LETTERS

Central pontine myelinolysis temporally related to hypophosphataemia

Central pontine myelinolysis (CPM) is known to be associated with the rapid correction of severe hyponatraemia. However, there have been case reports of CPM occurring in normonatraemic patients.[1] Here we describe two patients in whom chronic alcohol abuse led to profound hypophosphataemia that was closely temporally related to the development of CPM.

Case 1

A 29 year old woman was admitted for investigation of painless jaundice of 10 days' duration. She had consumed 100–140 units of alcohol a week for the preceding 18 months and had been noted to have mildly deranged serum transaminase levels one year previously.

On admission she was fully oriented with normal speech and gait. She had a mild postural tremor but no asterixis. A plasma biochemical profile showed her sodium to be 122 mmol/l, potassium 2.1 mmol/l, and urea 5.9 mmol/l. Serum creatinine was 182 µmol/l, phosphate 0.65 mmol/l, magnesium 0.59 mmol/l, and total corrected calcium 2.18 mmol/l. She was immediately given potassium and magnesium supplements, chlordiazepoxide, and intravenous vitamins including vitamin K and thiamine.

Three days after admission she developed a *Staph aureus* septicaemia secondary to a peripheral venous cannula infection. This required treatment with intravenous cefuroxime and flucloxacillin. She subsequently became drowsy and by day 10 had developed a severe spastic dysarthria and profound spastic tetraparesis. There was a bilateral lower motor neurone pattern of facial weakness and gaze evoked nystagmus. The clinical suspicion of CPM was supported by magnetic resonance imaging of the brain, which showed symmetrical signal hyperintensity in the pons on T2 weighted images, as well as generalised cerebral atrophy.

A review of the biochemistry results during her admission showed that the maximum increase in serum sodium concentration over a 24 hour period was only 7 mmol/l (from 123 to 130 mmol/l). Potassium and magnesium concentrations were corrected to the lower end of their normal ranges. However, she developed profound hypophosphataemia (0.16 mmol/l at nadir) which was rapidly corrected to 0.8 mmol/l within 72 hours. The rapid rise in plasma phosphate coincided with the onset of the patient's neurological deterioration. With supportive care she made a gradual recovery such that two months after admission she was safe to be discharged, with only a mild residual left hemiparesis and slight spastic dysarthria, which were improving.

Case 2

A 44 year old woman was admitted with a three day history of progressive dysarthria, seven days of difficulty in walking, and dysaesthesia affecting all four limbs and the perioral region. She had consumed at least 80 units of alcohol a week for several months before presentation.

Examination on admission revealed a mild tetraparesis, dysarthria, and subjective sensory loss in both legs and the left arm. Her admission blood profile revealed a plasma sodium concentration of 136 mmol/l and potassium of 3.4 mmol/l. The serum phosphate concentration was profoundly low at 0.13 mmol/l. T2 weighted and FLAIR sequence MRI done three days after admission showed abnormal signal within the central brain stem suggestive of CPM (fig 1).

She was treated with oral thiamine, multivitamins, and minerals including phosphate. She made a rapid improvement such that her dysarthria had resolved and gait improved sufficiently for her to be discharged 11 days after admission.

Comment

The pathophysiology of CPM is not well understood. Rapid correction of severe hyponatraemia is frequently implicated as a causative factor, but CPM has been reported in the presence of normonatraemia,[1] hypokalemia,[2] and hypophosphataemia.[3] In these cases a hypothesis based on osmotic trauma must be questioned.

Recently an apoptotic hypothesis has been proposed.[4] It is suggested that a depletion of the energy supply to glial cells might limit the function of their Na^+/K^+-ATPase pumps. This could reduce their ability to adapt to relatively minor osmotic stress caused by small changes in serum sodium concentration, and ultimately lead to apoptosis. A preliminary study of necropsy material from five cases of CPM compared with controls has provided some support for this theory. Using immunohistochemistry, an imbalance was shown between proapoptotic and antiapoptotic factors in glial cells with the appearance of oligodendrocytes.[5] Furthermore the serum sodium concentrations in two of the patients remained normal from the onset of symptoms to the time of death.

