and cerebellum at the base of the brain.

The 2nd, 4th, 6th, 7th, 9th, 10th and 11th cranial nerves all appeared atrophied. Of these the optic nerves showed most atrophy and the optic chiasm was decreased in size by about 40%. Posteriorly, at the base of the brain, the foramina of Luschka were greatly enlarged measuring 8 mm in their longest diameter. The foramen of Magendie was also widened but to a lesser extent as it measured 5 mm in the vertical dimension. The cerebellum also showed an extreme degree of atrophy, most apparent inferiorly, mainly affecting the vermis but also spreading laterally to involve the hemispheres. The tonsils of the cerebellum were less affected. The flocculonodular nodes appeared normal. There was, however, diffuse generalised atrophy of the neocerebellum.

The cerebral hemispheres sectioned in the coronal plane revealed the cerebral cortex, white matter, basal ganglia, thalamus, Ammon's horn and lateral ventricles to be symmetrical and normal in

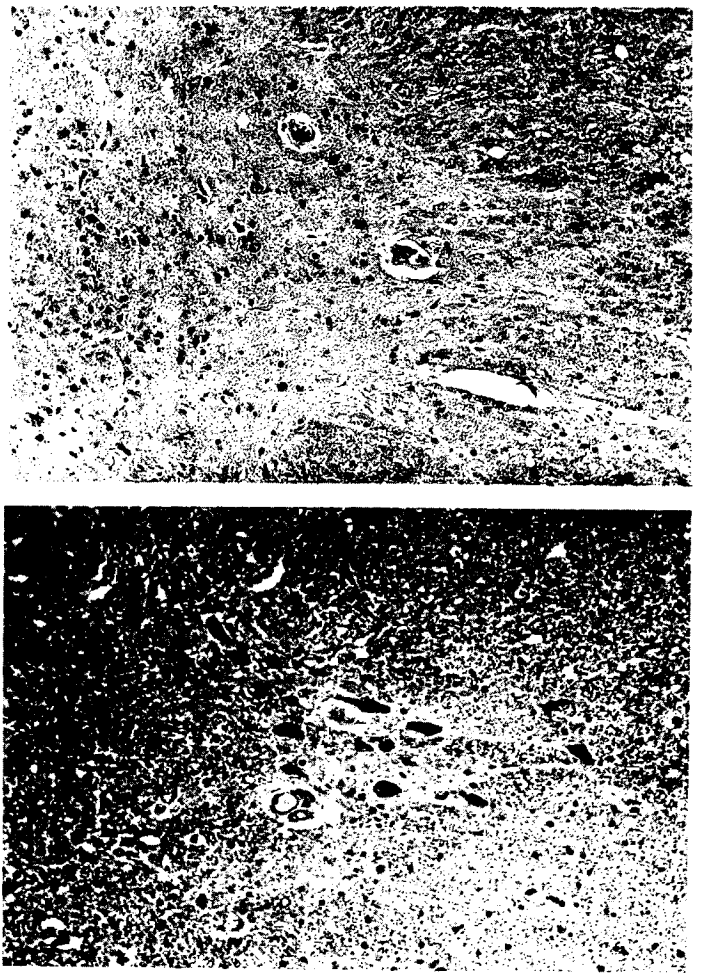

Figure 2. (a) The intermediolateral column of the spinal cord at T6 from Case 2, shows almost a total loss of neurons. The nuclei visible belong to the few surviving nerve cells and the majority to astrocytes (H and E, x175). (b) Control, intermediolateral column from a normal spinal cord showing the usual complement of nerve cells for comparison with (a) (H and E, x175).

size. In particular, the hypothalamus was normal in its naked eye appearance. On section of the hind brain structures, the cerebellar white matter was also reduced in quantity and the dentate nucleus obscured on both sides. The "roof" nuclei could not be identified. The midbrain was a little contracted in its overall dimensions but the substantia nigra was well pigmented. The aqueduct was normal. In the transverse plane the pons was symmetrically reduced in size. The brachia pontis, superior and inferior cerebellar peduncles were also very atrophic The medulla showed shrinkage, mainly of the olivary nuclei. Macroscopically the spinal cord was also slightly reduced in size.

Microscopically the basal ganglia of the cerebral hemispheres revealed no changes. The cerebellum showed advanced atrophy with loss of cells from all folial layers together with advanced gliosis. The dentate nuclei were also very atrophic and gliotic. The few surviving Purkinje cells showed large axonal "torpedoes". The substantia nigra and locus caeruleus were microscopically normal. The pons and medulla were severely atrophied. Neurones were lost mainly from the basis pontis and olivary nuclei. The neurons of the intermediolateral column of the thoracic spinal cord were deficient in number and, in some areas, totally absent (Figure 2). Peripheral nerves, sympathetic and parasympathetic ganglia were histologically normal.

Case 3

Clinical Features

A 70 year old female patient had noticed slowness in movement, giddiness, and weakening in her voice for about 3 years. She suffered a number of falls. As time progressed, giddiness on standing became more persistent and her blood pressure was recorded to be 110/60 mm Hg in the erect position. The orthostatic hypotension was treated with ephedrine with some benefit. On examination, slurred speech and tremor of the tongue were noted together with ataxia of the upper limbs. She also had minor signs of Parkinsonism with tremor and dyskinesia. One year before death she developed urinary incontinence which was soon followed by renal tract infections. At this time her blood pressure was 160/90 mm Hg supine and 90/50 mm Hg on standing. In the final stages of her illness she became bedridden.

General Necropsy Findings

The cause of death was a perforated gastric ulcer and peritonitis.

Neuropathological Findings

The brain weighed 1270 g. The cerebral hemispheres were normal to the naked eye. Coronal sections through the cerebral hemispheres showed dilated lateral ventricles. The basal ganglia and diencephalon were unremarkable. The cranial nerves appeared normal to the unaided eye. Transverse section of the brain stem revealed pallor of the substantia nigra. The pons, medulla and cerebellum together weighed 110 g. There was severe atrophy of the pons. The middle cerebellar peduncles were greatly attenuated. The inferior olives of the medulla were very atrophic. The pyramids appeared normal. The cerebellum showed cortical atrophy mainly involving the vermis but also of the adjoining lateral lobes. The floccular-nodular lobes were least affected. The 4th ventricle was enlarged. The spinal cord was normal to the naked eye.

Microscopically, the cerebral cortex was normal. In the basal ganglia there was loss of neurons with gliosis in the lateral and inferior region of the putamen. Partial loss of cells was found in the substantia nigra but definite Lewy bodies were not present. Neuromelanin was present within macrophages situated in the vicinity of blood vessels. There was severe atrophy of the nuclei pontis and of the transverse pontocerebellar fibres. However, the locus caeruleus was microscopically normal. The inferior olives were better preserved than the basis pontis. In the thoracic spinal cord, nerve cells were lost from the intermediolateral cell column.

Discussion

The neuropathological findings in the 3 cases presented are representative of those described in the literature by others[5]. The first patient, who had shown Parkinsonian features in life, had corresponding lesions in the pigmented nuclei of the brain stem including large numbers of Lewy bodies. He thus conformed to Oppenheimer's type IA. At necropsy, the other 2 patients showed multiple system atrophy, with pontocerebellar degeneration in both and putaminal degeneration in one. Therefore they belonged to Oppenheimer's type II. In all 3 patients there was loss of neurons from the intermediolateral columns in the thoracic segments of the spinal cord. This lesion was thought responsible for the central preganglionic, postural hypotension.

Although clinical neurological abnormalities were known to occur in some patients with orthostatic hypotension the association was not well defined until 1960 when Shy and Drager[4] reported their cases. It was then that the frequent occurrence of neurological symptoms in patients with orthostatic hypotension was appreciated and the autonomic failure recognized to be of preganglionic type. In Shy and Drager's[4] report, the neuropathological changes consisted of neuronal degeneration in the caudate nucleus, substantia nigra, locus caeruleus, olives, dorsal vagal nuclei with loss of Purkinje cells from the cerebellum. In the spinal cord they found nerve cell loss from the ventral and lateral grey columns of the thoracic cord. Fichefet et al.[6] described a patient with progressive orthostatic hypotension who later developed Parkinsonism. In this patient lesions, typical of Parkinson's disease with Lewy bodies, were found in the pigmented nuclei of the brain stem. In other reported cases pure autonomic failure without Parkinsonism and with lesions confined to the intermediolateral columns of the spinal cord[7] have been described. Most cases are sporadic but familial incidence was reported by Lewis[8].

Oppenheimer[1] collected 51 reports from the European and American literature and carefully evaluated the findings. He recognized a consistent pattern and, as a result, he was able to group the disorder into type I, with lesions in the pigmented nuclei of the brain stem in which there were always Lewy bodies and type II, characterized by "multiple system atrophy". Type IA includes those patients with clinical Parkinson's disease while type IB designates those patients with clinically pure autonomic failure but in whom lesions of the substantia nigra, including Lewy bodies, are found at necropsy. In the majority of the reports (41 of 51) examined by Oppenheimer[1], "multiple system atrophy" involving the pontocerebellar structures occurred in combination with changes in the striatonigral system. Therefore, they belonged to Type II. In all 3 types, nerve cells are lost from the intermediolateral columns on the spinal cord. The spinal cord lesions underlie the progressive central autonomic failure which is the essential characteristic of the syndrome.

Clinically, the disorder may consist purely of orthostatic hypotension but other autonomic disorders such as impotence and sphincter disturbances are usually associated. Otherwise, and more commonly, Parkinsonian features, dysarthria, dysphagia and cerebellar symptoms and signs develop later. It is a noteworthy feature that sensory abnormalities do not occur.

We believe that the classification introduced by Oppenheimer is clinically useful because it encompasses the several neurological and neuropathological manifestations of the preganglionic autonomic failure syndrome. Further details can be found in a recent review of the subject by Oppenheimer[9].

Summary

The neuropathological features of the "Shy-Drager syndrome" have, in the past, been unsettled. The position was recently clarified by Oppenheimer[1] who reviewed the 51 reported patients with progressive autonomic failure in whom neuropathological findings were given. He divided these cases into two groups. Group I included those with lesions of the pigmented nuclei of the brain stem which contained Lewy bodies. These he further subdivided into subgroups IA or IB according to whether or not the patient showed clinical evidence of Parkinson's disease in addition to the common denominator of orthostatic hypotension. In group II he placed those patients in whom multiple system atrophy was found at necropsy. These were the majority. Loss of neurons from the intermediolateral columns of the thoracic spinal cord, thought to be the cause of the postural hypotension, was present in all cases.

To illustrate the new classification the necropsy findings in 3 patients taken from the files of the Royal Perth Hospital are described. One of these showed the lesions of Parkinson's disease with Lewy bodies, and thus conformed to Oppenheimer's type IA. The two other patients showed multiple system atrophy and thus belonged to Oppenheimer's type II. All three showed loss of neurons in the intermediolateral columns of the thoracic spinal cord. We believe that Oppenheimer's classification of progressive orthostatic hypotension improves the clinicopathological understanding of the syndrome and is thus useful as well as informative to the practising neurologist.

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Cryoglobulinaemic Neuropathy — a Clinical Spectrum

R.F. Peppard, E. Byrne*, R. McD. Anderson† and B.G. Clarke‡*

Cryoglobulins are serum proteins which precipitate with cooling and redissolve with warming[1]. Immunoelectrophoresis has allowed identification of IgM, IgG and mixed cryoglobulin subgroups. Cryoglobulinaemia may be secondary to a number of other disease processes which produce a polyclonal or monoclonal gammopathy, or may be found as a primary disorder, essential cryoglobulinaemia[2].

Neuropathy occurs in about 7% of patients with cryoglobulinaemia but it is not always clear whether the neuropathy and cryoglobulinaemia are causally related in secondary cases. In this paper we present 2 patients with peripheral nervous system disease associated with cryoglobulinaemia.

The first patient, who developed a subacute mononeuritis multiplex after a 7 year history of Raynaud's phenomenon and purpuric leg ulceration, represents a case of essential cryoglobulinaemia with probably causally-related neuropathy. Her case is noteworthy in view of the successful treatment with immunosuppression and plasmapheresis.

The second patient presented with a chronic demyelinating neuropathy with conduction block and was a heroin addict with chronic hepatitis. She resembled the patients reported by Lewis and Asbury[3] both in her presentation and in her dramatic response to steroid therapy, but differs in that a circulating cryoglobulin was identified.

Case 1

A 67 year old woman presented with a 7 year history of Raynaud's phenomenon and a purpuric ulcerating rash over the lower limbs which flared up each winter. Skin biopsy had established the presence of a cutaneous leucocytoclastic vasculitis but the aetiology was not established. In early

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Figure 1. Mottled cyanosis and residual scarring from ulcers of lower extremities in Case 1.

1984 she developed weakness and sensory loss affecting the right hand which progressed over a few days and was followed by similar symptoms in the left hand.

On examination, cyanosis of the extremities with readily elicitable Raynaud's phenomenon in the hands, and scarring over both lower legs from old ulcers, were noted (Figure 1). There was marked weakness of the left abductor pollicis brevis, left flexor pollicis longus, and median two heads of flexor digitorum profundus and mild weakness of left ulnar-innervated small hand muscles. There was weakness in the right hand in an ulnar distribution and the left extensor hallucis longus was moderately weak. The ankle reflexes were absent. The clinical picture suggested a mononeuritis multiplex.

Electrophysiological Studies

Electromyography confirmed denervation with a reduced interference pattern in the abductor pollicis brevis, left abductor digiti minimi and left first dorsal interosseous muscle.

Motor Studies: the left median nerve showed distal latency 3.9 m/sec, forearm conduction velocity 52 m/sec (normal greater than 48 m/sec). The left ulnar nerve showed distal latency 2.5 m/sec, conduction velocity above elbow to wrist 61 m/sec (normal greater than 48 m/sec), axilla to above elbow 65 m/sec.

Sensory action potentials could not be recorded in the median and ulnar nerves on either side, nor in the left sural nerve.

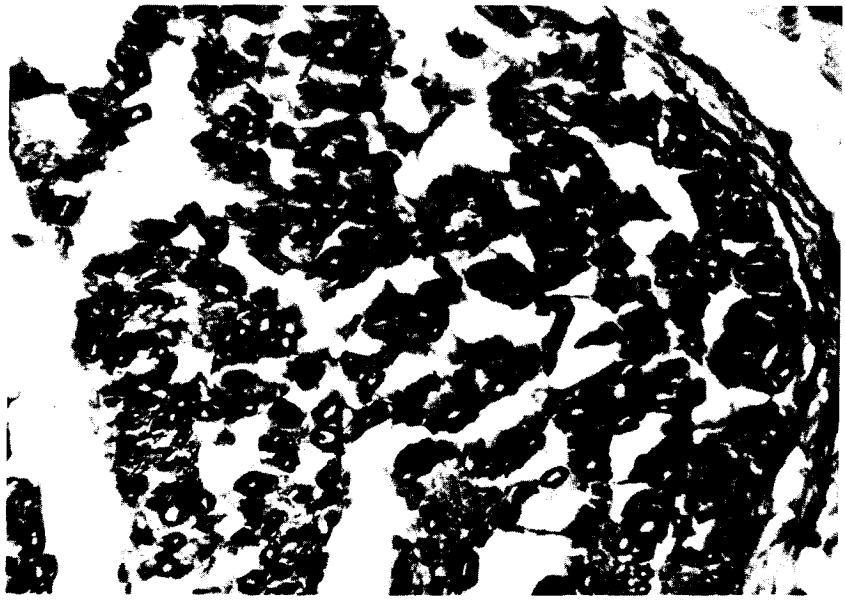

Figure 2. Transverse section of sural nerve from Case 1 (H and E, Osmium Tetroxide, x 400)

Laboratory Investigations

The ESR was 10 mm/h. Serum complement activity was normal. ANF was not detected but rheumatoid factor was present in low titre. Serum immuno-electrophoresis revealed a normal immunoglobulin profile. Serum cryoglobulins were detected and immuno-electrophoresis of serum enriched for the cryoglobulin showed a polyclonal IgM pattern. No definitive IgG content was detected.

Pathological Findings

A sural nerve biopsy (Figure 2) showed moderate loss of myelinated fibres, particularly large diameter fibres. Axonal clusters were prominent. Endarteritis obliterans was seen in several arterioles without significant inflammatory reaction and one artery showed recanalisation (Figure 3)

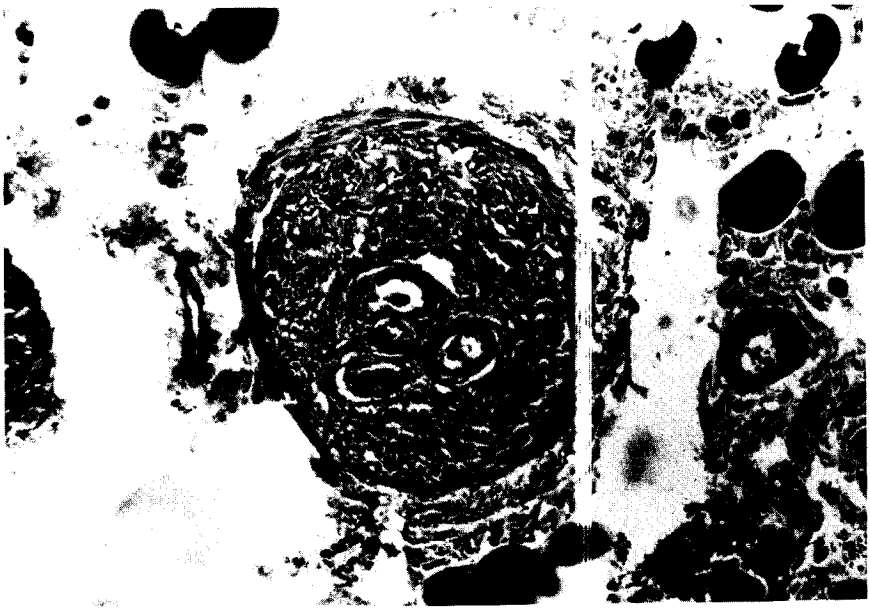

Figure 3. Endarteritis obliterans with recanalisation of vasa nervorum in sural nerve of Case 1 (x 200)

Progress

The patient was treated with azathioprine, 100 mg/day, prednisolone and plasmapheresis (with twice weekly treatments for 2 weeks, then monthly treatments for 6 months). A steady improvement began some months after the onset of treatment with marked improvement in strength in both hands one year later.

Case 2

A 35 year old woman with a 10 year history of heroin abuse presented with a 12 month history of paraesthesiae and numbness in the fingers and toes, extending gradually to an elbow and mid-thigh level. Weakness involving both hands and legs developed 3 months before presentation and progressed to a point where she was unable to feed or dress herself without assistance and required support to walk. She had no history of Raynaud's phenomenon or cold sensitivity. She had had infectious hepatitis 9 years before.

On examination, moderate symmetrical distal wasting with severe distal weakness was evident in all limbs and the deep tendon reflexes were absent. Mild proximal limb weakness and wasting were noted. Symmetrical stocking and glove distribution sensory loss involving pain, temperature and light touch modalities was found to the elbow and mid-thigh level. Vibration and position sensations were depressed distally. No thickened nerves were palpated. There was mild hepatomegaly without stigmata of chronic liver disease and no cutaneous evidence of vasculitis was seen.

Laboratory Investigations

Investigation revealed an ESR of 18 mm/h. The following tests were normal: full blood examination, blood glucose, chest radiograph, treponemal serology, antinuclear factor, rheumatoid factor, urinary porphyrin screen, heavy metal screen and vitamin B_{12} level. The CSF was acellular with a mild elevation in protein level of 0.54 g/L (normal less than 0.4 g/L). Serum aspartate transaminase level was 400 units/L (normal less than 65). Hepatitis B surface antigen was negative but hepatitis B core antibody was detected, indicating past hepatitis B virus infection. Serum protein electrophoresis showed a polyclonal increase in gamma globulin. Total IgM level was 6.2 g/L (normal 0.4 — 2.3), IgG level 15.4 g/L (normal 5.6 — 17.6) and IgA level 0.99 g/L (normal 0.8 — 3.8). Immunoelectrophoresis revealed the presence of a mass of aggregated protein close to the origin consistent with the presence of a cryoglobulin. Centrifugation of cooled serum revealed a cryocrit value of 2%. The cryoglobulin was not characterised further.