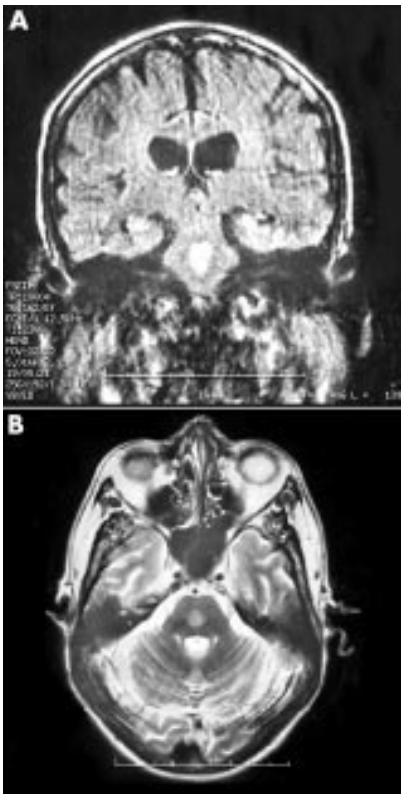

Figure 1 Coronal FLAIR magnetic resonance image (MRI) (A) and axial T2 weighted MRI (B) from case 2, showing high signal within the pons consistent with central pontine myelinosis.

The two patients presented here showed aclose temporal association between severe hypophosphataemia and the development of CPM. Both patients abused alcohol, and the first patient had moderate hyponatraemia with hypokalaemia. They may therefore have been particularly susceptible to CPM for a variety of reasons. It is possible, however, that severe hypophosphataemia adversely affected the Na^+/K^+-ATPase pump and finally triggered apoptosis and CPM. The temporal association of neurological deterioration with the rapid correction of profound hypophosphataemia in case 1 is unlikely to relate to osmotic stress in view of the small contribution of phosphate towards total osmolarity. The rapid change in plasma phosphate may, however, increase cellular stress, contributing to eventual apoptosis.

Both patients described here made good recoveries with phosphate replacement and supportive care. This suggests that widespread apoptosis had not occurred. In these patients the speed and degree of recovery might reflect the resolution of pontine oedema that could accompany less widespread or incomplete apoptosis.

There are useful practical conclusions to be drawn from the observed association of CPM with hypophosphataemia. First, one must suspect the diagnosis of CPM in susceptible patients even without "typical" electrolyte abnormalities. Second, as severe hypophosphataemia in itself has been correlated with increased mortality[6] it would seem prudent to check and treat low serum phosphate concentrations in susceptible patients. This particularly refers to alcohol abusers or malnourished patients treated with intravenous glucose, diuretics, and steroids which may lower serum phosphate concentrations.

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Spastic movement disorder: what is the impact of research on clinical practice?

One expects that convincing research results would have an impact on clinical practice. However, whether or not a new concept becomes transferred to an application in clinical practice is dependent on the medical

field and on the therapeutic consequences. The issue discussed here concerns spasticity, a common motor disorder in, for example, patients who have had a stroke or a spinal cord injury.

The traditional concept

Over many years it was widely accepted that spasticity consists of muscle hypertonia (that is, "a velocity dependent resistance of a muscle to stretch"[1]) caused by exaggerated reflexes, leading to the spastic movement disorder.[2] This concept was based on animal experiments (for example, in the decerebrate cat[3]) and on the physical signs evident on clinical examination at the bedside. Consequently, the aim of any treatment was to reduce reflex activity by antispastic drugs. Possible differences in pathophysiology between the clinical signs of spasticity and the spastic movement disorder which hampers the patient were not considered.

The new concept

Early clinical observations[4] and studies in the 1980s on spastic movement disorders[5] clearly failed to support the traditional concept. In the subsequent 20 years an increasing number of studies using different technological approaches with electromyographic (EMG) and biomechanical recordings focused on the relation between muscle EMG and reflex activity and muscle tone during various functional[6–8] and clinical[9–12] conditions. All these studies fused into a new concept of spasticity (reviewed in several articles[13–15]). This concept has never been questioned in its basic aspects.

The new concept was based on the following observations. First, in the active muscle (that is, during movement) the presence of exaggerated tendon tap reflexes is associated with a loss of the functionally essential polysynaptic or longer latency reflexes, with the consequence that overall muscle activity is reduced during functional movements. Second, as a response to the primary lesion, changes in non-neuronal factors (muscle and connective tissue) compensate for the loss of supraspinal drive and essentially contribute to spastic hypertonia in both passive[9 12] and active[8] muscles.

The *scientific consequence* of this is that the physical signs obtained during the clinical bedside examination are an epiphenomenon rather than the cause of the functional condition (which impairs the patient). During movement, essential reflex mechanisms are involved which cannot usually be assessed by clinical testing. Consequently, the clinical examination required for diagnostic purposes has to be separated from functional testing, which should determine the therapeutic approach. For example, motor function can be assessed by a walking index, such as WISCI.[16]

The *therapeutic consequence* of these observations is that antispastic drugs should be used only with caution in the mobile spastic patient, as a decrease in muscle tone achieved by these drugs could be associated with an accentuation of paresis, impairing the performance of functional movements.[17 18] Consequently, spastic muscle tone is required so that a patient can walk again after a stroke.

Facts and consequences

Although this new concept has become well established scientifically in journals with a mainly scientific orientation during the past 20 years, there has been little transfer to clinical practice. This is reflected in recent review articles in journals with a practical orientation[19–21] read predominantly by clinical neurologists.

The following factors may contribute to the persistence of some old fashioned concepts in clinical neurology:

- The old concept was simple to understand and had a clear therapeutic consequence: the prescription of antispastic drugs. It is seemingly logical that exaggerated reflexes cause muscle hypertonia. The new concept is more complex and its implications—that antispastic drugs should *not* generally be used—make the doctor somewhat resourceless.
- It is not rewarding for a neurologist to take care of patients after a stroke and to have to explain that there are limited therapeutic options (that is, that it will be impossible to restore normal function, and that physical exercises will be more helpful than drug treatment).
- It is, of course of no interest for companies producing antispastic drugs to support graduate medical education in this new concept, with its limited opportunities for drug treatment.

The *consequences* of this experience should be as follows. First, scientific research results should be translated into an understandable and pragmatic format, to convince doctors and patients of the superiority of the new concept. Second, such a novel concept should initiate the development of new forms of treatment (for example, in the field of active physiotherapy); at very least it should be associated with a well structured physical treatment programme which allows the doctor to become involved. Third, the concept should emphasise that immobilised patients may benefit from the use of antispastic drugs (for example, in the management of spasms and for easier nursing); this would make the concept more acceptable to the drug companies. Finally, the concept should include perspectives and limitations of any possible achievements.

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Intracranial hypotension after chiropractic manipulation of the cervical spine

The aetiology of intracranial hypotension is not fully understood, but CSF leakage from spinal meningeal diverticula or dural tears may be involved. In the majority of patients without a history of mechanical opening of the dura the cause of intracranial hypotension is unknown and the syndrome is termed "spontaneous" intracranial hypotension. We report a case of intracranial hypotension ensuing after a spinal chiropractic manipulation leading to CSF isodense effusion in the upper cervical spine.

Case report

A 40 year old woman undertook a spinal chiropractic manipulation. The chiropractioner grasped the head of the supine patient and exerted axial tension while rotating the head. During this manoeuvre the patient complained of a sudden sharp pain in her upper neck, and the procedure had to be stopped immediately. Subsequently she complained of headaches and after 24 hours she developed nausea and vomiting. Her headaches worsened, and lying down gave the only measure of limited relief. On the sixth day she developed double vision and presented to the neurology department of a community hospital.

She had a right abducens palsy and pachymeningeal gadolinium enhancement on magnetic resonance imaging (MRI). The first

working diagnosis was encephalomyelitis and steroids were given. Six days later a repeat lumbar puncture showed 60 cells per mm^3 and raised lactate. The second working diagnosis was basal tuberculous meningitis and treatment with a antituberculous regimen was started. Another MRI was performed, and now showed bilateral subdural effusions. At this point blood leucocytosis was found and a subdural empyema was postulated as the third working diagnosis. The patient was referred to our neurosurgical university hospital for surgical evacuation and leptomeningeal biopsy.