Pathological Findings

A sural nerve biopsy (Figure 4) revealed mild loss of myelinated fibres with prominent axonal clusters. Occasional fibres in longitudinal section showed axonal degeneration and some fibres showed paranodal axonal swelling. No inflammatory cells were seen. Teased fibre preparations were not done. Muscle biopsy showed denervative changes with target fibres. A liver biopsy examination showed mild periportal fibrosis, lymphocytic infiltration of portal areas and occasional necrotic hepatocytes. The histological picture was suggestive of a chronic persistent hepatitis.

Electrophysiological Studies

EMG studies with a concentric needle electrode revealed chronic denervation with a marked reduction in interference pattern with giant polyphasic units in the abductor pollicis brevis, abductor digiti minimi, tibialis anterior and extensor digitorum brevis muscles without fibrillation. Less marked denervation changes were seen in several proximal muscles. Motor conduction velocity in the right median nerve in the forearm was grossly reduced to 14 m/sec (normal greater than 48 m/sec). In the right ulnar nerve in the elbow to wrist segment, the velocity was normal at 55 m/sec (normal greater than 48 m/sec), but it was reduced across the elbow (above elbow to wrist 38 m/sec) and in the upper

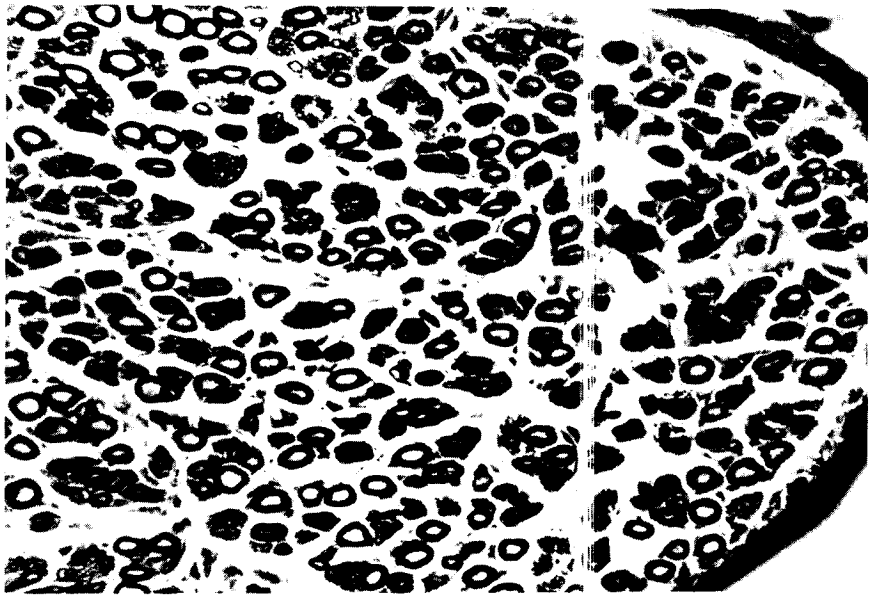

Figure 4. Transverse section of sural nerve in Case 2 (H and E, Osmium Tetroxide, x 400) showing loss of myelinated fibres with axonal clusters

arm (axilla to above elbow 10 m/sec). In the right tibial nerve, conduction velocity was reduced at 31 m/sec knee to ankle (normal greater than 45 m/sec), but normal in the common peroneal nerve 51 m/sec knee to ankle (normal greater than 45 m/sec).

A marked reduction in the amplitude of the compound action potential recorded over the thenar, hypothenar and extensor digitorum brevis muscles was seen with proximal as opposed to distal stimulation of the relevant nerve trunk: median nerve to abductor pollicis brevis distal stimulation 7.2 mV, proximal (elbow) 2.0mV (Figure 5); ulnar nerve to abductor digiti minimi distal stimulation 3.7 mV, proximal (elbow) 0.4 mV. In the common peroneal nerve the amplitude of response over the extensor digitorum brevis with stimulation at the ankle was 3.8 mV, and with stimulation at the knee 2.2 mV.

Sensory studies revealed an ulnar sensory action potential at the wrist of 7 μV amplitude (normal greater than 10 μV) and peak latency 2.7 m/sec (normal less than 4.0 m/sec). The median nerve sensory action potential at the wrist was 10 μV (normal greater than 8 μV). The sural nerve action potential amplitude was 15 μV, with a conduction velocity of 44 m/sec.

Progress

The patient was observed in hospital for a period of 6 weeks without treatment. A progressive deterioration in muscle strength occurred over this period. Prednisolone (60 mg/day) was then introduced and within 2 weeks a steady improvement began. Assessment 12 weeks later revealed a

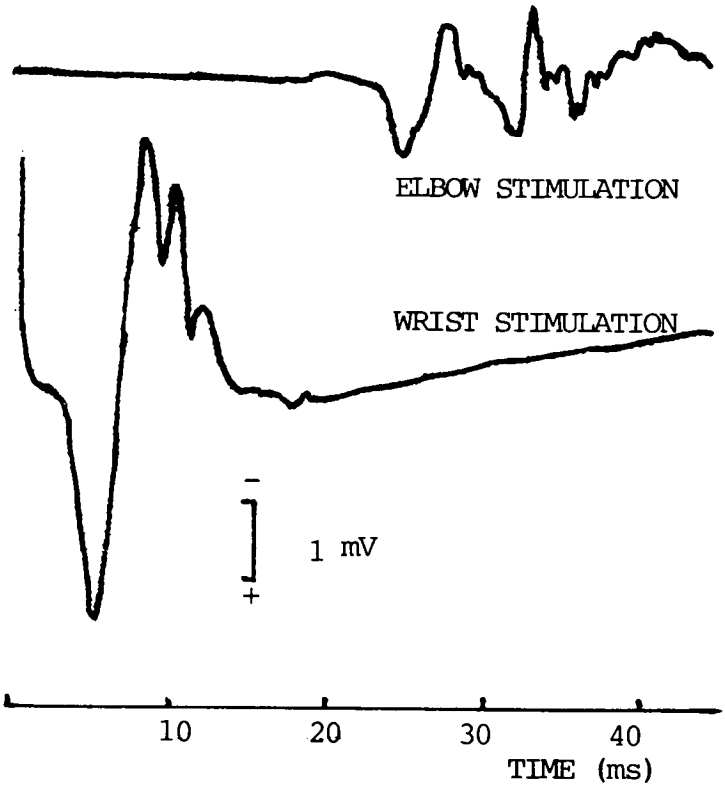

Figure 5. Conduction block in the median nerve. Needle recordings from abductor pollicis brevis.

full functional recovery with only minimal distal weakness and impaired pinprick sensation on examination. Cryoglobulins could not be detected in the serum at that time and liver function tests had returned to normal.

Discussion

The first patient, with a long history of Raynaud's phenomenon and purpuric ulceration of the legs in winter, presented with a mononeuritis multiplex. Investigation revealed cryoglobulinaemia consisting of a polyclonal IgM. The patient presented

a typical picture of essential cryoglobulinaemia. This disorder can be associated with either mononeuritis multiplex[5,6] or with a more symmetric neuropathy[2,4]. The course is usually slowly progressive, with peripheral pain and paraesthesiae worsened by cold.

Suggested mechanisms of nerve damage include monoclonal antibody assault on peripheral nerve myelin as in benign IgM paraproteinaemia[7], intravascular deposition of cryoglobulin in vasa nervorum causing bland occlusion and ischaemic nerve injury[8] and inflammatory vasculitis involving the vasa nervorum with immune complexes with cryoglobulin properties initiating complement activation[9,10]. The finding of a bland arterial occlusion in our patient in a nerve biopsy examined soon after the onset of a florid mononeuritis multiplex favours the hypothesis that intravascular deposition of IgM cryoglobulin with non-inflammatory occlusion, rather than complement-mediated vasculitis, may underlie the peripheral nerve damage. It is possible, however, that more active vasculitis changes may have been present in the nerve at a higher level.

Most patients with essential cryoglobulinaemic neuropathy have either not been treated actively and have continued to progress[6,11] or have stabilised without improvement[9]. One case who had an excellent response to immunosuppressive treatment has been reported[12] and Chad et al.[2] recently reported a patient who improved with plasmapheresis over a 12 month period. Our patient adds further support to the view that active treatment with immunosuppression and/or plasmapheresis may be helpful in cryoglobulinaemic neuropathy. It is not clear whether immunosuppression or plasmapheresis alone represents adequate treatment, but experience with other chronic immune complex diseases favours a combined approach.

The second patient presented with a slowly progressive distal sensorimotor neuropathy and nerve conduction studies suggested a severe demyelinating neuropathy with conduction block. Sural nerve biopsy revealed distal axonal degeneration which may be secondary to severe demyelination. Teased fibre preparations were not studied. This patient closely resembles those reported by Lewis et al.[3] as having multifocal demyelinating neuropathy with persistent conduction block. Cryoglobulin assays were not reported in their paper and it is of interest that one of their patients was also a heroin addict. The presence of polyclonal increase in IgM and of chronic persistent hepatitis in Case 2 suggests that the peripheral nerve involvement was immunologically mediated. This proposition is supported by the dramatic improvement with steroid medication. A causal link between neuropathy and cryoglobulinaemia has not been established in this patient. The disappearance of cryoglobulins from the plasma coincided with clinical recovery, but they may represent a disease marker rather than having a central role in peripheral nerve damage. Cryoglobulin complexes and peripheral neuropathy have been reported in one other patient with chronic inflammatory liver disease[8]. This case illustrates a further association between chronic hepatitis, cryoglobulinaemia and neuropathy. Patients presenting with chronic multifocal demyelinating neuropathy with conduction block should have a cryoglobulin assay as part of their workup.

Summary

In this report we present two cases who illustrate both ends of the spectrum of neuropathy with cryoglobulinaemia. Both patients responded well to treatment. A cryoglobulin assay should be done routinely in patients with mononeuritis multiplex of unknown cause, cutaneous vasculitis with cold sensitivity and chronic demyelinating neuropathies of unknown cause.

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Non-bacterial Thrombotic Endocarditis and Stroke

*R.A.L. Macdonell, †R.M. Kalnins and *G.A. Donnan

Cerebral infarction or an episode of transient cerebral ischaemia, due to an embolus, is a common clinical event. The likely sources of embolism are either the carotid bifurcations or the heart. In 75-88% of patients a potential source of embolus may be found in the carotid artery following detailed angiography[1,2]. Cardiac sources of emboli are best sought utilizing clinical findings in combination with electrocardiography and echocardiography. In patients with clinical evidence of cardiac disease or arrhythmias, who have suffered cerebral ischaemic events, the presence of an intracardiac thrombosis or valvular vegetation is not uncommon (22%)[3]. However in the absence of such evidence of cardiac dysfunction the diagnostic yield on echocardiography is much lower, to the extent that it has been recommended that this procedure should not be part of routine investigations following cerebral ischaemic episodes [3,4,5].

Echocardiography, particularly when M-mode and 2D imaging are combined, is a sensitive and reliable method of detecting potential cardiac sources of emboli. Mitral and aortic valve vegetations greater than 2-3 mm in size are reliably detected by good quality echocardiography[6]. Left ventricular mural thrombus may be detected using 2D imaging with a sensitivity of 92% and a specificity of 88%[7], which is superior to the accuracy of ventricular angiography which will detect 57% of left ventricular clots[8]. Left atrial cavity thrombi may be detected on 2D echo with a sensitivity of 75% but at present thrombus in the left atrial appendage is often missed[9]. In order to be visualized using 2D echo, cardiac thrombi need to be greater than 2mm in size and need to have an adequate reflective interface, that is to have become organized[4]. Consequently small or recently formed thrombi may be missed. Despite investigations directed at finding a carotid or cardiac source of emboli there remains a group of patients (8-9%) in whom no source of embolus can be identified[10]. The prognosis of this group is somewhat controversial at present. In one series followed over 5.4 years, 20% had further TIA's and 16% had serious cerebrovascular episodes[11].

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A criticism of this latter study, however, is that no attempt was made to separate cortical from capsular ischaemic events and, as there was no CT correlate, it was not possible to say what percentage of the serious cerebrovascular episodes were due to haemorrhage or capsular infarction as distinct from cortical infarction, and this is obviously relevant in terms of pathophysiology. A later study suggested a somewhat better prognosis for 32 patients over a 16 month follow up[10]. In this group there was one further TIA and no serious cerebrovascular episodes.

A condition which may present as recurrent cerebral embolic events with angiographically normal carotid arteries and normal cardiac investigations clinically is non-bacterial thrombotic endocarditis (NBTE) or marantic endocarditis. It is a particular complication of adenocarcinoma and is notoriously difficult to diagnose.

Case Reports

Case 1

A 52 year old housewife presented to hospital after awakening that morning with a heavy, clumsy left arm. She was able to walk without difficulty and her speech was unimpaired. There was no headache or sensory disturbance. By the time she arrived at hospital some four hours after first noticing the weakness there had been considerable improvement in the left arm strength.

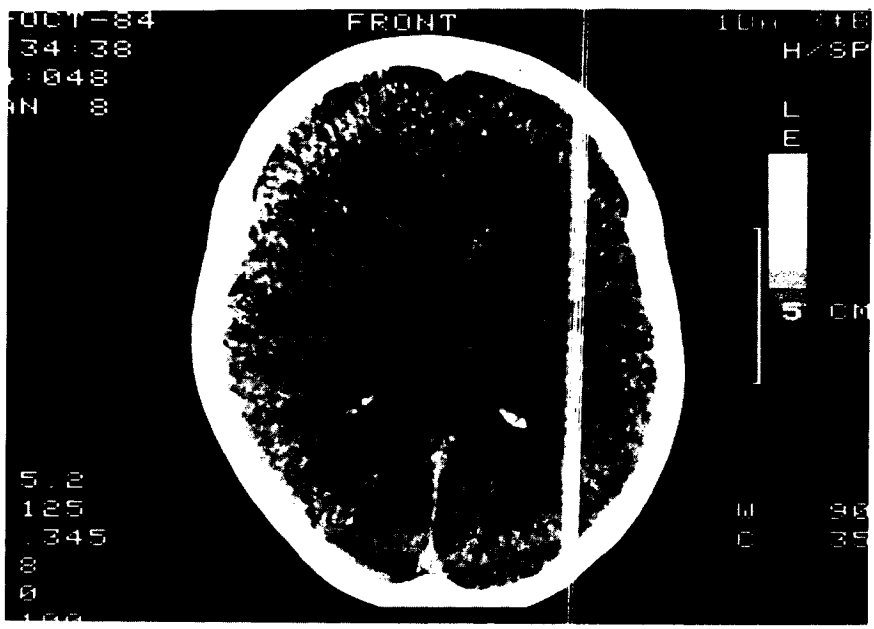

Figure 1. CT scan depicting a hypodense area in the right insula consistent with infarction.

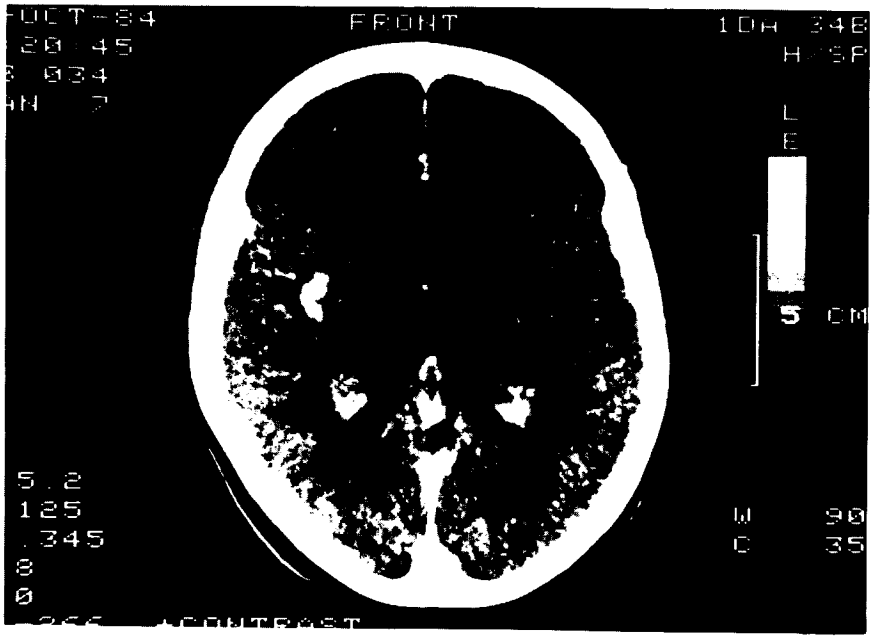

Figure 2. CT scan repeated 7 days after Figure 1, with contrast. The hypodense area shows contrast enhancement confirming it as a recent infarct.

On further questioning she recounted 6 episodes over the previous 6 years involving visual disturbance affecting the left eye. She described these as like a curtain descending across the eye for several minutes. The last episode of this nature had occurred 3 weeks prior to her presentation. No other neurological symptoms were associated with this symptom and their pathophysiology was never satisfactorily explained. Cerebrovascular risk factors included hypertension which had been treated with a thiazide diuretic for 5 years and smoking (20 cigarettes per day).

Examination confirmed an isolated left arm weakness without sensory impairment. No abnormal cortical signs were present and the face and leg were uninvolved. Her heart was in sinus rhythm, she was normotensive and there were no cardiac or carotid bruits. The left arm weakness resolved completely over the next 48 hours.

A CT scan performed 24 hours after the onset of symptoms without contrast media disclosed a right insular infarct. A repeat scan 10 days later again showed the infarcted area which enhanced with contrast (Figures 1,2). A carotid angiogram was performed (Figure 3) which disclosed no embolic source and echocardiography showed no vegetations or mural thrombi. Her blood count and film were unremarkable (Hb 13.0 g/dL, WCC $11{,}000 \times 10^9$/L, platelets $190{,}000 \times 10^9$/L), her ESR was 4 mm/h, her ECG showed nonspecific ST segment changes and her chest radiograph was normal. She was discharged with the diagnosis of probable embolic infarction without a demonstrated source of thrombus. She was reassessed at monthly intervals and had no further neurological events.

Figure 3. Right carotid angiogram performed 8 days after admission showing a smooth atheromatous plaque at the origin of the right internal carotid artery without significant stenosis.

Three months following discharge she presented again in a cachectic state with ascites.She was semi-conscious and irritable with no focal neurologic signs or cardiac murmurs. Cytology of the ascitic fluid showed adenocarcinoma and full blood examination suggested disseminated intravascular coagulation (DIC) (Table 1).

She died within 24 hours of admission, following cardiac arrest.

At autopsy she was found to have adenocarcinoma of the stomach with widespread abdominal dissemination. Her carotid bifurcations were normal but examination of the heart disclosed a 1.5 cm sterile vegetation on the aortic valve. The brain showed infarcts of various ages (days to weeks) in the right fronto-parietal cortex and white matter, right insula, right putamen, and left occipital cortex (Figure 4). In addition there was evidence of thromboembolic small vessel occlusion of various ages (Figure 5).

Case 2

The second case was an 82 year old woman. 6 years previously she had presented with left iliac fossa pain and was found to have a carcinoma of the descending colon. A distal hemicolectomy was performed and the lesion proved to be a Dukes stage A well differentiated adenocarcinoma. She made a good recovery following the operation and was well until 4 years later when she presented with vaginal bleeding and was found to have a mass in the pouch of Douglas. A hysterectomy and bilateral oophorectomy were performed. At operation metastatic

Figure 4. Coronal slice through right cerebral hemisphere at the level of the mammillary bodies showing old insular cortex infarction (solid arrowhead), recent haemorrhagic cortical infarction (open arrowhead), and old small white matter infarcts (Case 1).

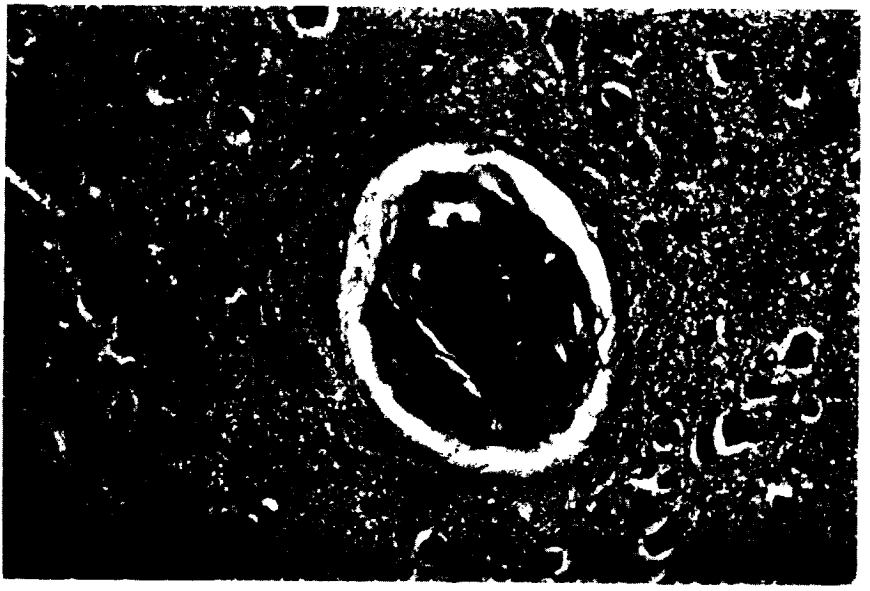

Figure 5. Organizing thromboembolic material in cerebral cortical arteriole from Case 1 (H and E × 200).

deposits of adenocarcinoma were seen in the left ovary. Despite this she remained well and independent at home. 12 months later she presented with a small bowel obstruction due to multiple tumour deposits disseminated through the abdomen and with a large mass at the root of the mesentery which was partially resected.

She recovered from this operation and was managing at home with her elderly husband with the aid of support services until her final admission. Her husband was awakened by groaning sounds coming from his wife. He found her semi-conscious and unable to move her left arm and leg. She was transferred by ambulance to the Austin Hospital where she was found to be drowsy and profoundly dysarthric. Examination revealed a left homonymous hemianopia and a left hemiplegia (face, arm and leg). Her eyes were deviated to the right. Her conscious state did not permit accurate sensory testing. Her heart was in sinus rhythm, there were no carotid or cardiac bruits and she was normotensive. She had no known cerebrovascular risk factors.

Table 1. Haematological findings in Case 1.

Hb	8.0 g/dL
P	19,000 × 10^9/L
WCC	8,000 × 10^9/L
KPTT	>240 sec
Thrombin time	>180 sec
FDP	80μg/ml
Fibrinogen	1.7 g/L

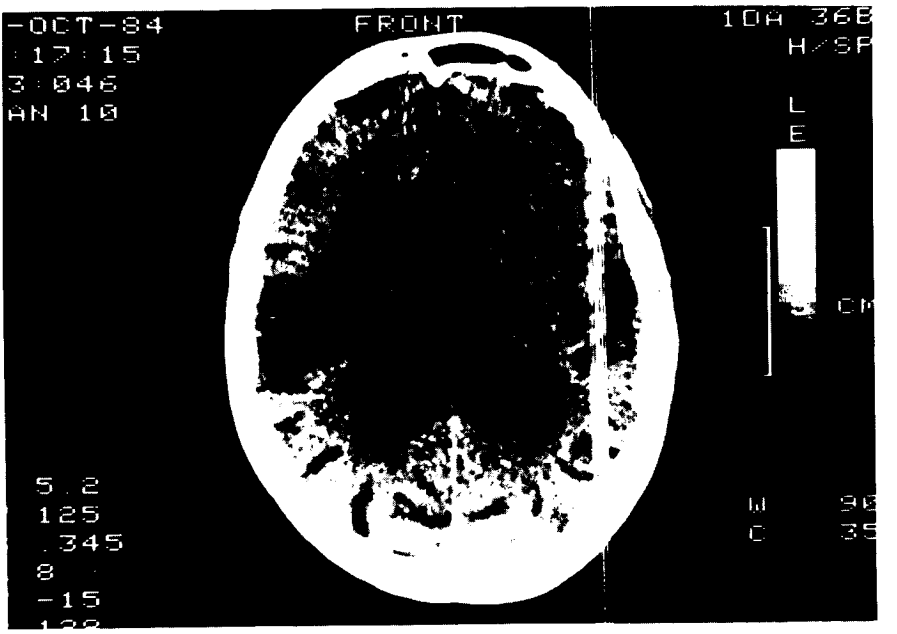

Figure 6. CT scan (Case 2) demonstrating recent right parietal infarction.

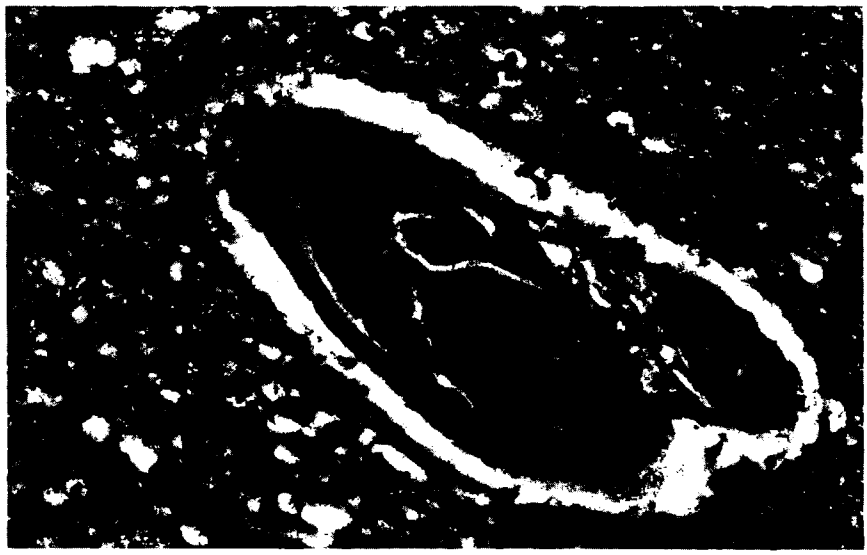

Figure 7. Section through cerebral hemisphere white matter (Case 2) showing a small artery occluded by thromboembolic material resembling that on the valve (H and E × 200).

Figure 8. Section through mitral valve (Case 2) showing tenuously adherent fibrin-platelet bland thrombus (H and E × 32).

A CT scan showed a large right parietal infarct (Figure 6). She had a haemoglobin of 11.5 g/dL and a platelet count of $115{,}000 \times 10^9$/L. Her chest radiograph was normal and a right bundle branch block was present on ECG. In view of her age and the severity of her stroke further investigations were not performed. She died of bronchopneumonia, 8 days following admission having shown no signs of neurological recovery.

At autopsy there was right cerebral hemisphere infarction consistent with a duration of one week in the distribution of the right middle cerebral artery. In addition there was a recent infarct (less than 24 hours old) of the left parietal lobe. The vessels of the circle of Willis were patent and showed minimal atheroma. The carotid arteries and bifurcations were free of atheroma. Focal recent occlusion of small arteries by thromboembolic material was seen (Figure 7).

Cardiac examination revealed friable vegetations on the mitral valve, measuring 8 mm in maximal extent. The histological appearances suggested that this material was the source of the cerebral emboli (Figure 8). Adenocarcinoma was found to be disseminated throughout the abdomen.

Discussion

Marantic endocarditis or non-bacterial thrombotic endocarditis was initially described as a form of terminal endocarditis associated with mucus secreting adenocarcinomas and was thought of no importance clinically[12]. However it has become apparent that this form of endocarditis can give rise to systemic emboli, with consequent infarction of various organs including the brain. Although malignant neoplasms, particularly adenocarcinoma of the pancreas, lung and stomach are found in approximately 50-80% of patients with this condition, several other disorders have been associated with it[13] (Table 2). The aortic and mitral valves are most commonly involved (70-80%).

Table 2. Conditions associated with NBTE

Adenocarcinoma (lung, pancreas, stomach): 60% — 80%
Rheumatic heart disease
Pregnancy
Amitriptyline overdose
Vasculitis
Lymphoma/Leukaemia
Cirrhosis

The pathogenesis of marantic endocarditis is poorly understood but most probably relates to a disturbance of coagulation mechanisms allowing adherence of platelets and fibrin polymers to the valve, producing sterile vegetations. Fragments of these may then dislodge, embolizing to distant organs. This theory is supported by the fact that 20-30% of patients have evidence of a chronic form of disseminated intravascular coagulation, ie. thrombocytopenia, elevated fibrin split product levels and decreased fibrinogen levels[14]. In addition spontaneous migratory thrombophlebitis has been associated with NBTE and at post mortem thrombosis of large veins is not infrequently seen. Valves previously damaged by rheumatic fever may be involved by this same process without any other underlying condition or in association with a remote carcinoma. Such valves are slightly more susceptible in the presence of an

underlying carcinoma when compared with normal valves. NBTE itself may be complicated by colonisation with organisms, thus causing subacute bacterial endocarditis (SBE).

It is at times extremely difficult to differentiate NBTE from culture negative SBE[13]. The characteristic presentation of NBTE is with embolic phenomenon to the brain (often causing hemiplegia), or to other organs eg. the heart (causing myocardial infarction), the spleen (splenic infarction), the kidneys (renal infarction and haematuria). The findings on examination usually do not suggest a cardiac source as the vegetations are generally small and do not interfere with valve function, so that murmurs are absent in most patients[15].

Echocardiography is unreliable, as the vegetations are often less than the 2 mm size needed for adequate resolution. Investigations which may suggest the presence of NBTE include CT brain scanning which may disclose a number of infarcts of varying ages in both cerebral hemispheres suggesting a cardiac source, particularly if some are haemorrhagic[16]. Other evidence of systemic embolism such as haematuria or evidence of a coagulation disturbance on laboratory testing may also suggest the diagnosis. Patients presenting with stroke or TIA should be suspected of having NBTE when a source of emboli cannot be found, particularly if they are older than 60 years of age, when the likelihood of an underlying carcinoma is higher[15].

In patients already known to have carcinoma approximately 1% will develop non-bacterial thrombotic endocarditis, as opposed to 0.5% in the community as a whole, based on autopsy figures[17]. It may be argued that, as patients with carcinoma have a reduced life expectancy, they will not benefit from diagnosis and treatment of the endocarditis. However strokes associated with this condition have a high morbidity and mortality. Post-mortem series have shown that the underlying carcinomas have been found to be potentially resectable and possibly curable in a number of patients[14]. In addition the effects of a "stroke" on the quality of life of patients suffering from carcinoma also makes this a complication requiring prevention if possible.

Although uncommon, NBTE has been described in children and should be included in the differential diagnosis of embolic stroke in childhood. There is an association with malignancy, particularly haematological malignancy, and also with pulmonary artery (Swann-Ganz) catheters in patients with pre-existing cardiac malformation[18]. This association has also been reported in adults and suggests that such catheters should be withdrawn as soon as possible. In such cases there is a higher incidence of right sided valve involvement. Prevention of NBTE would appear best achieved by the use of antiplatelet agents and removal of the tumour, if resectable. If these measures prove ineffective, anticoagulation may play a role or ultimately valve replacement, which has been performed in one instance for a patient with NBTE[19]. Study of NBTE may shed light on the clotting abnormalities found in malignant disease and consequently alter the therapeutic approach to the management of DIC.

Summary

Two cases of non-bacterial thrombotic endocarditis are described associated with stroke. This is followed by discussion of the pathophysiology of the disorder.

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Evaluation of an Introductory Course in Neurology

J.I. Balla and H. Edwards†*

Most clinicians who teach medical students are dedicated to the task and pride themselves on being good teachers. Therefore it is of interest to analyse what makes for good teaching, as this is likely to lead to improved teaching methods. This study looks at an established and well regarded course in introductory neurology taught to fifth year students. It contrasts this with another, unpopular course, clinical decision making (CDM), given by the same teacher and looks at the reasons for the success of the neurology course. The method of evaluation and details of the CDM course were the subject of a previous communication[1]. Now, in a preliminary way, we also consider features which make the neurology course successful.

These considerations are particularly significant when we realise that in most traditional medical schools, where preclinical and clinical teaching are segregated, students retain little useful accessible knowledge for clinical problem solving. This is in contrast to the expert who has readily available and relevant stores of knowledge[2]. Figure 1 shows the contrast between experts and students.

On reaching the clinical years students are taught new skills related to methods of information gathering. The objective is to marry this newly acquired knowledge with that already gained in the preclinical years, in order to solve the clinical problems they are now meeting. One way of defining successful teaching would therefore be the ability to present a course in such a manner that students would readily access their preclinical knowledge and make it useful for clinical problem solving.

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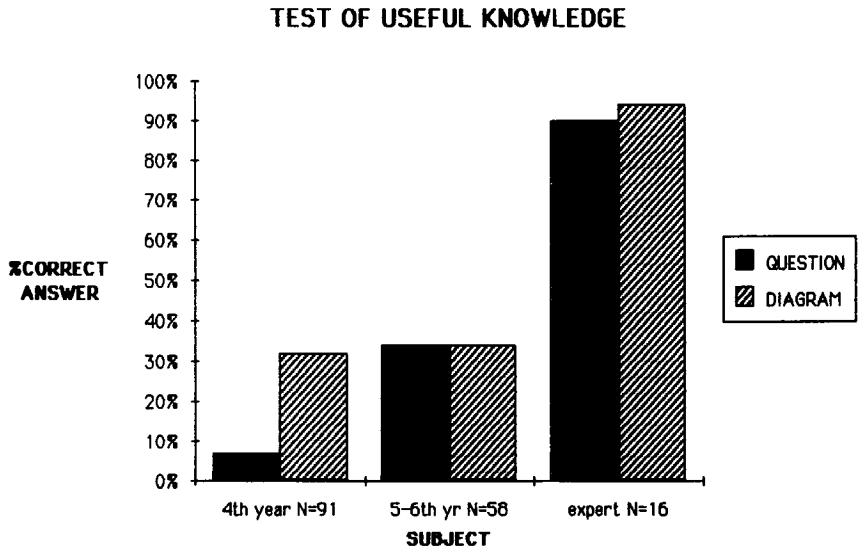

Figure 1. Relationship between experience of subjects tested and percentage of correct answers.

Methods

Using a tutorial format in groups of 10, fifth year medical students were taught 4 × 1 hour sessions in each topic, CDM and neurology. A total of 40 students was studied, 36 of whom responded to the questionnaires.

CDM teaching

This was concerned with the assessment of the validity of data and revision of opinion with new information. Teaching was around real life clinical examples, referring to recently seen cases in the wards or video tapes of patients. Paper and pencil cases were used to further stimulate discussion.

Neurology teaching

This was taught at the bedside. The principles of history taking and basic physical examination techniques were emphasised, as was the interpretation of data in terms of the students' previously acquired knowledge of anatomy and physiology. Relying on these correlations, they were expected to localise lesions to the various central nervous system pathways and regions. Specific disease entities were rarely discussed. Students were encouraged to form early hypotheses, and always consider actively the reasoning processes involved in reaching a diagnosis.

Evaluation

The evaluation compared student reactions to the two courses. In that the objective of the course was to change behaviour, it was felt that student perceptions were a valid end point of the evaluation. Previous studies of student evaluation of teaching have also demonstrated the validity and reliability of such ratings[3,4].

The evaluator attended all classes. Data gathered in this way were complemented by responses to a questionnaire which students completed at the end of the course. Small group discussion provided further data. The goal of the evaluation was to understand how the program worked for both teacher and students, and from this to develop questions for further study[5].

Contrary to the expectations of the teacher and the evaluator, based on student behaviour, the quantitative results of the evaluation showed remarkable consistency between groups. This demonstrates the need for systematic evaluation of teaching if we are to progress beyond vague impressions of what we are doing[1].

Results

Student Perception of subject matter

Figure 2 shows statistically significant differences between the two topics. Students tended to see the immediate relevance of neurology to their work, in contrast to CDM. They saw clinicians using neurology in the wards and could also use it themselves.

Ethnographic analysis

This showed contrasts between teaching of CDM and neurology as seen in Table 1. There was more active student participation in neurology and it fitted in with previous experiences. CDM gave a new framework of thinking and no procedural rules for individual problems to be solved.

Discussion

Results indicated that, in neurology, there was a high rating for enjoyment and interest. This contrasted with CDM where the lack of models amongst their clinical teachers was likely to have been a most significant factor in producing a poor attitude, as also was the lack of formal examinations in CDM, a well known hindrance to students' learning experiences. The results of the ethnographic analysis showed differences in teaching and learning attitudes between the two courses. Students like the hands on experience of neurology in contrast to the class room style of CDM. In the neurology program they had some knowledge about the basic mechanisms

underlying neurological abnormalities, although not in a form useful for dealing with clinical problems. They were then given "recipes" to convert their preclinical knowledge to a direct clinical application. In contrast, CDM was completely new to them. They were not given recipes for use in specific cases but general guides to a process.

Table 1. Ethnographic analysis of teaching

Teaching style	Neurology	CDM
Hands on patients	+ + + -	0
Student activity	+ + +	+
Procedural rules supplied	+ + + -	+
Students problem solve in class	+ + +	+
Students initiate questions	+ + +	+
Fits in with other experiences	+ + +	0
Will be examined	+ + + -	0

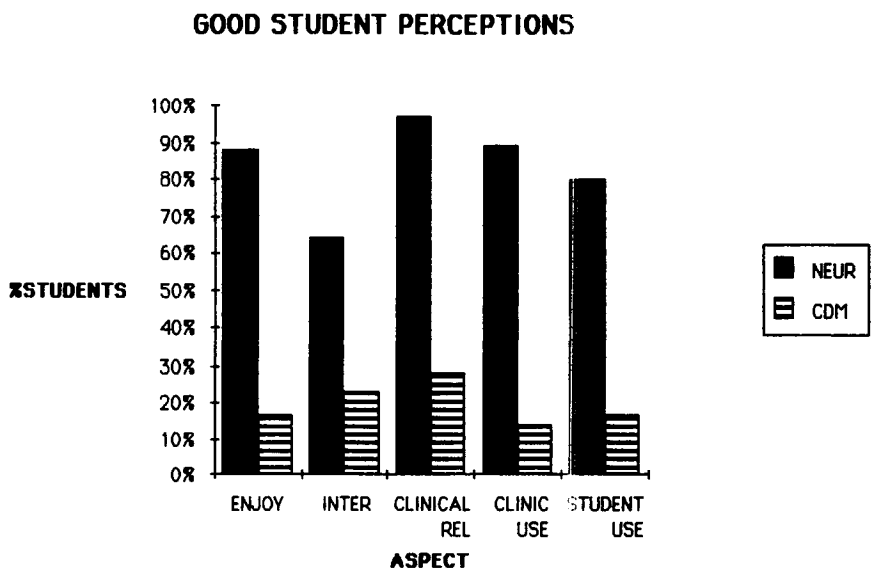

Figure 2. Student perceptions of the neurology and CDM courses.

Enjoy	=	Student enjoyed it
Inter	=	Found it interesting
Clinical Rel.	=	Student found subject clinically relevant
Clinical Use	=	Student could see clinicians using it in the ward
Student Use	=	Students were able to use it in the ward

The second and ongoing part of the study, using the same methodology both for teaching and evaluation as the first part of the study, looked at the neurology program in more detail but asked different questions. To this stage we have looked at 24 students and we are receiving some consistent answers from each group that we have looked at.

Patient contact

This is essential and there are significant qualitative differences from the preclinical demonstrations familiar to all. This new learning is taking place in a setting of reality. The students are seeing real problems, patients who are in hospital because they are ill. They are taught by a clinician who seems to know what he is doing and is responsible for final decision making about the patient. Previous work has shown that the experience of problem solving as a learning exercise will be affected by the context in which the problem is presented to the student[6]. This also raises some questions about the value of the standard case presentations practised in the preclinical years.[7].

We may tentatively conclude that the two essentials for effective clinical teaching are:

(a) the setting has to be realistic.
(b) the teacher should be someone with clinical credentials.

History taking

Sequential relevant questioning is stressed. This way students are able to relate to their preclinical knowledge. Anatomy and physiology come to life by the realisation that specific questioning leads to a diagnosis of relatively specific anatomical lesions.

Examination

The specifics of the exact technique are important to the students. Also, once more they are able to relate examination findings to their preclinical learning.

Therefore we conclude that the course appears to give students a perspective to the preclinical years. This is achieved by meaningful, sequential questioning and examination of a patient with the aim of demonstrating the clinical relevance of their anatomical and physiological knowledge. The experience has to occur in a realistic setting and they should be taught by a clinician who appears to be responsible for making decisions about the patient.