On examination there were no signs of meningitis and apart from an incomplete right sixth nerve palsy the cranial nerves were intact. Neuropsychologically she was fully oriented but with slowed reactions. On general examination she showed no signs of a connective tissue disorder. All blood tests were within normal limits.

The diagnosis of intracranial hypotension was established by the typical clinical and radiological signs and antibiotics were stopped. On MRI a suspected CSF leak at the level of C1–C2 could be identified, with a CSF isodense fluid accumulation in the paravertebral soft tissue and musculature (fig 1). MRI of the complete spinal axis revealed no additional site of CSF leakage. The patient was discharged home and her symptoms resolved gradually over several weeks. A high resolution CISS-MRI of the upper cervical spine eight weeks after discharge no longer showed a CSF isodense effusion and there was no additional underlying pathology.

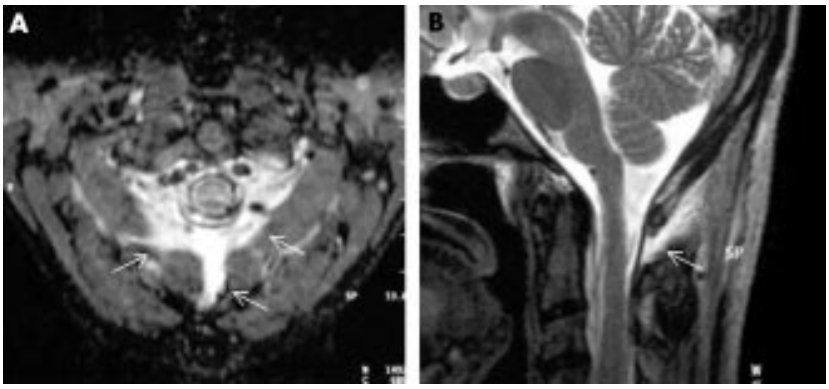

Figure 1 Axial (A) and sagittal (B) T2 weighted MRI scan at the level of the C1/C2 interspace after spinal chiropractic manipulation. There is marked CSF isointense fluid accumulation (arrows) in the dorsal perivertebral space around the dural sac. The subarachnoid space around the myelon is flattened. The level of maximum extradural CSF isointense fluid accumulation was at C1/C2; no other site of spinal CSF leakage could be detected.

Comment

The aetiology of spontaneous intracranial hypotension is unknown. Mechanical disruption of the spinal dural thecal sac with subsequent loss of CSF seems to be the major pathophysiological mechanism. Spinal meningeal tears are thought generally to be spontaneous. There are structural abnormalities related to the syndrome of intracranial hypotension which include spinal meningeal diverticula or Tarlov cysts. It has been shown that some cases of spontaneous intracranial hypotension are associated with microfibrillopathy in the context of a connective tissue disorder.[1 2] Jeret reported one case of a presumed spinal dural tear after chiropractic manipulation, though there was neither dural contrast enhancement nor evidence of a CSF leak.[3]

To our knowledge, this is the first case of a patient presenting with "spontaneous" intracranial hypotension in whom spinal chiropractic manipulation coincided with the development of symptoms, and where a CSF isodense fluid collection in the upper cervical spine was demonstrated radiographically. Neither an underlying meningeal diverticulum nor any other anatomical abnormality could be detected on repeated MRI, including a CISS sequence. Furthermore MRI of the complete spinal axis did not reveal any other site of CSF loss. This suggests that a dural tear in this region was the cause of the intracranial hypotension. We think this is more likely than the interesting alternative concept suggested by Yousry *et al*,[4] that CSF loss from another site in the dural sac may be followed by a CSF isodense effusion in the C1–C2 region, caused by exudation or transudation from the paraspinal venous plexus.

In a series of 30 patients with intracranial hypotension, Chung *et al* reported one who had also undergone spinal chiropractic manipulation.[5] A spinal CSF leak could not, however, be identified. In their study, thorough history taking in all the patients revealed risk factors for a possible traumatic origin of intracranial hypovolaemia in seven of the 30 patients, including playing golf, vigorous physical activity, swimming, yoga exercise, and upper respiratory infections with severe cough.