We believe that these conclusions bear relevance for curriculum planners when choosing teachers and developing strategies for introductory clinical courses. The place of sporadic clinical demonstrations in the preclinical years also needs to be re-evaluated.

Summary

The aim of this study was to distinguish factors which may influence student perception of what constitutes a good introductory course in clinical neurology. This should lead to the development of improved teaching techniques. Previous work has shown that even those students who retain accessible knowledge of preclinical subjects, such as neuro-anatomy, find it difficult to use this in a clinical context. This study is preliminary to looking at correlations between student perception of what they like about a clinical topic and the ability to integrate clinical knowledge with pre-existing knowledge structures.

The evaluation was carried out on 36 fifth year students who were taught clinical neurology in small groups concurrently with another topic, clinical decision making (CDM), by the same teacher. Neurology consistently rated at over 80% for enjoyment, interest and perceived clinical relevance. This contrasted with low ratings of $<25\%$ on all these parameters for CDM. An analysis of teaching methods showed that in neurology, contrasting with CDM, procedural rules were supplied for the application of preclinical knowledge at the bedside, students had an opportunity for active participation and problem solving in class, as well as frequent patient interaction.

All these factors are important for student acceptance of a course, but further studies are needed to look at the interplay of preclinical knowledge and the acquisition of clinical expertise. The findings of this preliminary work may have significant implications for curriculum planners when developing introductory clinical courses.

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Lumbosacral Nerve Plexus Compression by Ovarian-Fallopian Cysts

*P.T. Yeo and A.C. Grice**

Compression of the lumbosacral plexus by malignant and benign neoplasm is rare and literature descriptions relate mainly to single cases or small number of patients. Frequent causes are lymphomas[1] carcinoma of the cervix[2] uterine leiomyoma[3] and carcinomas of the colon and rectum[4].

In this report, we present a case of lumbosacral nerve compression caused by large fallopian cysts in association with small ovarian cysts.

Case Report

A 43 year old laundress, twisted her left ankle because of "weakness" in December, 1983. Two months later, she noticed wasting of left calf, episodic weakness of the left knee and numbness of the inner aspect of the thigh and calf. Weakness of the knee and calf gradually worsened and she started to complain of cramping pain of the foot. In August, 1984, she experienced, over a 2 week period, several episodes of sharp iliac fossa pain occurring both spontaneously and during sexual intercourse. She had intended to consult a gynaecologist because she had a history of "diseased tubes", but had not done so because symptoms resolved on their own accord.

Physical examination showed a sickly woman with a sallow complexion. There was obvious wasting of the left calf, the circumference taken 10 cm below the tibial tubercle being 28 cm compared with 31 cm for the right calf. The circumference of the thigh taken 20 cm above the tibial tubercle was 44cm on both sides. The left knee jerk was depressed and the left ankle jerk was absent. Pin prick sensation was markedly diminished over the L3 and L4 dermatomes and slightly diminished over L1, L5 and S1 dermatomes on the left side. Vibration and position sensation were intact. Straight leg raising was 90° for both sides; there was no tenderness over the lumbosacral spine. Deep palpation of the iliac fossa revealed a moderately tender vague mass.

Full blood examination was normal; the ESR was 4 mm/h. The blood sugar was within the normal range. Electrophysiological studies (Table 1) showed normal motor conduction velocities in the posterior tibial and lateral popliteal nerves and there was no significant difference in the values between the two sides. The H reflex was absent on the left side. The latencies of F responses from

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Table 1. Electrophysiological studies. Calf motor conduction velocity was measured in the posterior tibial (PT) and lateral popliteal (LP) nerves. F waves were recorded from flexor hallucis brevis (FHB) and extensor digitorum brevis (EDB) muscles.

NERVE CONDUCTION STUDIES			
		Right	Left
Motor Conduction Velocity	(PT)	45.7 m/s	45.7 m/s
	(LP)	47.2 m/s	49.1 m/s
F Wave Latency	(FHB)	48.0 ms	47.6 ms
	(EDB)	51.0 ms	49.5 ms
H Reflex Latency		32 ms	Abs ms
EMG			
Denervation potentials			
1. Plentiful: Soleus, Tibialis anterior, Quadriceps, Gluteal			
2. Occasional: Thigh Adductors			
3. Nil: Paraspinal			

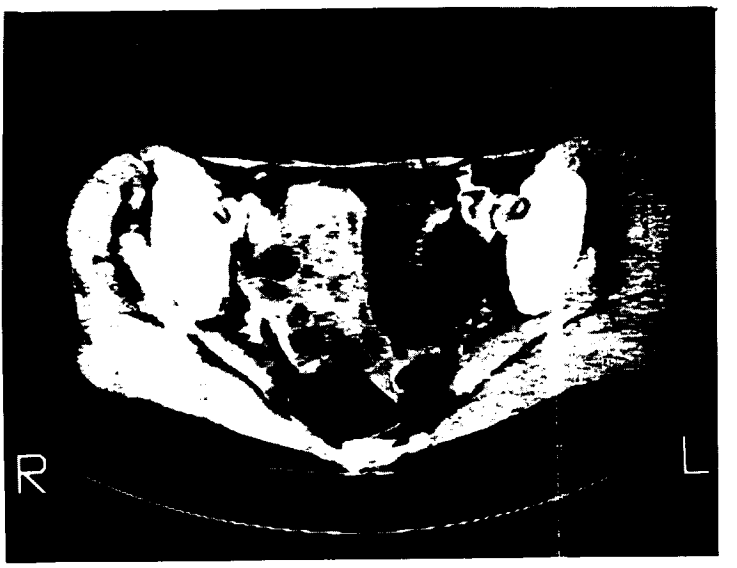

Figure 1. CT scan of pelvis. Three well defined cystic structures are seen on the left side.

the flexor hallucis brevis (FHB) and extensor digitorum brevis (EDB) were normal but the motor response from the left FHB muscle was very small. With electromyographic studies, plentiful denervation potentials were recorded from the left soleus, tibialis anterior, quadriceps and gluteal muscles; occasional denervation potentials were recorded from the thigh adductors. The paraspinal muscles were electrophysiologically normal. CT scan of the lumbosacral spine was essentially normal except for mild hypertrophy of the ligamenta flava. CT scan of the pelvis (Figure 1) showed large cystic

Figure 2. Ultrasound of the pelvic cavity demonstrating the cystic structures.

Figure 3. Uterus and adnexal structures. Note grossly dilated left fallopian tube.

structures on each side of the pelvis, bigger on the left than the right. There were increased blood vessels on both sides of the pelvis, more marked on the left at the region of the sciatic notch. Ultra sound studies of the pelvic cavity (Figure 2) showed tortuous fluid-filled structures on both sides of the pelvis, thus confirming the CT scan findings.

The patient was referred for gynaecological management and subsequently underwent total hysterectomy and bilateral salpingectomy. The removed tissues (Figure 3) consisted of a macroscopically normal uterus with its adnexal structures distorted by a bilateral hydrosalpinx. The tubes had undergone variable distension and fibrosis with creation of large cystic spaces which contained clear fluid. The ovarian parenchyma was oedematous in many areas and several follicles and corpus luteum scars were evident. The patient made an uneventful recovery from the operation and was discharged after 10 days.

Discussion

The lower limb is supplied by nerves from the lumbosacral plexus which is formed by the second lumbar to the fourth sacral nerve roots. Lesions of the plexus are characterised by multisegmental motor and sensory loss. The most common conditions affecting the lumbosacral nerve plexus are diabetes mellitus, trauma and intra-pelvic malignancy. The course of the lumbosacral plexus makes it vulnerable to compression or direct invasion by intrapelvic neoplasms. Specifically with reference to gynaecological causes, carcinoma of the cervix can cause direct invasion. Meralgia paresthetica has been reported as a symptom of lumbar plexus compression from enlarged uterine fibroids[5]. The sciatic nerve has been reported as vulnerable to compression from the foetal head during labour[6]. We present this report as an example of an interesting case of lumbosacral plexopathy with predominant involvement of the sciatic component. We are not aware of other similar cases in the literature. The nerve plexus was most probably damaged by direct mechanical compression but we suspect part of the pathology could be attributed to pelvic wall adhesions. Clinically, the patient presented with symptoms and signs predominantly due to sciatic nerve involvement. EMG studies confirmed profound denervation in the muscles supplied by the sciatic nerve but also revealed involvement to a lesser extent of the femoral nerve motor supply. Sparing of the paraspinal muscles is in keeping with the definition of plexopathy[1]. CT scan and ultra sound have made diagnosis of pelvic masses relatively simple and safe. Their value in defining the nature of the lesions was attested to by the operative findings in this patient.

Summary

A 43 year old woman presented with a 10 month history of pain, progressive weakness and wasting of the left calf. Electromyography demonstrated denervation at the level of the lumbosacral plexus, particularly of its sciatic component. CT and ultrasound examination revealed intrapelvic cysts which were confirmed on surgical exploration to be fallopian and ovarian cysts.

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Genito-Femoral Neuropathy

*R.H. Rischbieth**

Compression neuropathy of the genito-femoral nerve was first described by Magee[1] under the title of genito-femoral causalgia in 1942. He claimed it was a previously unrecognised syndrome characterised by pain typically aggravated by walking and by hyper-extension of the hip, and by paraesthesiae in the distribution of the genito-femoral nerve. He described 7 cases he had seen within 12 months. Characteristically, there was inguinal pain with tenderness along the inguinal canal and over the internal ring radiating to the upper inner thigh, relieved by flexing the thigh, and with or without hyperaesthesia in the sensory territory of the genito-femoral nerve. The majority of cases, 5 of 7, had right-sided symptoms coming on subsequent to an appendectomy. The two left-sided cases had followed trauma to the groin and a left psoas abscess, respectively. Five operated cases were reported as subsequently being symptom free.

Lyon[2] reported 3 further previously appendicectomised cases, seen over an 18 month period and operated on by neurectomy, with satisfactory relief of pain. Lyon suggested the alternative and now generally accepted name of genito-femoral neuralgia. Laha and co-workers[3] reported a 46 year old male with bilateral genito-femoral neuralgia, the onset on each side having followed ipsilateral inguinal herniorrhophy. The patient described electric shock-like pain radiating towards the groin and the right testis, together with dull pain in the groin. Genito-femoral nerve resection, after inspecting the nerve as it lay on psoas muscle and stimulating it to elicit a cremasteric reflex, resulted in cure of the pain with no sensory deficit, but produced bilaterally absent cremasteric reflexes. Histologically the nerve showed endoneurial fibrosis, similar to the changes reported by Lyon[2], who described patchy demyelination and perineurial fibrosis also. Both Magee[1] and Lyon[2] had reported adhesions of the caecum or terminal ileum to the genito-femoral nerve which was under tension. Laha et al.[3] commented on the differential diagnosis from neuralgia of the ilio-inguinal nerve or lateral cutaneous nerve of the thigh (meralgia paraesthetica) and recommended genito-femoral neurectomy by an extra-peritoneal approach.

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In all, 11 cases had been reported in the literature when O'Brien[4] described his case from Guy's Hospital in 1979, although the disorder had been well described by Staal[5] in the Vinken-Bruyn Handbook of Clinical Neurology. In the 1984 edition of their book "Peripheral Neuropathy" Dyck, Thomas, Lambert and Bunge[6] devoted a bare half page to the subject in the chapter on compression and entrapment neuropathies. O'Brien[4] reported a 20 year old female model who noticed an area of numbness 5 cm in diameter just below the middle of the inguinal ligament, which was sore to the touch, and at times tingled unpleasantly. Symptoms were aggravated by standing, when her hip would ache, and by modelling jeans. Examination disclosed impaired pin prick and cold perception with hyperpathia to light touch in the cutaneous distribution of the femoral branch of the genito-femoral nerve i.e. the upper part of the femoral triangle. O'Brien described a special technique needed to pull on jeans which are several sizes too small, and postulated that too-tight jeans may have been the initiating cause.

The technique for putting on jeans that are several sizes too small requires the help of three assistants. The model wears nylon pants which extend from the waist to the knees to overcome friction. Two assistants, one on each side, help pull on the jeans while the model lies on her back. The third assistant kneels at the head of the model holding a wooden coathanger, whose hook is looped into the zip fastener of the jeans ready to pull the fastener as soon as a special device to hold the front of the jeans together has been applied (and provided the material does not tear). Once the model is encased it is impossible for her to stand up without help, or sit down once she has stood up. His patient was relieved for four months by the injection of depot methyl prednisolone below the inguinal ligament, only to reappear, again being relieved by local injection of steroid.

Case Report

A girl, aged 14 years, first noticed in 1983 tingling, numbness and soreness to touch of an area on the anterior aspect of her left thigh at the lower level of the pants line. This discomfort had waxed and waned, worsening if she wore briefs with elastic in them, or bumped the area, but it never wholly cleared. The patient had grown some 18 cm in height in the previous 12 months. Apart from exercise-induced asthma and mild reading retardation with look-and-say errors, a past history of appendectomy at the age of 13 and tonsillectomy at the age of 5, her previous health had been good.

Physical examination revealed an area of impairment of pin prick and touch sensation and the presence of hyperalgesia to cold stimulation over an elliptical area on the anterior aspect of the left thigh immediately below the middle of the inguinal ligament. There were no motor signs, and no mass could be felt in the inguinal region either with the patient supine, or standing.

It was concluded that Miss C.M.F. had sustained a genito-femoral compression neuropathy associated with her rapid gain in height. The dysaesthesiae provoked were of only mild severity and it was decided to defer steroid injection or surgical intervention. Nine months later the patient reported improvement in, although not complete disappearance of, her symptoms.

Discussion

The cutaneous branches of the lumbar plexus which form the genito-femoral nerve have variable courses. The nerve is derived from the first and second lumbar roots and runs through the substance of the psoas major. It emerges on the psoas surface where the external spermatic and lumbo-inguinal elements may run together, or in two or three branches, with free communication with each other and with the ilio-hypogastric and ilio-inguinal nerves. The genital, or external spermatic, branch enters the inguinal canal through the deep inguinal ring and continues to supply the cremaster, upper lateral part of scrotum or mons pubis and the labium majus. The femoral branch accompanies the external iliac artery and passes under the inguinal ligament, enters the femoral sheath lateral to the femoral artery and supplies the upper part of the femoral triangle.

Pressure from clothing, usually corsets, is a well recognised cause of damage to the lateral cutaneous nerve of the thigh (causing meralgia paresthetica) but this nerve is more superficial and more lateral, whereas the genito-femoral nerve is relatively protected in the hollow of the groin. It seems that tight clothing such as jeans or elastic in undergarments, may under some circumstances result in a genito-femoral neuropathy. More frequently pelvic surgery, e.g. appendicectomy, or psoas infection or local trauma are predisposing factors.

Summary

A 14 year old female, who had undergone a sudden growth spurt, developed symptoms of a left-sided genito-femoral neuropathy, made worse by wearing tight elastic-adorned garments.

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Transfer Factor as a Therapy for Multiple Sclerosis: a Follow-up Study

J.A. Frith, J.G. McLeod, A. Basten, J.D. Pollard, S.R. Hammond, D.B. Williams and P.A. Crossie. *

A two year, prospective, double blind, controlled trial[1,2] was initiated in 1977 to examine the value of transfer factor (TF) in the treatment of multiple sclerosis (MS). Sixty patients with symptoms and signs of definite MS were involved. They were divided into two groups of 30 patients. One group received TF and the other received placebo. The two groups were matched for age, sex, disability, relevant HLA phenotypes and duration of disease. Neurological assessments were performed on each patient before the trial and at six monthly intervals for the duration of the trial. The patient's disability was assessed on the Kurtzke[3] scale and individual functional systems (pyramidal, cerebellar, sensory, brainstem, bowel and bladder, visual and mental) were graded. The number of relapses since the previous examination was recorded. Visual, cortical, spinal and brainstem evoked potentials were recorded for each patient before the start of the trial and every six months thereafter.

The trial showed that there was significantly less clinical deterioration in patients who had received TF for 18 months or more, compared with those who had received placebo (Figure 1). Patients who were only mildly affected at the outset seemed to benefit more from TF than those who were more severely affected. No complications were recorded as a result of the TF therapy. Conclusions drawn from these results indicated that TF from cohabitant donors slowed the rate of progression of disease in patients with mild to moderate disability, but TF did not prevent the formation of new lesions.

These findings justified the development of further clinical trials in order to assess in more detail the effect of TF on MS. Three lines of clinical investigation have been pursued:

1. a follow-up study of 45 patients from the original TF trial,

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2. an open study of TF (1981-84), and
3. a double-blind controlled trial of Interferon and TF (AUSTIMS) (trial in progress).

The methods, results and conclusions of the follow-up study of 45 patients and the open study are described below.

Methods

Patient selection

1. Follow-up study (1981-84).

All the 58 people who had participated in the original TF trial were offered TF as a long-term treatment. Forty-five of these patients decided to accept TF treatment and went on to receive second monthly injections of TF (1 unit) for three years. Of these 45 patients, 23 had been receiving TF in the original trial and 22 had received placebo. These two subgroups were still matched for age, sex, disability, relevant HLA phenotypes and duration of disease. They had neurological assessments performed after one year and after three years of therapy. Their disability was assessed (as in the original trial) on the Kurtzke[3] scale. This scale ranges from 0, which is a normal neurological examination, to 10 where the patient has died as a result of MS; grades 0-3 represent mild or moderate disability only; patients in grade 6 require assistance for walking and those in grade 7 are restricted to a wheelchair.

2. Open study of TF (1981-84).

TF was offered to patients within New South Wales who had clinically definite MS but were only mildly affected (0-3 on the Kurtzke scale). Over the last three years, 470 people have been accepted into this open study of TF. Each of these people has received monthly injections of TF (1 unit) for the first six months, and second monthly injections thereafter. Neurological assessments using the Kurtzke scale[3] have been done at the end of one and of three years of treatment.

Transfer Factor

TF is a cell free dialysable leucocyte extract which has been shown, *in vitro* and *in vivo*, to transfer cell mediated immunity[4,5]. Preparation is by harvesting white cells by leucophoresis from donors who cohabit with MS patients. Mononuclear cells are separated on "Ficoll-Hypaque" gradients and a crude cell free extract is prepared by repeated freeze-thawing[4]. After ultrafiltration, the final product is frozen until required. The concentration of TF is adjusted so that each ml contains 2.0×10^8 cell equivalents. 1 unit of TF is arbitrarily defined as 4.0×10^8 cell equivalents. Cohabiting donors are used since they are presumed to have been exposed to the same pathogenic agent in the environment that has contributed to the patient

having MS, yet the donor has "immunity". The administration of Transfer Factor is an attempt to transfer this "immunity" to MS patients.

Results

1. Follow-up study (1981-84).

The data on the 45 patients who chose to receive long term TF treatment are presented in Figure 2 as the mean change in disability status score (DSS) at each time of review. It can be seen that all patients were receiving TF after 36 months from the commencement of the original trial and that all patients had a slower rate of progress of their MS regardless of whether they received TF or placebo during the original trial. In fact there was no significant difference in the rate of change of disability between the two groups after they both received TF.

2. Open study of TF (1981-84).

Preliminary results after the third year reassessment of 209 of the 470 patients revealed slow progress of disease. The mean change in disability status score per year for this group was 0.25. A similar calculation has been done to find the rate of change of the DSS per year in a group of 353 New South Wales MS patients not receiving TF, who have been observed over a five year period in the National Multiple Sclerosis Society's Epidemiological Study. The patients in this group had a DSS of 0-3 and fulfilled the same selection criteria as those patients included in the open study of TF. Their mean change in DSS/year was 0.34. No side effects were recorded in any patients receiving TF.

Discussion

In the initial trial, it was shown that patients receiving TF had significant slowing of progress of their MS. This study was double blind and there was a control group which was well matched with respect to prognostic variables. However, only a relatively small group of patients was involved and they were observed for only two years. Moreover, the rate of progression of disability was more rapid than usually seen. If TF was of benefit for this group with such aggressive disease, it should also help patients pursuing a more usual course. Since the initial trial, 45 trial patients received Transfer Factor for 3 years. During this time, the progress of the disease in the original placebo group, who later received TF, slowed and in fact there was no significant difference in progress of the disease between this group and those who received TF since the commencement of the trial. This confirms the conclusions drawn from the original trial.

In the open trial where 209 people out of a total of 470 have been observed on TF over 3 years, the rate of progression of disease appeared slower than in a control

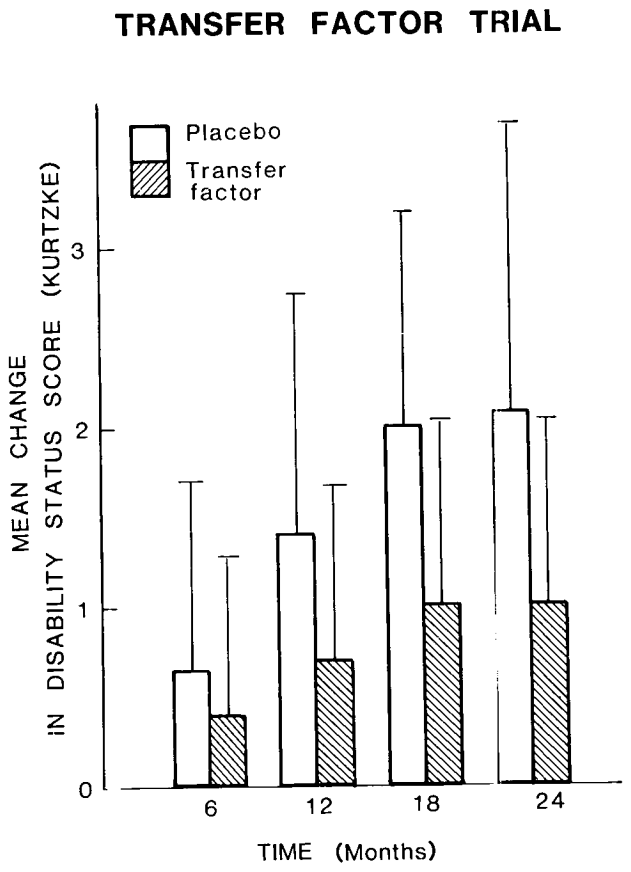

Figure 1. Change in disability status score (DSS) of control patients (open bars) and patients receiving TF (shaded bars) at 6, 12, 18 and 24 months. Means are represented, ± 1 SD.

group. The problems with this study were that it was not blind, and that the patients were not matched. However, useful information has been obtained since a large group of patients was being continually assessed over a long period of time and the rate of progress was being compared with the rate of disease progression in patients not receiving treatment. Follow-up studies seem to confirm the original observation that TF has some effect on slowing the course of MS while causing no recorded side effects.

In the future, follow-up studies will continue and the areas of research will expand with the Australian Trial of Transfer Factor and Interferon in MS (AUSTIMS), supported by the Commonwealth Serum Laboratories. This is a nationwide, double

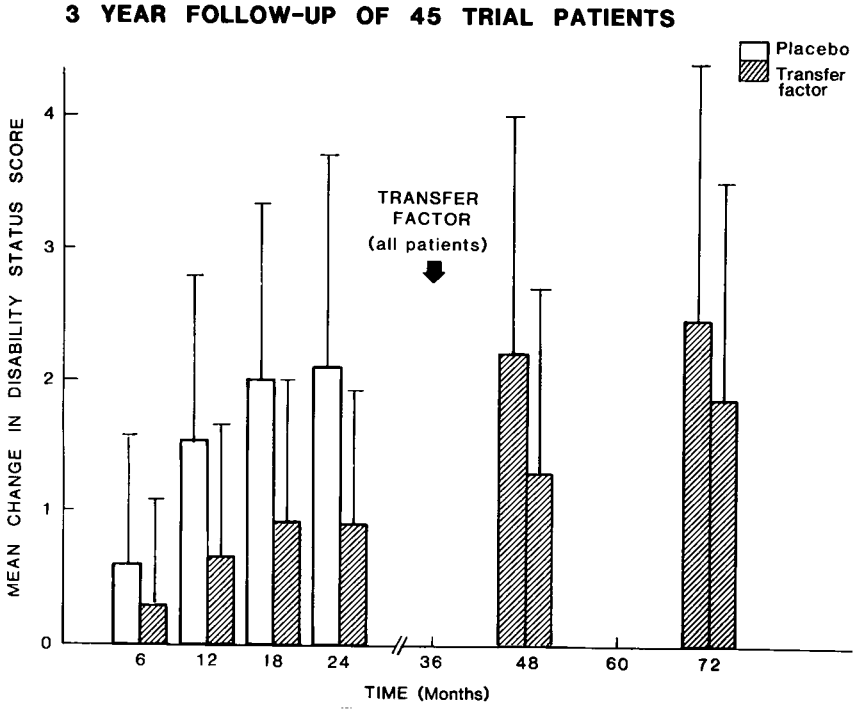

Figure 2. Change in DSS of the 45 original trial patients who went on to receive long term TF therapy. At 6, 12, 18 and 24 months, open columns represent the mean DSS for patients on placebo and shaded columns the DSS for those on TF. From 36 to 72 months, both groups received TF.

blind, controlled trial in which 225 patients are involved for 3 years. There are 75 patients in each of 3 groups receiving TF, Interferon or placebo. In this trial, the effects that TF and Interferon have on MS are being examined in more detail. It is a comprehensive study incorporating a battery of immunological tests as well as neurological assessments in order to elucidate the role of immunopotentiating agents in the treatment of multiple sclerosis.

Summary

The result of a two year, double blind, controlled trial of Transfer Factor (TF) in the treatment of multiple sclerosis (MS) were reported in 1980. It was demonstrated that TF significantly reduced the rate of progression of the disability but the benefit of therapy was not apparent until 18 months after its commencement. After the completion of the trial, TF treatment was offered to all the trial participants. Forty-five of these people accepted TF as treatment and have been followed for the subsequent

three years. The twenty-three people who had received TF during the trial, and continued on TF after the trial, consistently had a slower rate of progression of their MS. Although the twenty-two patients initially on placebo had a significantly faster rate of progression during the trial, this slowed with commencement of TF treatment. After 3 years of TF, the rate of progression of disease was similar to that of the group receiving TF continuously for 5 years.

In addition, 470 patients with clinically definite MS are being treated in New South Wales in an open study of TF. The rate of progression of the disease is being monitored by neurological assessments and appears to be similar to that of patients who had received TF in the original trial.

The follow-up study of the 1980 TF trial patients and the open study of 470 MS patients confirm the original observation that TF has some effect on slowing the course of MS.

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The Neurochemical and Clinical Effects of 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine in Small Animals

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In 1983 Langston described three young drug addicts with apparent Parkinson's Disease[1]. By astute deduction he established that the pyridine derivative, 1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) found in the synthetic heroin used by the addicts was responsible for producing the Parkinsonism. He correlated his findings with a previously reported case of similar type where, at post mortem, destruction of the zon compacta of the substantia nigra was seen[2]. An inclusion body which resembled a Lewy body was also found, thus suggesting to some a close relationship between MPTP-induced Parkinsonism and true Parkinson's disease.

Although the aetiology of true Parkinson's disease remains a matter of conjecture, the possibility that a toxin similar to MPTP may be responsible now seems a much more realistic possibility. Previous theories included implication of viruses, hereditary or toxic factors. Recent twin studies showed no increased concordance in twins of Parkinsonian patients[3] and although encephalitis lethargica virus and other viruses may cause a syndrome of Parkinsonism, sero-epidemiological surveys do not support a viral basis for true Parkinson's disease[4].

A logical step following the discovery of the effects of MPTP in man was to develop an animal model so that mechanisms of MPTP action could be studied more closely. Primate models with clinical manifestations of Parkinson's disease have now been developed where selective destruction of dopaminergic neurons in the substantia nigra and striatum occurs, while mesolimbic projections are spared[5,6,7,8] However, the expense and inconvenience of managing such large animals has

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resulted in a continued search for a suitable small animal model. We report the clinical and biochemical effects of MPTP on a series of small animals, particularly the C57 black mouse.

Methods

MPTP used in the initial experiments was in base form, while later MPTP as the HCl salt was employed. The advantage of the latter is its lack of volatility and its ready water solubility while the MPTP base needs to be dissolved in alcohol and is volatile. Animals tested were rabbits, guinea pigs, rats (Sprague Dawley) and mice (C57 black). Equal numbers of male and female animals were used. All injections were intraperitoneal except in the rabbits, where intravenous injections were given. Control animals were used in all cases in equal numbers and received equal volumes of ethanol (when MPTP base was used) or water (for MPTP HCl). All animals were observed for 30 minutes post injection and then at hourly intervals for the next 3 hours.

Precautions were taken while handling MPTP. In general, no touch techniques were used and all dilutions were performed in a fume cupboard using double gloves, gown and mask. Injected animals were kept in a separately ventilated isolation area and waste disposed of as "toxic waste". Stock solutions of MPTP were made up in sealed vials and diluted as necessary. Animals were weighed to determine injected dose per kilogram.

Dopamine assays were performed on the striata of C57 black mice using HPLC with electrochemical detection[9]. Pathological specimens were prepared in isolation and sections of cortex, striatum, midbrain and pons stained with haematoxylin and eosin, luxol fast blue and cresyl violet.

Results

Clinical Effects

The clinical effects of MPTP in all animal, groups and routes of administration are shown in Table 1. In Sprague-Dawley rats, low doses i.p. (< 15 mg/kg) appeared to have little effect, while higher doses (30 mg/kg) produced an acute neurological syndrome which consisted of bradykinesia, drooling, ataxia, limb weakness and seizures. This lasted for approximately 20 minutes, following which almost complete recovery occurred. Of 24 Sprague Dawley rats injected daily with MPTP i.p. (30 mg/kg) for 15 days, the mortality was 78%. Doses of 50 mg/kg invariably caused seizures and were uniformly fatal.

MPTP injections in other animals had similar clinical effects; there was little change in clinical state with low doses (< 15 mg/kg), even if given daily for 15 days. In higher doses (> 30 mg/kg) almost all animals developed the acute neurological syndrome previously described with apparently few long term sequelae. In rabbits, MPTP was also given intravenously (slowly). It caused similar clinical changes, but at a lower dose (10 mg/kg). One rabbit died acutely after MPTP administration i.v. (30 mg/kg) after repeated generalized seizures.

Table 1. MPTP administered in small animals: clinical effects.

	Number of animals	Number of injections	Route	Dose mg/kg	Acute response	Chronic response
Rabbits	7	1-4	IV	10-30	seizures, ataxia, bradykinesia	Nil
Rat	24	1-18	IP	15-50	seizures, ataxia, bradykinesia	Nil
Guinea pig	22	1-13	IP	15-50	seizures, ataxia, bradykinesia	Nil
C57b mouse	20	1-15	IP	15-50	seizures, ataxia, bradykinesia	Hyperactivity

Striatal Dopamine Levels

These assays were performed in C57 black mice only. A series of single i.p. injections ranging from 10 to 50 mg/kg helped establish that the most useful dose regime was about 30 mg/kg (Figure 1). All animals injected with 50 mg/kg MPTP i.p. had seizures and died acutely. Serial daily injections of MPTP caused a steady reduction in striatal dopamine levels with a relative plateau of effect after 4 injections (Figure 2). At this level an 87% reduction in striatal dopamine occurred compared with control animals injected with water. Animals given a single injection of MPTP (30 mg/kg) showed some tendency to restoration of dopamine levels with time, but this trend was not statistically significant (Figure 3). Similarly, after 4 injections a trend towards recovery of striatal dopamine levels was seen, but again did not reach statistical significance (Figure 4).

Pathological changes

Both Sprague Dawley rats and C57 black mice were examined pathologically. On haematoxylin and eosin staining in rats, 5 brains (10 MPTP injections of 30 mg/kg) were compared with controls. Little change could be seen, although in the MPTP injected brains some cytoplasmic vacuolation of neurons was visible in the region of the substantia nigra compacta in the mid brain and trigeminal nuclei in the pons. This change may have been artefactual since its appearance bore little relationship to the number of MPTP injections received and was observed very occasionally in control brains.

Brains of C57 mice (10 MPTP injections 30 mg/kg) were sectioned and stained with haematoxylin and eosin, and luxol fast blue. In spite of careful and blinded

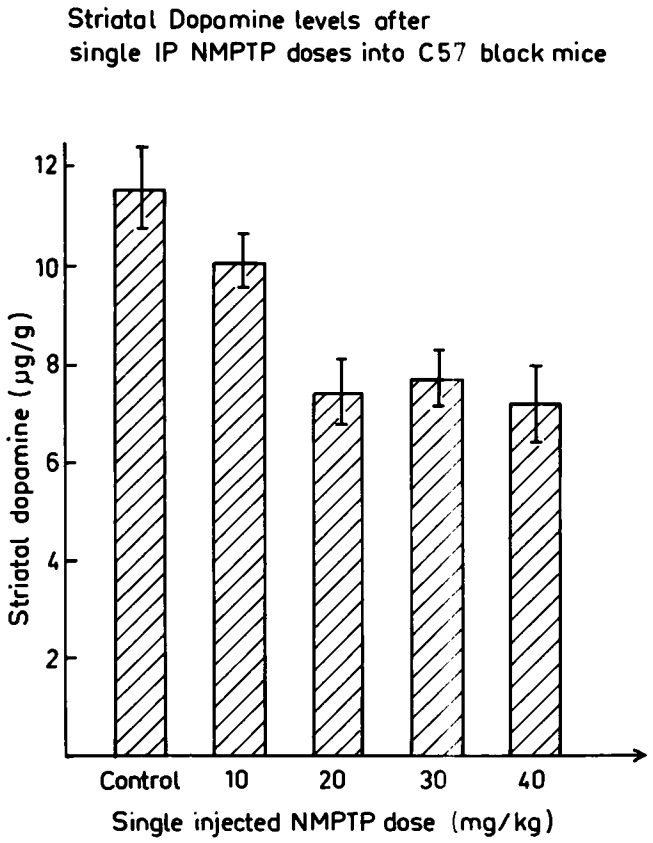

Figure 1. Single injections MPTP i.p. in C57 black mice. A minimum of 5 animals was used in each group. A single injection of 30 mg/kg reduced striatal dopamine to 65% of control values (means ± SEM).

examinations of 5 injected and control brains, particularly in the corpus striatum, substantia nigra and locus coeruleus, no alteration in neuronal morphology or numbers could be detected (Figure 5).

Discussion

The current study clearly indicates that none of the small animals tested are suitable as clinical model of Parkinson's disease, but the C57 black mouse promises to be an excellent neurochemical model. Other workers have demonstrated that in animals such as rat, guinea pig and cat, little change in striatal dopamine levels occurs after

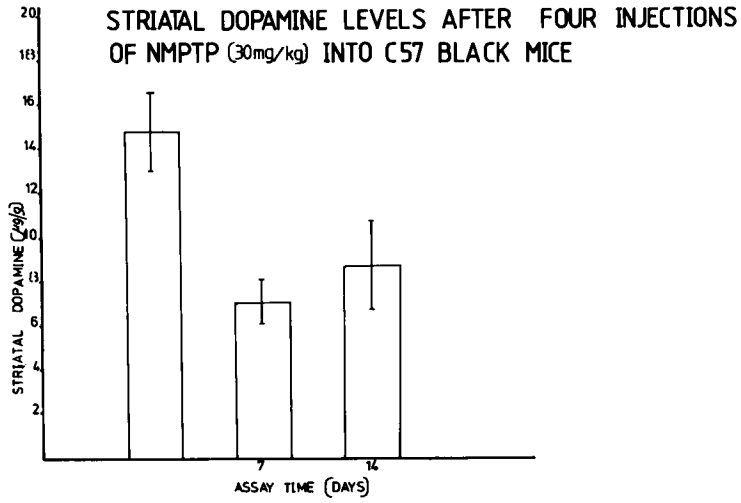

Figure 2. MPTP administration in C57 black mice. 30 mg/kg was given IP to each animal and a minimum of 5 animals used in each group. After 4 injections striatal dopamine levels were 13% of control values (mean ± SEM).

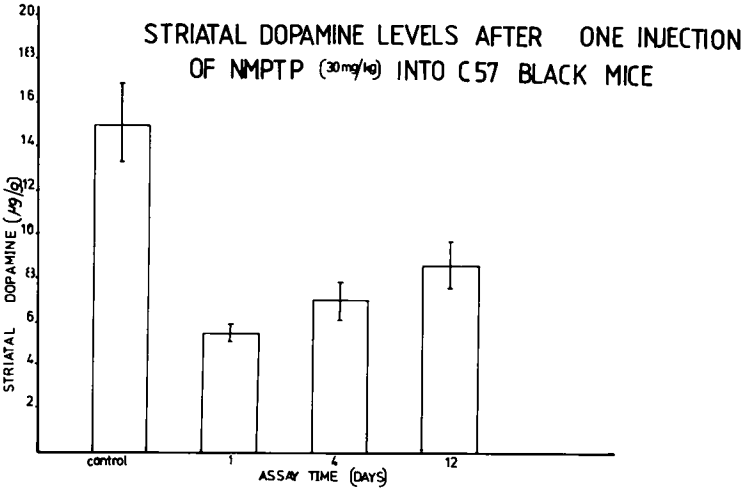

Figure 3. Single injections of MPTP i.p. in C57 black mice with time course of striatal dopamine levels (mean + SEM). There was a trend towards recovery of dopamine levels, but not significantly ($F = 0.80$; $P < 0.50$; ANOVA test). Five animals were used in each group; controls on the left.

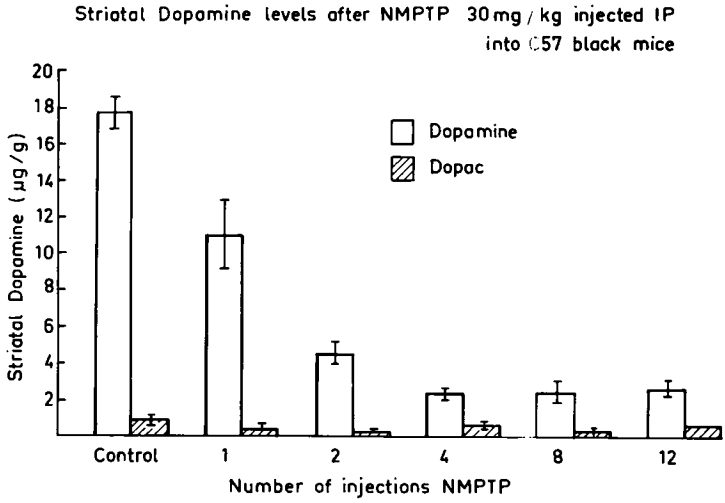

Figure 4. Time course of striatal dopamine levels after 4 injections MPTP i.p. in C57 black mice. Again, a trend towards recovery of dopamine levels was seen, but not significant ($P > 0.4$: "t" test). Five animals were used in each group; controls on the left.

MPTP administration[10]. Although striatal dopamine levels were not assessed for the rabbit in the current study the animal was unsuitable as a clinical model. If a neurochemical model is to be sought, the C57 black mouse would appear to be ideal. The small size of the C57 black mouse and the consistent and profound reductions in striatal dopamine levels after MPTP administration[11] should facilitate studies where large numbers of animals are required.

Although little change in striatal dopamine levels has been observed in the rat, and only a 50% reduction in guinea pigs[9], these animals have already proven to be useful in elucidating the mechanism of action of MPTP. It was the similarity between the autoradiographic distribution of [H^3] MPTP and monoamine oxidase (MAO) distribution in the rat which first raised the possibility that MPTP may be a substrate of MAO[12]. This was later confirmed by Chiba et al[13] using rat brain mitochrondrial preparations. Furthermore, MAO type B appeared to metabolize MPTP selectively while MAO-A did not. A clonal line of rat phaeochromocytoma cells, PC12, was used by Denton and Howard[14] to demonstrate that MPTP inhibits dopamine uptake while corpus striatum slices of rat brain were used by Schmidt et at[15] to demonstrate that MPTP may stimulate monoamine release from CNS tissue. Rat striatal synaptosomes have been used to show that the hydroxylated form of MPTP inhibits dihydropteridine reductase, a required cofactor for tyrosine hydroxylase[16]. Thus, in a neurochemical sense, the rat has provided much information about the presumed actions of MPTP, much of which may be extrapolated to other species.