Trauma, even if mild, may be a risk factor and may account for a substantial proportion of patients with "spontaneous" intracranial hypotension. Our case shows that spinal chiropractic manipulation can lead to intracranial hypotension. History taking should include a thorough inquiry about trauma, with a special emphasis on chiropractic manoeuvres and mild traumatic events. The syndrome of intracranial hypotension must be added to the list of differential diagnoses in cases of subdural effusion or meningeal enhancement because of the favourable outcome with conservative treatment. A substantial number of unhelpful meningeal biopsies and empiric intravenous courses of antibiotic drugs may be avoided by considering this syndrome in the differential diagnosis.

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Clinical and electrophysiological improvement of adrenomyeloneuropathy with steroid treatment

The two most common phenotypes of X-linked adrenoleucodystrophy are the childhood cerebral form and adrenomyeloneuropathy, which occurs mainly in adults and affects the long tracts in the spinal cord most severely.[1] Most patients with the cerebral forms have an inflammatory demyelinating process, while the principal pathology of adrenomyeloneuropathy is a non-inflammatory distal axonopathy, although 30% of patients with adrenomyeloneuropathy also develop some degree of inflammatory brain pathology.[2] All forms of X-linked adrenoleucodystrophy are caused by a defect in the gene ABCD1 which codes for the peroxisomal membrane protein ALDP and is associated with the abnormal accumulation of very long chain fatty acids. Most patients with X-linked adrenoleucodystrophy have primary adrenocortical insufficiency. Although adrenal hormone treatment is considered mandatory and may be life saving, most investigators have expressed the opinion that it does not alter neurological status. We report a patient with a variant of adrenomyeloneuropathy in whom adrenal hormone replacement therapy improved neurophysiological function and clinical status.

Case report

A 39 year old man was evaluated for adrenoleucodystrophy at the Kennedy–Krieger Institute (KKI) in 1985, because his nephew had been diagnosed with childhood onset adrenoleucodystrophy. The nephew died aged nine years and had necropsy confirmation of the diagnosis. Our patient had no neurological symptoms at that time. In 1996, he returned to KKI with complaints of "leg stiffness" and "being off balance." His plasma adrenocorticotrophic hormone (ACTH) level and serum very long chain fatty acids were both raised. Brain magnetic resonance imaging (MRI) showed "subtle white matter changes in the posterior periventricular region that were either at the upper limit of normal or minimally abnormal" (not shown).

In July 2000, he presented to the Buffalo VA Medical Center with complaints of leg stiffness and balance problems. Physical examination showed mild hyperpigmentation, especially in the palmar skinfolds. On neurological

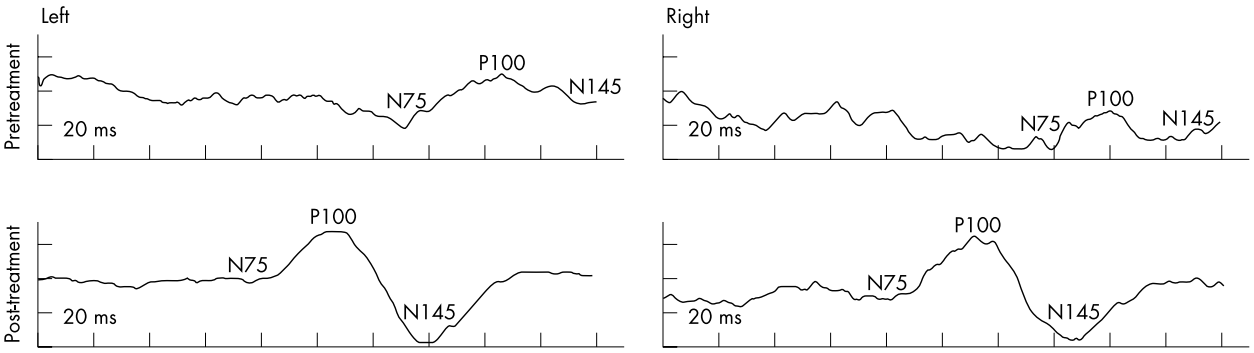

Figure 1 The average visual evoked response obtained from three trials before and six months after prednisone treatment was started. Note the improvement in the P100 latencies which were sustained in the 15 month follow up study (not shown).

examination there was increased tone and decreased vibratory and positional sensation in the lower extremities only. His gait was spastic, with hyperactive deep tendon reflexes and extensor plantar responses.

Before steroid treatment was begun, brain MRI and evoked potential testing were undertaken, as follows:

- visual evoked response: OS/OD, P100 = 166.0/159.6 ms;
- brain stem auditory evoked response: AS, wave I, 2.00 ms; II–V absent; AD, wave I, 1.94 ms; II, 2.88 ms, III–V absent;
- peroneal nerve somatosensory evoked response: left/right, L3 = 8.64/9.44 ms, P27 = 54.60 ms (delayed)/absent;
- median somatosensory evoked response and upper and lower extremity peripheral nerve conduction velocities: normal.

Brain MRI showed mild to moderate confluent hyperintense lesions on T2 weighted and fluid attenuated inversion recovery images (FLAIR) in the posterior periventricular white matter (not shown).

After six months of oral prednisone, 20 mg twice daily, the patient had significant improvement in his leg stiffness and gait. Reflexes became normal, but the sensory deficits were unchanged. ACTH levels declined from 3122 to 26 pg/ml. On visual evoked response testing, P100 latencies became normal (OS/OD, P100 = 106.6/110.0 ms; fig 1). Brain stem auditory evoked responses showed improvement by the appearance of wave II and III in the left side, but no change in the right side. The left peroneal somatosensory evoked response became nearly normal, with a P27 latency of 35.5 ms; the right P27 peak appeared at a latency of 44.8 ms. Median somatosensory evoked response and peripheral nerve conduction velocities were unchanged. The visual evoked response and brain stem auditory evoked response findings were sustained at the 15 month follow up studies (not shown). Following six and 15 months of prednisone treatment, interval MRI showed that the lesions were stable compared with the pretreatment scan. There was no clear progression of MRI involvement (not shown).

Comment

The neurological findings and history in this patient are typical of adrenomyeloneuropathy, and this diagnosis was confirmed by the abnormally high plasma levels of very long chain fatty acids. In addition, brain MRI studies showed the presence of moderately severe cerebral inflammatory involvement, as occurs in approximately 30% of patients with adrenomyeloneuropathy.[1] The demyelinating or inflammatory lesions affecting the spinal cord and brain stem long tracts that are characteristic of this disorder are the likely causes of the gait disturbance, the prolonged interpeak latencies of the peroneal somatosensory evoked response, and the abnormalities of brain stem auditory evoked response before prednisone treatment. The posterior periventricular lesion noted on MRI indicates that the patient had inflammation or demyelination in the visual radiations, which probably correlates with the initially abnormal visual evoked response. Adrenocorticosteroid replacement therapy restored the plasma ACTH level to normal, improved the gait disturbance, and completely corrected the visual evoked response latencies.

Prolonged interpeak latencies of the somatosensory evoked response and the brain stem auditory evoked response, with nearly normal or normal amplitudes, reflect demyelination. The reduced interpeak latencies from the brain stem auditory evoked response and the peroneal somatosensory evoked response after treatment indicate remyelination.[3] No patients with X-linked adrenoleucodystrophy appear to have spontaneous remissions.[1] Therefore the clinical and evoked response improvement is likely to be attributable to prednisone treatment. Although two male patients with adrenomyeloneuropathy showed neurological improvement after starting on prednisone, neither patient had simultaneous improvement in their evoked responses and MRI.[4 5] Our findings are thus consistent with the hypothesis that steroid replacement therapy ameliorated the inflammation or demyelination in our patient. His improvement with prednisone replacement suggests that a more systematic analysis of the neurological effects of corticosteroid treatment in X-linked adrenoleucodystrophy is warranted.

Acknowledgements

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Acute anterior radiculitis associated with West Nile virus infection

Our knowledge of neurological syndromes associated with West Nile virus (WNV) infection continues to evolve. Recent reports during the 1999 outbreak in New York City have most commonly described an encephalitis and aseptic meningitis associated with the infection, but muscle weakness was also found to be an unexpected but prominent feature.[1] Although electrodiagnostic testing in some cases revealed a predominantly axonal polyneuropathy, the mechanism of this weakness remains unclear. The first attempt to account for WNV associated weakness was described in a 1979 case report, suggesting acute anterior myelitis as the aetiology.[2] More recently, involvement of the anterior horn cell was implicated in several cases of WNV poliomyelitis, as localised by electrodiagnostic studies.[3 4] We present the first known case of a WNV poliomyelitis-like syndrome with associated magnetic resonance imaging (MRI) findings, and propose an alternate explanation for the associated weakness.