The C57 black mouse appears to be even more suitable as a neurochemical model

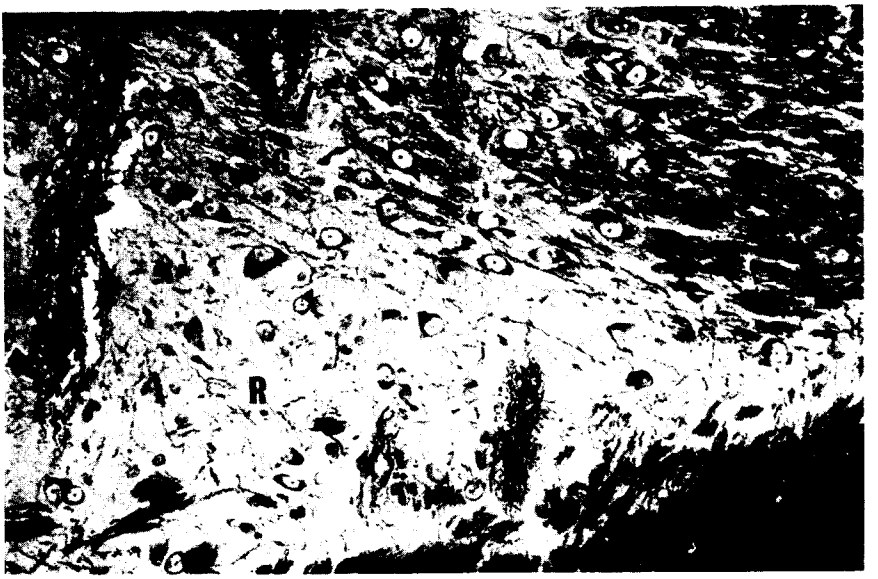

Figure 5. Substantia nigra of MPTP treated C57 black mouse (Kluver-Barrera stain, X 200) showing no loss or abnormality of neurons in compact (C) or reticular (R) zones.

since striatal dopamine levels in our study were reliably depressed to about 20% or less of control values by 4 injections of 30 mg/kg MPTP. These findings are in accord with those of others[17,18,19], although some controversy appears to exist as to whether actual pathological change is seen in the substantia nigra in the mouse after MPTP administration. Certainly in our study, using routine staining methods, no such change was seen, even after 10 injections of 30 mg/kg MPTP. Using Swiss Webster mice, Heikkila et al.[17] suggested that a depletion of neurons occurred in the pars compacta of MPTP treated mice, but no comment was made about other morphological changes. Fluorescence histochemistry does show reduction in monoamine fluorescence in the pars compacta of the substantia nigra (A9 region in the rat), whereas the dopamine cell bodies in the ventral tegmental area (A10 in the rat) seem to be unaffected[18,19].

Our observations suggest that there is a trend towards recovery of striatal dopamine levels with time after NMPTP administration. However, persistently depressed levels were seen up to 2 weeks after the last injection in our study and, by other workers, for up to 10 weeks[17,18,19]. While these findings suggest that permanent damage to dopamine neurons has occurred, the possibility exists that a long lasting dopamine depletion has occurred without actual toxic cellular destruction. Further studies with more specific cell counting techniques are required to resolve this issue. In the monkey model of Parkinsonism, however, clear pathological evidence exists that actual loss of nigral neurons occurs[5,6,7].

The mode of action of NMPTP is still not clearly established, but interesting

observations have been made. It appears that NMPTP is metabolized by MAO-B in mouse and monkey brain to the 1-methyl-4-phenylpiridinium species MPP^+, an ion impermeable to the blood brain barrier[20]. Furthermore MPP^+ appears to selectively accumulate in the substantia nigra, an area in humans and monkeys where neuromelanin is present. MPTP appears to have a high melanin affinity[21]. Since rat brain contains mainly MAO-A, this may in part explain the lack of toxicity in this animal, while in humans, mice and monkeys, abundant amounts of brain MAO-B exist, thus allowing toxic metabolites to be produced. It is unclear which, if any, of the MPTP metabolites is responsible for the observed neuronal damage in humans, mice and monkeys. Pargyline, a MAO-B inhibitor, blocks the formation of an unstable intermediate 1-methyl-4-phenyl-1-2,3-dihydropyridinium ion ($MPDP^+$), but not the conversion $MPDP^+$ to MPP^+ and MPTP, which suggests that the oxidation step MPTP to $MPDP^+$ is critical[22]. One postulate is that during the oxidation process high energy potentials stimulate increased dopamine turnover, thus causing release of excessive free radicals[23,24,25]. Under normal circumstances these radicals are scavenged by the endogenous enzyme systems of glutathione peroxidase, catalase and superoxide dismutase. However, under conditions of excessive free radical reduction these systems may be overloaded and neuronal damage then results from direct free radical action on lipid membranes[23,24].

Other actions of MPTP, some of which have already been outlined, cause pharmacological depletion of dopamine. Dopamine uptake into neuronal cells of the PC12 line is impaired[13], dopamine release from rat brain slices is stimulated[14], and tyrosine hydroxylase activity is reduced by way of inhibition of dihydropteridine reductase[15]. There is no evidence at this stage that any of these means of reducing neuronal dopamine is permanent in its consequences. A reasonable interpretation may be that these mechanisms contribute to the acute dopamine depletion in the mouse, but the actual neuronal damage is incurred by a separate mechanism, perhaps via excessive free radical production[23].

Since the discovery of the selectively neurotoxic effects of MPTP there has been much speculation about whether MPTP itself is responsible for true Parkinson's disease. It would appear unlikely that this is the case, although perhaps related molecules may be implicated. Studies of the distribution of related compounds, their toxicities, and their relationship to observed cases of Parkinson's disease need to be carried out.

Summary

The recent discovery that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes a syndrome of Parkinsonism in man and monkey has stimulated the search for a small animal model of Parkinsonism. In this study, MPTP was administered to a series of small animals and observations made on clinical and neurochemical changes. The clinical effects of MPTP in rabbits, guinea pigs, and rats were short lived, and no chronic Parkinsonian syndrome developed. The C57 black mouse, however, although also not showing clinical changes, proved to be an ideal neurochemical model in which to study the effects of MPTP since striatal dopamine levels were

reliably reduced to 13% of control values after 4 intraperitoneal injections of 30 mg/kg MPTP. Pathological study of the striatum and substantia nigra in the mouse model failed to show any alteration in neuronal morphology or numbers. Although the effect of MPTP on striatal dopamine lasted for up to 2 weeks after the last MPTP injection, the possibility exists that no neurotoxic effects occur and the observed dopamine depletion is pharmacological only.

Acknowledgement

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Normative Data for Somatosensory Evoked Potentials from Upper Limb Nerves in Middle-aged Subjects

*V.M. Synek**

Evoked potential techniques have become an integral part of neurophysiological assessment and have contributed substantially to the understanding and diagnosis of several neurological disorders[1,2,3,4]. In particular, short-latency somatosensory evoked potentials (SEPs) have assumed a secure position in the diagnosis of disorders of the brachial plexus, spinal nerve roots and the spinal cord itself[5,6,7,8,9,10]. While the use of these techniques may be necessary to gain significant diagnostic information and the investigations are quite easy to perform, there is a dearth of normative data in the literature, from middle-aged persons in particular, with which results in individual patients can be compared. It would be ideal if everyone using these techniques in the clinical field had established his or her own normative material, but this is in practice almost impossible. Only laboratories with a long experience in performing these tests can provide such reference data. Our Department has been involved in the acquisition of SEP data in normals and patients for ten years. So far, more than four thousand normal persons and patients have been investigated using a range of evoked-potential techniques. It is the purpose of this article to provide normative SEP data gained from stimulation of main upper limb nerves in normal middle aged persons, and to outline conditions where applications of SEPs may provide diagnostic information.

* From the Department of Clinical Neurophysiology, Auckland Hospital, Auckland, New Zealand. (With technical assistance from S.P. Russell, D.A. Munro, P.A. Hine and B.C. Reeves).

Methods

The median, ulnar and superficial branch of the radial nerve were stimulated separately at the wrist at a rate of 4.1 per second using 0.15 msec square wave pulses delivered through an isolation transformer and saline-soaked 3 mm diameter pads. The cathode was 2.5 cm proximal to the anode. Median and ulnar nerve fibres were stimulated at an intensity causing a mild twitch in the relevant muscles, and radial nerve fibre stimulation was adjusted to an intensity producing a strong tingling sensation. The stimuli were easily tolerated and no sedation was required. Recordings were performed in a quiet, electrically shielded room at a constant temperature. Subjects reclined on a couch and were asked to relax and reduce eye movements. Platinum alloy subdermal needle electrodes were attached 2 cm above the midpoint of the clavicle (Erb's point), to the skin overlying the seventh and second cervical vertebrae and over the contralateral scalp (2 cm posterior to the C3 and C4 areas defined in the 10 - 20 International System for EEG electrode placement). A mid-forehead electrode (^{Fp}z in the 10-20 International system) was used as the reference electrode for all derivations. Electrode impedance was kept below 5 k ohm sec. Four channels of activity were recorded simultaneously through high-impedance biologic amplifiers and a Tracor Northern TN 3000 was used as an averaging computer. Samples of 40 msec activity were collected after each stimulus presentation; 500 samples were averaged and then each run repeated twice to ensure reproducibility. EMG, EEG and cardiac activities were rejected automatically if their amplitude exceeded 50μV. The filter bandpass was 10 Hz to 3 kHz (— 3dB). Peak amplitudes at Erb's point and the skin overlying the cervical spinal cord were measured from the baseline as it presented and the amplitudes from the scalp were measured to the following positivity. In accordance with internationally accepted practice the negative peak potential from Erb's point is labelled as N9, potentials from the cervical spine as N13 and from the contralateral scalp response as N20. In most subjects an additional notch, usually designated as N11, was also recorded at the level of seventh cervical vertebrae.

The subjects were all paid volunteers, being employees of the hospital and University staff members. The total number was 23, comprising 7 males and 16 females. The age range was 36 - 62 years (mean age 47.4). None had a history of neck problems, neurological illness or significant trauma and none was taking any medication. The testing was reported by most subjects as painless, and each investigation took less than two hours.

Results

Satisfactory results were obtained in all 23 subjects. A normal recording of SEPs after stimulation of the median, ulnar and radial nerve in one subject is shown in Figure 1 (a), (b) and (c). The latencies of individual potentials were measured in m sec to their peaks. There was a small variability in the latencies of individual peaks at different recording places depending on the variation in length of the peripheral

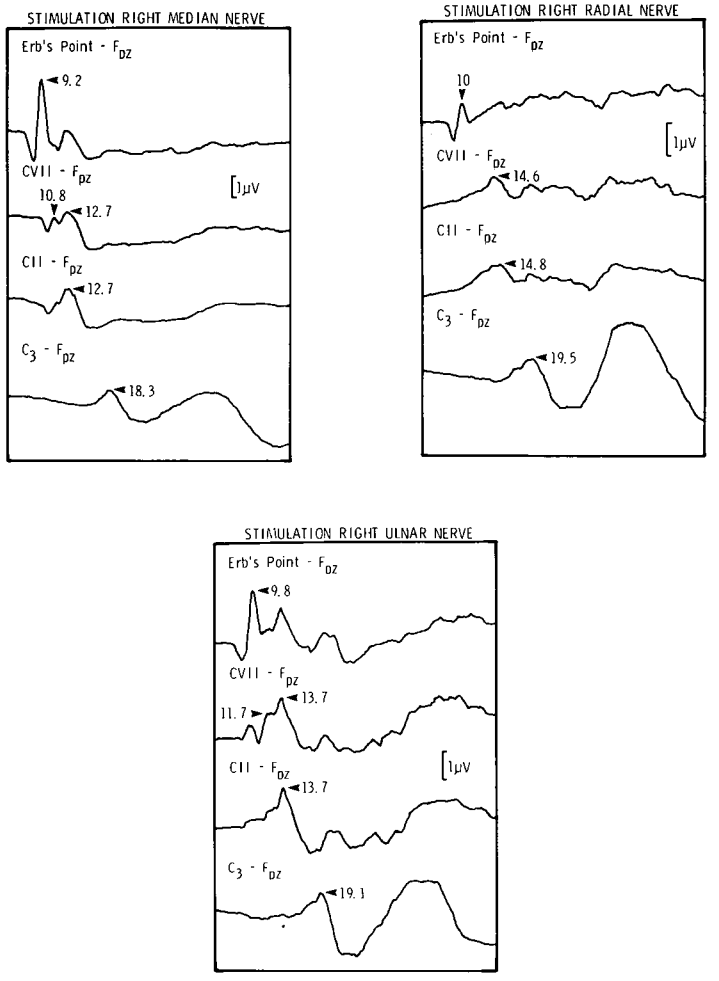

Figure 1 (a), (b) and (c). SEP results after stimulation of median (box a) ulnar (box b) and radial nerves (box c) are shown in this Figure. Individual peak latencies are indicated in m sec at four different levels: Erb's point, seventh and second cervical vertebrae and contralateral scalp. Amplitude is indicated in μV. (First SEP in (a) and (b), at the level of seventh cervical vertebrae shows N11; the second is N13).

nerves. Ulnar and radial nerve peak latencies were slightly longer than latencies of median nerve SEPs. Since publishing our last set of normative values[5] we have tried to improve our technical skills to achieve smaller standard deviations; the mean and standard deviation for right and left differences at individual recording levels has decreased. In our study there is no significant difference between the latency of the potential recordings from the skin overlying the seventh and the second cervical vertebrae, which is due to the use of a frontal electrode as a reference. The relatively long distance between the frontal and cervical electrodes minimises differences between latencies of potentials recorded at the neck. Peak latencies of individual potentials at Erb's point, the seventh and second cervical vertebrae and the contralateral scalp after stimulation of the median, ulnar and radial nerves are shown in Table 1 (a). The amplitude of SEPs varied, being greatest at Erb's point, of intermediate size at the cerebral level and smallest when recorded over the cervical cord. The amplitude of SEPs varied, between the three nerves according to their size. In all 23 subjects SEPs at all levels were clearly identifiable. Amplitudes of individual peaks as measured at different levels are indicated in Table 1 (b). In routine diagnostic work we often take note of transmission times between individual levels, as a useful measure of normality. The interpeak intervals are shown in Table 1 (c).

We consider a potential is abnormally delayed if its peak exceeds 3 S.D. from normal mean values. There is no unanimity in the literature regarding the significance of amplitude asymmetries. We regard potentials as attenuated if they are diminished more than 50% when compared with normal values and with values from the non-affected side. Potentials attenuated by 90% are regarded as very attenuated. The negative potential from Erb's point may be also seen at the cervical cord recording level. Cervical potentials may be seen both in the scalp and at Erb's point recording if mid-frontal reference, as in our material, is used. Reflected activity is usually much weaker and is time-locked to the potentials from which it is generated. In most normal recordings of upper limb SEPs from the level of seventh cervical vertebrae a small negative

Table 1a.

	Mean Peak Latencies in msec							
	Erb's point		C7		C2		C_3 C_4	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Median R	10	0.6	13.2	0.7	13.2	0.7	19.1	0.8
Median L	10	0.7	13.2	0.8	13.3	0.8	19.0	0.9
Ulnar R	10.6	0.8	14.1	1.1	14.2	1.0	19.7	1.1
Ulnar L	10.4	0.8	14.1	1.0	14.2	1.0	19.5	1.1
Radial R	11.1	0.7	15.2	1.2	15.3	1.2	20.6	0.9
Radial L	11.1	0.7	14.8	1.1	15.1	1.1	20.6	1.25
	Left/right difference							
	Erb's point		C7		C2		C_3 C_4	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Median	0.16	0.13	0.2	0.16	0.21	0.13	0.36	0.3
Ulnar	0.25	0.19	0.39	0.33	0.33	0.31	0.56	0.48
Radial	0.44	0.35	0.34	0.27	0.43	0.34	0.52	0.34

Table 1(b)

		Mean Amplitudes in microvolts							
		Erb's point		C7		C2		C_3 C_4	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Median	R	4.14	1.9	1.73	1.03	2.05	1.05	3.25	2.16
	L	4.34	2.1	1.6	1.1	1.97	1.1	2.9	2.26
Ulnar	R	1.97	1.15	1.42	0.72	1.38	0.71	1.88	1.25
	L	1.55	1.04	1.1	0.78	1.09	0.81	1.88	1.29
Radial	R	1.62	0.87	0.99	0.55	1.02	0.59	1.81	1.65
	L	1.31	0.99	1.0	0.76	0.92	0.55	1.69	1.52
		Left/right difference							
		Erb's point		C7		C2		C_3 C_4	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Median		1.5	1.31	0.68	0.68	0.73	0.87	0.94	0.73
Ulnar		0.79	0.6	0.66	0.52	0.54	0.46	0.5	0.52
Radial		1.03	0.73	0.77	0.58	0.61	0.53	0.53	0.46

Table 1(c) Interpeak latencies in msec

	Right			Left		
	Erb-C7	Erb-C2	Erb-C3	Erb-C7	Erb-C2	Erb-C4
Median nerve						
Mean	3.2	3.3	9.2	3.3	3.3	9.1
S.D.	(0.3)	(0.4)	(0.6)	(0.4)	(0.4)	(0.6)
Ulnar nerve						
Mean	3.7	3.9	9.4	3.8	3.9	9.2
S.D.	(0.6)	(0.4)	(0.6)	(0.6)	(0.6)	(0.8)
Radial nerve						
Mean	4.2	4.3	9.5	4.0	4.1	9.6
S.D.	(0.8)	(0.8)	(0.6)	(0.9)	(0.8)	(1.0)

Table 1 (a), (b) and (c). SEP results from 23 normal subjects. In box (a), at the top, peak latencies are indicated in m sec including S.D. at all four levels. In the middle part of Table (b), amplitudes of SEPs are indicated in μV at individual levels (including S.D.). In the bottom part of Table (c), interpeak intervals between Erb's point and cervical cord and contralateral scalp are indicated in m sec (including S.D.)

peak named N11 is usually seen, as is shown in Figure 1. This peak is believed to be generated from the dorsal columns of the spinal cord[3]. Stimulation of sensory fibres to cervical segments C5 and C6 in isolation is possible by activating the lateral cutaneous nerve of the forearm, which is the final branch of musculocutaneous nerve at the wrist. This technique is more difficult as identification of appropriate fibre is necessary with avoidance of stimulation of median nerve fibres, which lie close by. Results of SEPs following musculocutaneous nerve stimulation in normal persons have been published[7].

Discussion

Short-latency somatosensory evoked potentials recorded after electrical stimulation of peripheral nerve fibres represent the activity of afferent volleys in large fast conducting fibres chiefly mediating impulses from receptors for light touch, proprioception and pinprick[3,4,11]. Even if electrically evoked SEPs represent responses after activation of only part of the sensory system they are still most useful as easily obtainable responses of adequate amplitude are generated by the method. Techniques for the stimulation of temperature, pain and other receptor fibres have been described[12], but have never gained wide popularity. SEPs from electrical stimulation of peripheral receptors give relevant diagnostic information in a range of conditions such as coma, postinfectious polyneuropathies, demyelinating lesions, leucodystrophies and Huntington's disease[13,14,15,16] and have provided information which could result in the revision of traditional concepts of certain disorders such as motor neuron disease[17]. SEP techniques have proved essential in the assessment of diffuse brain lesions[18]. They have also been useful in the detection of developing intrinsic spinal cord lesions[6,9]. Perhaps the most important application of SEPs is in the differential diagnosis of proximal lesions of the peripheral nervous system otherwise not accessible to neurophysiological testing. By studying selected combinations of neural structures traversing the brachial plexus, information regarding the site of involvement can be obtained, particularly in traction injuries, metastatic disease and the thoracic outlet syndrome[4,5,7,8,10]. With spondylopathic root lesions these techniques help in selecting patients who could benefit from myelography or CT scanning[19]. Testing of median nerve SEPs alone can be informative in generalised disorders such as polyneuropathies, but yields relatively little diagnostic information when focal lesions involve limited areas of the brachial plexus.

Summary

Techniques for obtaining somatosensory evoked potentials after stimulation of radial, median and ulnar nerves are described. Results from a group of 23 healthy

middle-aged persons are presented in detail to provide normal value for comparison with results gained from patients. Indications of when these techniques could be useful are summarised.

Acknowledgements

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Abstract

Partial Cytochrome Oxidase Deficiency in Chronic External Ophthalmoplegia (CEO)

*E. Byrne, I. Trounce and X. Dennett**

Biochemical and histochemical studies were carried out in two patients with chronic progressive external ophthalmoplegia. Both patients had associated proximal myopathy and one patient had a pigmentary retinopathy. Histological findings were similar in both cases with prominent ragged red fibres (Gomori trichrome stain) and partial deficiency of cytochrome oxidase staining with a negative reaction in many ragged red and occasional morphologically normal fibres. Cytochrome oxidase levels were greatly depressed in muscle homogenate in both cases. A cytochrome oxidation/reduction spectrum was recorded in one case and revealed a severe deficiency of cytochrome aa_3. Polarographic studies with isolated skeletal muscle mitochondria revealed depressed state 3 respiration rates with flavoprotein and NAD-linked substrates. Histochemical data and biochemical investigation using three different approaches therefore confirm a partial cytochrome oxidase deficiency in some patients with CEO. It is not established whether cytochrome oxidase deficiency is central to disease pathogenesis or is an epiphenomenon in mitochondrial degeneration from another cause.

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Abstract

The Neurological Complications of Bone Marrow Transplantation

B.J. Brew, P. Darveniza, K. Atkinson and J. Biggs

Bone marrow transplantation is becoming an increasingly common form of treatment for haematological malignancies. Patients are subjected to the potential neurological complications of infection and drug side effects. Cyclosporin A is one of the major immunosuppressants and is being used more frequently in transplantation and autoimmune diseases.

This report reviews the neurological complications of bone marrow transplantation over the last ten years and focuses on cyclosporin neurotoxicity. Complications occurred in 25%. Infection was rare and occurred only in the setting of septicaemia. Cerebral haemorrhage was equally rare despite prolonged thrombocytopaenia. By far the most frequent complication was related to the immunosuppressant cyclosporin. Tremor, ataxia, confusion and a spinal cord syndrome were the major manifestations. The neurological syndrome was reversible on stopping or reducing the dose of the drug. It has been claimed that cyclosporin neurotoxicity is related to magnesium levels; this study could find no relationship between toxicity and magnesium levels.

Abstract

Oxygen Electrode Studies with Human Skeletal Muscle Mitochondria *in vitro* — a Re-appraisal

*E. Byrne and I. Trounce**

Polarographic measurement of respiration rates in skeletal muscle mitochondria is a valuable research tool in human disease but data in normal muscle are sparse and conflicting with a ten-fold variation in reported respiration rates adjusted for temperature. In this study, mitochondria were isolated from 18 normal muscle biopsies

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obtained at the time of orthopaedic surgery and state 3 respiration rates, ADP/oxygen ratios and respiratory control ratios were measured with glutamate, pyruvate/malate and succinate as substrates. Highly reproducible respiration rates with adequate RCR and ADP/O ratios were obtained in 13 biopsies. Mean state 3 rates of 280 na0/mg mitochondrial protein/min with glutamate, 214 na0/mg mitochondrial protein/min with pyruvate and 353 na0/mg mitochondrial protein/min with succinate were higher than in earlier reports and evidence is presented suggesting that lower rates in other reports reflect mitochondrial damage during isolation. Data suggesting selective uncoupling with glycerophosphate as a substrate or a partial site I deficiency were found in some experiments suggesting that studies attributing significance to similar findings in diseased muscle must be interpreted with caution. Slow respiration rates with loose coupling with all substrates tested indicated a damaged mitochondrial pellet. Many earlier papers in this area are probably reporting artefactual results and the need for cautious appraisal of patient data and for each laboratory to establish its own control range is stressed.

Abstract

Progressive Myoclonic Epilepsy

R.H. Rischbieth, P.C. Blumbergs and M.R. Newton

The clinical findings in six members from two generations of one family are briefly described, with autopsy findings in two brothers, which showed unusual pathological features.

Abstract

Addison-Schilder's Disease Revisited: Expression of a Long Chain Fatty Acid Storage Disorder within a Kinship

*K.J. Abbott, G.N. Thompson, A. Poulos, A.C. Pollard and D.M. Howard**

X-linked adrenomyeloneuropathy (AMN) and childhood adrenoleukodystrophy (ALD) are both associated with accumulation of long-chain fatty acids (LCFA's) in

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plasma, cultured skin fibroblasts and various tissues. Isolated reports have described their co-existence within kinships.

Three males and one carrier female are described. An 8 year old boy presented with progressive dementia, ataxia, bipyramidal signs and visual loss, suggesting ALD. LCFA's (C_{26}/C_{22} and C_{24}/C_{22} ratios) were elevated in plasma and skin fibroblasts; no evidence of adrenal insufficiency, or brain demyelination on CT scan, was found. His mother had mild leg spasticity, and LCFA values consistent with heterozygosity. The maternal uncle (aged 33) complained of recurrent gynaecomastia and recent gait disorder; he had had spastic paraparesis, recent skin pigmentation, and subtotal alopecia from early childhood. His LCFA's were elevated; other studies indicating primary adrenal insufficiency, hypogonadism and peripheral neuropathy. A maternal cousin had presented, aged 12 years, with melanoderma and adrenal failure. Aged 27, he was reported to be neurologically normal and had fathered two children. Results of investigation will be discussed.

AMN and ALD are phenotypic variants of a storage disorder, probably resulting from deficient enzymatic degradation of LCFA's. Males may present with childhood dementia, spastic paraparesis, or endocrine dysfunction; carrier females may have neurologic signs. A connatal form results in neonatal seizures and rapid deterioration. LCFA studies enable carrier detection and prenatal diagnosis.

Abstract

Intramedullary Spinal Cord Metastases: Clinical and Pathological Findings in Nine Cases

*J.W. Dunne, R. Pamphlett and C. Harper**

The clinical and pathological findings in nine cases of intramedullary spinal cord metastases are reported and the literature is reviewed. The diverse clinical picture and frequent diagnostic difficulties are illustrated. Intramedullary spinal cord tumours accounted for at least 3 to 4 percent of metastases involving the spinal cord, yet the diagnosis was rarely made during life. Symptoms might be present for many months before presentation, and few clinical signs might be present despite distortion and destruction of much of the spinal cord by tumour. No neurological symptoms or signs clearly differentiated intramedullary metastases from the more common extradural deposits and the many other causes of myelopathy. Transient clinical improvement might last several months. Half of the cases presented with spinal cord symptoms prior to the diagnosis of the primary neoplasm, of which there might be no clinical

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evidence and the extent of metastatic disease might remain limited. Myelography (± CT scanning) constituted the most important diagnostic procedure, but was normal in half the cases, and incorrectly suggested extradural compression or vascular malformation in others. Usually no radiological or autopsy evidence of vertebral involvement was present. Intramedullary spinal cord metastases were more common than is generally recognized, and the diagnosis must be considered, particularly when myelography is normal. Better imaging techniques of the spinal cord, such as high resolution CT scanning, may be helpful in the early diagnosis and treatment of this currently lethal condition.

Abstract

The Value of Metrizamide Myelography and Delayed CT Scan in the Diagnosis of Syringomyelia

*P.C. Gates, H.J.M. Barnett and A.J. Fox**

A retrospective study of 144 patients undergoing investigation for suspected syringomyelia revealed 32 with proven syringomyelia and 15 with an alternative proven diagnosis. In this group of patients a change in the calibre of the spinal cord (''cord collapse'') on metrizamide myelography had a sensitivity of 38% and a specificity of 87%. Central cord enchancement visualized on delayed CT scan had a sensitivity and specificity of 91% and 87% respectively.

Abstract

The Changing Presentation of Syringomyelia

B.J. Brew, D.J. O'Sullivan, W.J. Burke, K. Bleasel and T. Connelley‡

Syringomyelia is a well recognised disease with classical clinical manifestations. Signs such as wasting of the arms with areflexia, dissociated sensory loss and spastic

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paraparesis are well accepted as evidence of a syrinx. Up until recently the only definitive means of diagnosis was by inspection of the cord at operation and sometimes biopsy. The possibility of a tumour was always of major concern. Treatment with posterior fossa decompression has given variable results. Long term follow-up is limited. In the last few years radiological demonstration of the syrinx with post-myelography CT scanning has helped to confirm the disease. This present report describes 15 patients with syringomyelia. The clinical features of patients in whom the diagnosis was made on CT are contrasted with those having more classical signs. It is observed that early forms of the disease may present with signs that are far from classical. The influence of surgical procedures on the disease is discussed.

It is suggested that post-myelography CT scanning be employed in any patient with a myelopathy or bulbar signs in whom the myelogram is non-diagnostic. With the use of such techniques earlier atypical forms of the disease are becoming apparent. Better surgical results may eventuate as earlier diagnosis and treatment become possible.

Abstract

Gait Analysis in Parkinson's Disease

*Chong Piang Ngok, G. Devathasan, Lee Eng Hin, J. Goh and K. Bose**

The gaits of 10 patients with Parkinson's disease were analysed. A computer based opto-electronic gait analysis system trade-named "VICON" was used. Three dimensional assessment of the patient's movements was provided by a 5 camera system. Foot-floor reaction forces were measured by a Kistler piezo-electric force plate. Dynamic electromyography was measured by an 8 channel system using either surface or fine-wire electrodes. Only patients with stages III and IV (Hoehn & Yahr's scale) were included. The walking-cycle time was prolonged. The stance/swing phase ratio was increased beyond the usual 6:4 ratio indicating postural instability. This was also reflected in the prolonged double support time. Stride and step lengths were smaller. Walking speed and cadence were also affected. The static joint angles showed abnormal flexion of the hips, knees and ankles and the degree of flexion generally corresponded to the severity of the disease. A state of "dynamic flexion deformity" was also noted during walking. Dynamic electromyography of the quadriceps,

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hamstrings, tibialis anterior and gastrocnemius showed that the muscles did not contract in phase with each other. The information provided by gait analysis has introduced more objectivity in the assessment of Parkinson's disease and may provide a baseline for therapeutic and progress assessment.

Abstract

Predicting Optic Nerve Damage from Raised Intracranial Pressure using the Pattern Visual-Evoked Response (PVER).

*K.J. Abbott, P.F. Weston and J.I. Manson**

Clinical testing may fail to identify those patients with papilloedema at serious risk of visual deterioration. Subclinical optic nerve dysfunction, detected by the PVER, has seldom been reported in this context. 30 children (age range 2.7 - 15.5 years) presenting with papilloedema from raised ICP had monocular PVER studies at diagnosis, most having follow-up tests. None had lesions causing infiltration or tumour-compression of visual pathways. Initial studies were normal in 25 (83%), all of whom maintained their normal pretreatment vision; one child with PVER latencies at the upper limit of normal had subclinical optic neuropathy on later testing. 5 patients (ages 7-13.5 years) had abnormal PVER's, without visual loss, in one or both eyes. Optic nerve function recovered after correction of raised ICP in 3 of 5 cases, one case having transient monocular visual deterioration (initial P1 latency 121 msec, (N < 116 msec). Two patients, with significant PVER latency delays at presentation developed secondary optic atrophy despite correction of ICP.

Papilloedema due to raised ICP alone seldom affects the PVER. Significant PVER latency delay implies a high risk of secondary optic neuropathy, despite normal clinical vision. PVER testing may be useful in certain preoperative cases with raised ICP, and in patients with pseudotumour cerebri.

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Abstract

The Effect of Reflex Path Length on Clonus Frequency in Spastic Muscles

*R. Iansek**

The mechanism of clonus is still poorly understood and controversial. The two rival theories concern either a central spinal pacemaker or a peripheral self re-excitation circuit perpetuated by the constant stretch applied to the contracting muscle on a background of high gain in the motor neurone-spindle feed-back loop. The latter hypothesis was tested by comparing the reflex path length with the clonus frequency in different muscles in the same patient. It was found that clonus frequency varied inversely with reflex path length ($r = 0.84$, $p < 0.001$). The findings suggest that clonus is generated by a peripheral mechanism of self re-excitation rather than a central spinal pacemaker.

Abstract

Sleep Hypoxaemia in Chronic Neuromuscular Disease

*L. Davies, P.T.P. Bye, E. Ellis, G.M. Halmagyi and C.E. Sullivan***

We examined arterial oxygen saturation (ear oximeter) and respiratory movements during all-night sleep monitoring in 12 patients with chronic neuromuscular disease and impaired respiratory muscle function, to compare the influence of the two major sleep states [non-rapid-eye-movement (NREM) sleep, and rapid-eye-movement (REM) sleep] on breathing and oxygenation. The patients had a variety of illnesses (muscular dystrophy 5, post-polio cervical weakness 2, motoneurone disease 3, spinal muscular atrophy 1, post-encephalitic neuromuscular weakness 1), and displayed a range of respiratory insufficiency while awake. The mean daytime awake respiratory function measurements were: PaO_2 76 $\pm$ 16 mmHg, $PaCO_2$ 52 $\pm$ 12 mmHg, vital capacity 48 $\pm$ 19% of predicted. All patients had adequate awake arterial oxyhaemoglobin saturation (SaO_2%), mean 93 $\pm$ 6%. Ten patients had lower saturations during NREM sleep, with major falls in REM sleep (mean 53%; range less than 20 to 85%). In general the occurrence of REM sleep desaturation correlated

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with the daytime awake $PaCO_2$. Those with elevated $PaCO_2$ ($>$ 45) had major falls in saturation in REM sleep ($>$ 10% fall). However, two patients with normal daytime $PaCO_2$ levels also had major falls during REM sleep. In these patients the primary mechanism appeared to involve upper airway obstruction, whereas in the other patients the REM sleep desaturation appeared to result from insufficient respiratory pump muscle activity. Treatment of these patients included cuirass ventilation, positive airway pressure through a mouth seal, nose mask, or tracheostomy. Sleep hypoxaemia may play a key role in the outcome of patients with chronic neuromuscular disease.

Abstract

Intracranial Hypertension associated with Acute Posterior Multifocal Placoid Pigment Epitheliopathy

*P.A. Kempster, R.A. McDonald and R.D. Rollinson**

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) is a choroidal vasculopathy which may be associated with neurological complications. Although recognised by ophthalmologists, the entity has seldom been reported in neurological literature.

This case report concerns a 30 year old male presenting with rapidly developing bilateral visual impairment. The fundal appearances and fluorescein angiography were typical of APMPPE. CSF examination revealed lymphocytosis and symptomatic intracranial hypertension was suggested by CSF manometry, mild optic disc swelling and headache promptly relieved by lumbar puncture. Although vision remained poor, headache was controlled by corticosteroid medication. This condition has been reported in association with CSF pleocytosis and cerebral vasculitis, but not previously documented in combination with intracranial hypertension.

* Melbourne

Abstract

The Role of the Occipital Nerve in Headache

*M. Anthony**

Disturbances in the upper cervical spine have been known to cause pain both in the occipital and fronto-temporal areas of the head. The mechanism suggested is irritation of nerves in that area, and in particular of the greater occipital nerve (GON). To test this hypothesis, an injection of methylprednisolone acetate (Depo-Medrol) was given into the region of the GON ipsilateral to the headache in patients suffering from: (a) a bout of cluster headaches, (b) frequent unilateral migraine attacks, and (c) pain of occipital neuralgia. Relief was experienced by: (a) 18 of the 20 patients with cluster headache for 5 to 73 days, (b) 14 of the 15 patients with migraine for 13 to 66 days, and (c) 9 of the 10 patients with occipital neuralgia for 28 to 140 days.

It is generally accepted that the central connections between the trigeminal nerve and the upper three cervical roots (the components of the GON) form the pain centre for the head. If attacks of headache such as those described, are due to paroxysmal activity of this centre as a result of impulses received from its many connections, it appears that impulses arriving along the GON are the most significant and therefore their interruption leads to pain relief more regularly than interruption of other neural pathways employed so far.

Abstract

A Case of Vogt-Koyanagi-Harada Disease Successfully Treated with Cyclosporin

*B.J. Brew, P. Benecke, W.J. Burke, T. Playfair and R. Penny***

Vogt-Koyanagi-Harada disease is a rare entity primarily affecting the uvea, meninges and skin. It is currently felt to be related to a defect in immunological surveillance of melanocyte surface antigens. The disease is manifested clinically by headache, dysacousis, vertigo, impaired vision and vitiligo. Evidence suggests that steroids decrease the risk of permanent blindness. However, there is a propensity for recurrence.

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This report describes a typical case of Vogt-Koyanagi-Harada disease that failed to respond to steroids and cytotoxic agents. With the introduction of cyclosporin, the blindness and the neurological complications of vertigo and dysacousis promptly resolved. There have been no recurrences. This is the second report in the literature of the use of cyclosporin in this disease. It is suggested that consideration be given to the use of cyclosporin in this disabling disease.

Abstract

Familial Urticaria, Headaches, Vascular Disease, Deafness and Neuropathy

*D.B. Williams, G.K. Stewart and J.G. McLeod**

We describe a family which appears to present a previously undescribed syndrome. The inheritance pattern is consistent with autosomal dominant transmission, with 6 affected members in 4 generations.

The major features of the syndrome include an episodic urticarial rash, frequent severe vascular headaches, arthralgia and non-deforming arthropathy, and peripheral vascular disease. The specific neurological features are optic 'nerve pallor' with abnormal retinal vasculature, pupillary paresis, sensorineural deafness, peripheral neuropathy and abnormal CSF. Saddleback nose and flexion deformity of the 5th finger appear to be associated skeletal abnormalities.

Abstract

A Case of Brainstem Abscess due to Listeria monocytogenes demonstrated by Delayed CT Scanning

*B.J. Brew and G. Coffey***

Listeria monocytogenes is a rare cause of infection occurring primarily in the immunocompromised host. The clinical spectrum of this disease is wide-ranging, though neurological involvement is not at all uncommon. Such involvement may take the form of meningitis, encephalitis with micro-abscesses or cerebral abscess. To date only 6 cases of brain abscess due to this organism have been reported.

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Untreated, the disease carries a very high mortality, thereby making early diagnosis extremely important. To date the only reliable method of diagnosis is the demonstration of the organism in blood cultures. However, it usually takes several days to grow the organism and selective media may be required. This report describes the clinical features of an immunosuppressed renal-transplant patient who developed a brainstem abscess due to Listeria monocytogenes. The clinical picture was that of a midbrain lesion with a positive CT scan being obtained following the use of high dose contrast and delayed scanning. The patient improved on a regimen of ampicillin and gentamicin. Though a deficit remained, there has been no deterioration in the past 12 months.

Thus infection with Listeria monocytogenes should be considered in immunocompromised patients who develop a neurological illness so that appropriate microbiological techniques and early treatment can be instituted. Delayed CT scanning is a valuable adjunct in this context.

Abstract

A case of Granulomatous Angiitis of the Nervous System

*B. Brew, R. Garrick, S. Greenwell and W. Evans**

Granulomatous angiitis of the nervous system is a rare disease characterised by a vasculitis which is restricted to the central nervous system. There is some overlap with temporal arteritis and in a number of patients it has occurred in the setting of lymphoma. In most cases it is fatal. It is manifested clinically by headache, altered mental state and focal neurological deficits. Diagnosis may be made by biopsy of brain or leptomeninges. Several cases have responded to combined corticosteroid and cytotoxic treatment. This report details the clinical and pathological features of a case. To date there have been 22 cases that have come to autopsy and have shown no evidence of systemic vasculitis. In the present case involvement of the leptomeninges was noted.

It is suggested that in patients with clinical features consistent with this disease, consideration be given to leptomeningeal biopsy in an attempt at antemortem diagnosis and treatment.

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Abstract

Specific Skeletal Muscle cAMP-Dependent Phosphoproteins in Fast and Slow Muscle Fibres: Do They Represent a Form of Short-Term Memory in Muscle?

*G.A. Nicholson, J.G. McLeod and L.U. Luey**

Phosphoproteins play an important role in intercellular communication and act as cellular third messengers, responding to second messengers (cAMP, cGMP, calcium-calmodulin or phospholipids) by modulating the action of other proteins (protein kinases and phosphatases, proteins involved in DNA expression, cytoskeletal and contractile proteins, synaptic vesicle proteins, neurotransmitter receptors and ion channels). Many phosphoproteins are found in neuromuscular tissues. Their distribution varies in different brain regions and may be related to the control of neurotransmitter systems. Phosphoproteins have been proposed as a molecular mechanism for short term memory because of their short duration of action (seconds to minutes). In order to examine protein phosphorylation in different skeletal muscles, phosphoproteins in rat homogenates were separated by one and two dimensional polyacrylamide gel-electrophoresis after ^{32}P-ATP phosphorylation by endogenous protein kinases $\pm$ 20μM cAMP. Results were quantitated by auto-radiography of the dried gels. Many phosphoproteins were demonstrated. The phosphoprotein profile was quite distinct from those of heart or brain homogenates. The profiles of fast muscle (extensor digitorum longus) and slow muscle (soleus) were distinct with specific cAMP dependent phosphoproteins in each muscle.

Adrenalin stimulation of whole fibres and cAMP addition to skinned muscle preparations have been reported to produce short-term alterations of the contraction characteristics of slow-twitch fibres towards those of fast-twitch fibres. This mechanism may account for our finding of specific cAMP dependent phosphoproteins in fast and slow fibres. Our results may therefore represent a muscle analogue of the molecular events proposed for short-term memory.

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Abstract

Taste-Induced Facial Flushing limited to the Site of Post-Herpetic Scars

G.M. Boyce, J.W. Lance†, and P.D. Drummond†*

A 10 year old girl suffered right facial herpes zoster at the age of 6 years with residual patchy anaesthetic scars in the distribution of the third division of the trigeminal nerve. Since then, the taste of certain foods has produced flushing in the scarred areas after a latent period of seconds, lasting for 10-15 minutes. Thermography demonstrated an increase in temperature of 1-2°C limited to the areas of post-herpetic scarring, quite unlike the diffuse flush seen after thermocoagulation of the Gasserian ganglion or at the height of cluster headache. Flushing was not abolished by cocainization of the sphenopalatine ganglion. In view of the discrete nature of the flush, it is necessary to postulate an antidromic discharge of a vasodilator substance from the damaged trigeminal terminals in the anaesthetic areas. Taste fibres traverse the 7th and 9th cranial nerves to enter the tractus and nucleus solitarius which lie in apposition to the descending spinal tract of the trigeminal nerve. It is possible that ephaptic transmission takes place in this region, causing antidromic discharge in the trigeminal nerve which is known to contain serotonin and substance P, both with a capillary dilator effect. No similar example has been found in the medical literature.

Abstract

Hypoglossal-Facial Nerve Anastomosis: a Clinical and Electrophysiological Follow-up.

*R. Iansek, M.J.G. Harrison and J. Andrew***

Eight patients with acoustic neuroma and 5 patients with hemifacial spasm, who had undergone hypoglossal-facial nerve anastomosis 1-14 years previously, were reviewed clinically and electrophysiologically with an electrically elicited blink reflex. Functional recovery from the anastomosis, as judged on a scale of good, fair and poor, was fair to poor. Electrically the blink reflex was present in 8 patients, suggesting facial nerve re-innervation of the facial musculature. This feature was confirmed by the mild recurrence of hemifacial spasm in 4 patients. It was concluded

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that alternate operations should be performed for the treatment of hemifacial spasm because of the high recurrence rate and because of the unsatisfactory functional result of hypoglossal-facial nerve anastomosis. It was also concluded that alternate operations should be performed for facial palsy following removal of acoustic neuroma and that the finding of a blink reflex in some of these patients, despite the previous denervation, suggests an autogenous nerve graft as a possible procedure.

Abstract

Nutritional Amblyopia in a Patient with Crohn's Disease

*R. Iansek and C.J. Edge**

Bilateral visual failure associated with centro-caecal scotoma is a rare condition in which the aetiology is often unclear. The two hypotheses are that it is either due to the toxin cyanide, normally derived from tobacco smoke, or is due to nutritional deficiency of B group vitamins. The establishment of one cause to the exclusion of the other has yet to be documented in a given patient with this condition. We present a patient who smoked and who manifested such a syndrome in addition to night blindness secondary to a short bowel syndrome following surgery for Crohn's disease. The night blindness responded to replacement of vitamin A and the visual failure responded to replacement of vitamin B complex. Normal cyanide levels in this patient, in addition to unaltered diet, established vitamin B lack as the causative factor in this patient's syndrome.

Abstract

A Case of Optic Neuritis Secondary to Mycoplasma pneumoniae Infection

*B.J. Brew, R. Garrick and M. Steiner***

Mycoplasma pneumoniae is a well-recognised human pathogen. The spectrum of clinical manifestations is wide. The neurological complications include encephalitis, meningitis, acute psychosis, acute cerebellar ataxia, cranial nerve palsies, transverse myelitis, and a Guillain-Barré-like illness. There have been three reports of optic

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neuritis as complications but these have been in patients with other neurological involvement. The pathogenesis of the neurological complications is conjectural and includes direct invasion, superadded infection, auto-immune and toxic mechanisms.

This report describes the clinical features of a patient with optic neuritis as the only neurological complication of Mycoplasma pneumoniae infection of the lung. The results of serial visual-evoked potentials are discussed in relation to a presumed pathogenetic mechanism for the development of optic neuritis.

It is suggested that all cases of optic neuritis be checked for evidence of recent mycoplasma infection. This information will be helpful in defining the long term prognosis with respect to multiple sclerosis.

Abstract

Optic Nerve Involvement in Graves' Ophthalmopathy: a Case Report and Review

*J.W. Dunne and R.H. Edis**

A case of Graves' optic neuropathy is described, illustrating the clinical features, diagnostic difficulties and management. The literature is reviewed. Optic neuropathy in Graves' disease is an uncommon, but potentially treatable cause of disabling visual loss. Optic nerve damage is probably secondary to compression by swollen extraocular muscles at the apex of the orbit. The visual loss is usually bilateral and insidiously progressive, although accelerated visual loss, fluctuations in vision and features mimicking orbital cellulitis may occur. Ocular congestive symptoms and proptosis have no direct relationship to the severity of visual loss. Early diagnosis is facilitated by orbital CT scanning. Oral corticosteroids and radiotherapy, alone or in combination, are the primary modalities of medical treatment. Surgical decompression of the orbit can be used where medical approaches have failed.

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Abstract

An Analysis of the Decision-Making Process in the Management of Metastatic Spinal Cord Compression

*R. Iansek, M.J.G. Harrison and J.I. Balla**

The management of spinal epidural metastases is still controversial. Decision tree analysis was used to compare the treatment options of radiotherapy and laminectomy for the ambulant patient who presents with a painful epidural deposit and who has neurological evidence of spinal cord compression. The analysis balances the relative benefits of each treatment against the risks, and takes into consideration such factors as prevention of disease progression, pain relief, deterioration despite treatment and surgical morbidity and mortality. From probability estimates which were derived from the literature and from the estimates of the attractiveness of each outcome, as assessed by a neurologist, a quantitative assessment of each treatment option was calculated. The finding was that radiotherapy is the preferred first line treatment option for prevention of paraplegia and for pain relief.

Abstract

Alcohol-related Myelopathy

*B.J. Brew, P. Darveniza, D.J. O'Sullivan and R. Garrick***

The presence of pyramidal signs in alcoholics has been appreciated by clinicians for years. Both transient and permanent deficits have been noted. The aetiology of such dysfunction has been suggested to be related to central pontine myelinolysis or to the effect of decompensated liver disease.

This report describes the clinical features of 5 alcoholic patients with either a spastic paraparesis or quadriparesis. All patients were investigated, and 3 had myelography. No cause could be found in any of the patients. However, it was noted that following hospital admission and the cessation of alcohol intake the signs improved in 3 patients and remained static in 2. None had evidence of decompensated liver disease or central pontine myelinolysis. Though none of these patients has come to post mortem examination, it is postulated that alcohol or some closely associated factor was responsible. Full pathological examination especially of the spinal cord is needed to define the disease adequately.

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Abstract

Evoked Potentials in Cerebrovascular Disease

*G.A. Donnan, J.L. Borghesi and P.F. Bladin**

In spite of great advances in clinical and radiological diagnosis of strokes early delineation of the site and extent of cerebral infarction remains difficult. We have examined the possibility that evoked potentials [somatosensory evoked potentials (SSEPs), and brainstem auditory evoked potentials (BAERs)] may reflect physiological change earlier than CT change and therefore facilitate early stroke diagnosis. The correlation between changes in waveform morphology and late CT findings was also studied to determine site or origin of evoked potential generators.

Thirty-three patients admitted into the Stroke Unit were entered into the study. Wherever possible, SSEP and or BAER studies were performed prior to the late CT scan. Early CT scans (non-contrast) were performed usually more than 5 days post-event and late CT scan with contrast more than 7 days post-event to delineate the complete area of tissue involvement. A correlation of late CT findings with evoked potentials revealed the following. Of 10 cases of cortical and cortico-subcortical infarction (thalamus spared) on CT, unilaterally recorded N20, P25 and P45 SSEP wave forms were absent in all cases. 9 cases with capsular infarction exhibited absence of the P16, N20 complex with preservation of P25, while 2 further cases had complete absence of P16, N20 and P25. 2 cases of thalamic haemorrhagic infarct showed absence of the P16-N20 complex. 6 patients with pontine infarcts had normal SSEPs but components IV and V of the BAER were suppressed. 4 patients had normal late CT scans and showed normal SSEP and BAER morphology. 17 cases overall showed elecrophysiological change before CT change.

A study of evoked potentials in stroke disease may complement clinical examination in early localization of pathology.

Abstract

Inobvious Stroke: a Cause of Organic Mental Disorders — Acute and Delayed

*J.W. Dunne and P.J. Leedman***

The potential for stroke to manifest with the spectrum of acute and chronic organic mental disorders is illustrated. We describe 16 patients, all with focal cerebrovascular lesions, mostly right-sided, who presented either with delirium, an organic

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delusional state, the acute onset of dementia, or mania, mimicking psychiatric illness. None had a previous history of cognitive impairment, psychiatric disease, drug abuse or alcohol excess. Neuro-logical signs were inobvious, or mild and transient, although most had perceptual impairment or sensory inattention. The behavioural disturbance had a close temporal relationship to epilepsy in 3 patients. Post-mortem examinations in 3 patients showed no evidence of multiple lesions, Alzheimer's disease or metabolic encephalopathies.

The possible causative factors are discussed and the evidence for asymmetrical cerebral representation of emotion and for a relationship with epilepsy is reviewed. Careful neurological assessment and CT scan are indicated in all patients with organic brain syndromes where the cause is not apparent. Anti-epileptic therapy may be appropriate in some cases.

Abstract

Cerebellar Haemorrhage: Diagnosis and Treatment: a review of 50 cases

*J.W. Dunne and T.M.H. Chakera**

A retrospective study of 50 medically and surgically treated cases of intracerebellar haemorrhage is described. The diagnosis was established either by CT scan or at post-mortem examination. The study was undertaken to re-evaluate the features of clinical presentation, the reliability of clinical evaluation, and to define more clearly the natural history of the condition.

Although the clinical picture of cerebellar haemorrhage has previously been well defined, there is great disparity between the reported frequencies of presenting symptoms and signs. Some series suggest the diagnosis can be made on clinical grounds alone. Most observations have been made before the advent of CT scanning, when the diagnosis was confirmed at surgery or by post-mortem examination, probably excluding many patients with a benign course.

The study confirms the wide clinical spectrum which contributes to the observed poor clinical diagnostic accuracy of approximately 36 percent. The value of clinical and radiological criteria in assisting with management and prognostication is reviewed. The series included 12 patients with normal or mildly altered consciousness at presentation who were managed successfully with medical treatment, despite CT scan evidence of large haemorrhages, with compression of the fourth ventricle and hydrocephalus in some. Surgery should be reserved for those patients with a fulminating presentation, deteriorating course or marked hydrocephalus.

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Abstract

Cerebellar Infarction

*R.A.L. Macdonell, G.A. Donnan, P.F. Bladin, R.M. Kalnins and C.H.R. Wriedt**

Since the advent of CT scanning, cerebellar infarction has been found to be a much more common condition than was previously recognized clinically. The records of the Austin Hospital Stroke Unit were retrospectively analysed from the period August 1977 to July 1984 to identify the incidence, presenting features and natural history of this condition with CT correlation.

34 cases of cerebellar infarction were found from a total of 1997 admissions for cerebrovascular disease. 14 patients had past histories of cerebral ischaemia and, of these, 10 were related to the posterior circulation. The duration between ischaemic symptoms and definite infarction varied from 13 weeks up to one day with a mean of 39 days. 3 patients presented in a comatose state and certainty of diagnosis was not established until CT scan was performed. 10 patients had a mildly depressed conscious state (drowsy). 4 patients developed hydrocephalus, 3 of which were shunted and decompressed. There were 7 in-hospital deaths, 3 of which were thought to be due to direct brainstem compression, one due to extension of infarction into the brainstem, 2 due to aspiration and respiratory arrest and one to myocardial infarction.

Over a mean of 20 months' follow-up, 7 patients had further ischaemic events but only 2 required further hospitalization.

Cerebellar infarction is more common than previously realised. Mortality and morbidity are high, but may be reduced in selected cases by prompt decompression of the posterior fossa. Since ⅓ may have premonitory symptoms, efforts should be made to establish pathogenesis using newer imaging techniques.

Abstract

An Assessment of the Possible Protective Effect of Allopurinol in Acute Stroke

*R. Iansek, B. Aspey, M.J.G. Harrison and D. Packham***

Allopurinol has been shown to have a protective effect on ischaemic tissue by the indirect prevention of excessive purine loss. We tested this property in the gerbil model of acute stroke. A total of 69 animals were pretreated with intraperitoneal

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injection of either allopurinal (50 mg/kg) or sterile water and then subjected to unilateral ligation of the common carotid artery under general anaesthesia. The effect of the ligation was clinically grouped into 4 categories of normal, mild (splayed leg), moderate (turning behaviour) and severe (death, immobile). Fewer allopurinol treated animals were severely affected compared to controls ($P < 0.05$). However no difference was found in the other 3 categories. Histological examination of brain tissue from the normal and mild categories failed to reveal any difference in ischaemic damage between the 2 groups. It was concluded that allopurinol may have a protective effect in severe stroke and that this property requires further elucidation.

Abstract

Acetylcholine Receptor Antibody in the Diagnosis of Myasthenia Gravis: Results of Blood Specimens Dried on Paper and Sent by Mail

*G.A. Nicholson**

The acetylcholine receptor (Ach R) antibody test is now the test with the highest diagnostic yield in myasthenia gravis (MG), with in excess of 90% of patients with generalized MG and 60% of patients with purely ocular MG having positive results. The stability of Ach R antibody in blood samples dried on filter paper was examined and proved suitable for samples to be sent by mail. The Ach R antibody assay was adapted for the analysis of dried blood and serum samples.

Results of the conventional Ach R antibody test, using liquid serum samples from normal subjects, and patients with ocular and generalized MG, were compared with results of the same samples dried on paper. The diagnostic yield for dried serum samples was equal to that of the liquid assay, but a significantly lower yield was obtained using dried whole blood samples. Results for routine samples sent by overseas airmail will be discussed.

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Abstract

Metastic Carotid Body Tumour: an Unusual Cause of Spinal Cord Compression

*T.J. Ingall and G.D. Ogle**

Carotid body tumours (chemodectomas paragangliomas) are uncommon tumours which rarely metastasise. Only 44 cases of distant metastases have been documented. We describe a case of a 56 year old man who had a left carotid body tumour removed 9 years previously. He presented in 1984 with metastases in his lungs, ribs, left acromion and the C5 and C6 vertebrae. Histological confirmation was obtained from a left lower lobectomy. He had spinal cord compression at the C5-6 level due to tumour extension into the spinal canal. Surgery to relieve his quadriplegia was not attempted due to the marked vascularity of the tumour deposits. Radiotherapy to the cervical spine had no effect and the tumour was embolized in an attempt to reduce tumour bulk without success. His quadriplegia worsened and he died of bronchopneumonia, 6 months after presentation.

Metastatic carotid body tumour occurs in approximately 5% of cases, and most commonly involves lung and bones. 20 percent of the cases described have had spinal cord compression due to extradural deposits or vertebral involvement. Surgery is difficult because of the vascular nature of the tumour and radiotherapy has been useful in only a small number of cases. Chemotherapy appears to have no role in the management of these patients. We describe the use of embolization in the management of metastatic carotid body tumour for the first time. It was not successful in this case, but should be given consideration in other cases, either as a pre-operative technique or as a therapeutic manoeuvre in its own right.

Abstract

The Causes and Management of Chronic Meningitis

*N.E. Anderson and E.W. Willoughby***

We reviewed 89 patients with chronic meningitis presenting to a general hospital from 1968 to 1983. Patients with previously known malignancy were excluded. Causes were: tuberculosis (culture proven) 33, cryptococcus 11, malignant meningitis 7,

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syphilis 2, chronic eosinophilic meningitis 4, sarcoidosis 1, herpes zoster 1, leptospirosis 1 and undetermined cause 29. In the last group, 14 appeared to respond to antituberculous therapy, 10 responded to steroids, 4 recovered without sustained treatment and one did not respond to treatment. Although there were some differences in the clinical presentation among the groups, the clinical features and changes in cell count, protein and glucose in the CSF did not reliably distinguish one form of chronic meningitis from another. Identification of the cause largely depended on special investigations of the CSF but these were negative in one third of the patients. Delay in making a firm diagnosis often caused problems in management. The mortality was high in malignant (100%), tuberculous (36%), and cryptococcal (27%) meningitis and lower in chronic meningitis of undetermined cause (14%). Patients with idiopathic chronic meningitis responsive to steroids tended to follow a more prolonged, indolent course and usually required long-term immunosuppression to control symptoms.

Abstract

Neurological Complications of Cervical Manipulation

*T.J. Ingall and C.E. Storey**

Chiropractic manipulation is a common procedure. The occurrence of significant neurological symptoms resulting from such procedures is relatively uncommon. However the true incidence of such neurological symptoms is unknown.

We have seen 7 patients, 3 females and 4 males, with an age range of 31-60 years. 6 had no previous history of central nervous system disease. One had Parkinson's disease and hypertension but no symptoms of cerebrovascular disease. One patient developed severe neck and arm pain due to a nerve root traction injury. The other 6 patients developed symptoms of vertebrobasilar insufficiency. 2 patients had the onset of their symptoms during manipulation and the other 5 within 20 hours of manipulation. 3 had multiple manipulations. 2 had further manipulations to treat their symptoms of vertebrobasilar insufficiency. Clinically there was a spectrum of brainstem lesions (unilateral or bilateral) and cerebellar lesions. Cervical spine radiographs were normal or showed only minimal degeneration. CT head scans in 3 patients showed brainstem and/or cerebellar infarcts. Angiographic findings included a normal arteriogram, an intramural haematoma of the vertebral artery at the C2-3 level (the contralateral vertebral artery was hypoplastic) and a vertebral artery dissection extending to involve the other vertebral artery and the basilar artery. 2 patients died while the other 4 had either full or partial recovery.

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The vertebral artery is relatively fixed at the level of the atlanto-axial joint and is susceptible to mechanical compression and trauma when the head is rotated. An intimal tear can result from cervical manipulation, with subsequent dissection, pseudoaneurysm formation and intramural haematoma or thrombosis. In some cases where infarcts occur without damage to the vertebrobasilar system, severe spasm may be the underlying cause of ischaemia.

The majority of patients who sustain these lesions are young people with no history of central nervous system disease and no spinal disease. They often undergo multiple neck manipulations and have warning signs of ischaemia during the manipulation. Some of these patients may be at greater risk because of congenital vertebrobasilar anomalies. We strongly advise practitioners to be aware of these complications and their symptoms so that the possibility of ischaemic brain damage or death associated with manipulation of the spine may be avoided.

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Manuscript Preparation: Articles will be published in English. Submit two copies of the complete manuscript, including text pages, references, tables, legends, footnotes and figures. Only typed copy, doubled spaced on one side of preferably A4 (206mm x 294mm) typewriter paper, and with liberal margins is acceptable.

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4) Acknowledgements
5) List of references
6) Tables
7) Figures and captions
8) Footnotes

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Journals

Standard journal article — (List all authors when six or less; when seven or more, list only first three and add et al).

You CH, Lee KY, Chey WY and Menguy R. Electrogastrographic study of patients with unexplained nausea, bloating and vomiting. Gastroenterology 1980; 79: 311-314.

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

Weinstein L, Swartz MN. Pathogenic properties of invading micro-organisms. In: Sodeman WA Jr, Sodeman WA, Eds. Pathologic physiology: mechanisms of disease. Philadelphia: W.B. Saunders, 457-472 (1974).

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