Case report

A 29 year old right handed man with no significant past medical history reported

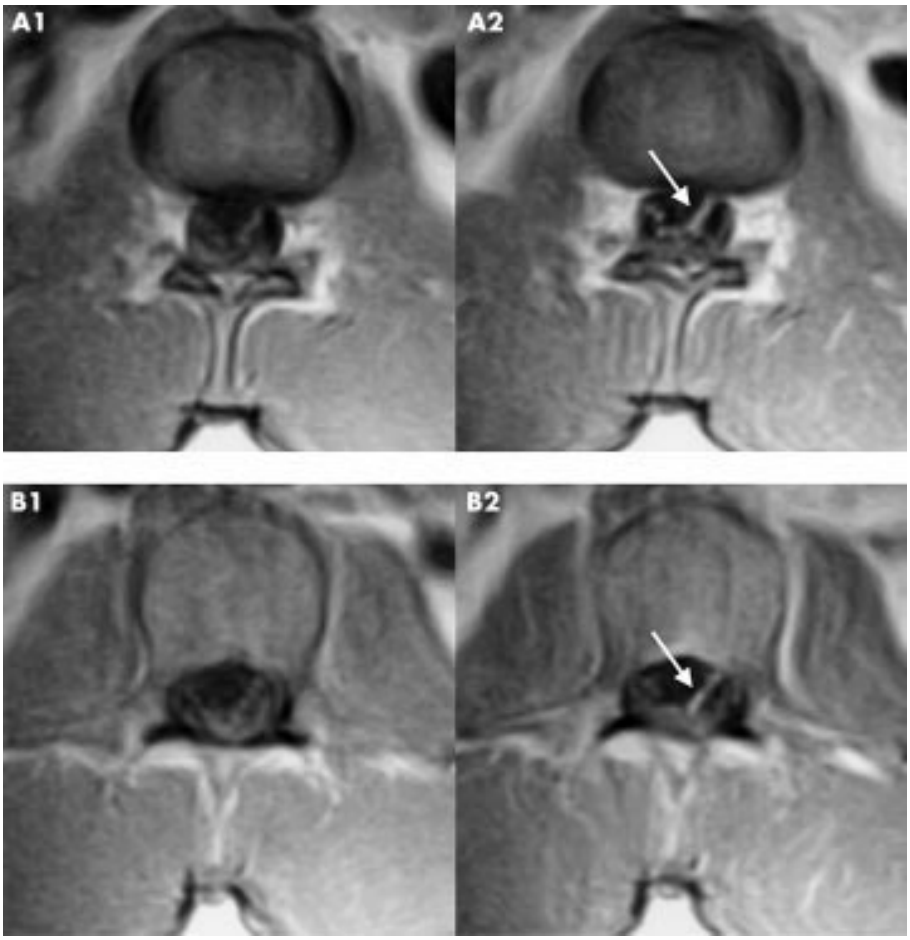

Figure 1 Magnetic resonance imaging of T1 weighted pre- (A1, B1) and post- (A2, B2) gadolinium axial sections of the lumbar cord. Levels L1–2 (A1, A2) and L2–3 (B1, B2) are pictured, showing greater enhancement of nerve roots on the left (arrows).

symptoms of fever, myalgia, nausea, vomiting, and neck stiffness several days after a fishing trip in the Chicago metropolitan area in August 2002. Simultaneously with these symptoms, he described dull, non-radiating left hip pain. On the following day he began to experience weakness of his left leg, which caused him some difficulty in walking. However, he consistently denied back pain or sensory symptoms. Within three days, his constitutional symptoms resolved, but the hip pain and leg weakness persisted. There was no relevant social history. Of note, he reported multiple insect bites while on that fishing trip.

On examination, he was afebrile, alert, and fully cognisant. General examination was unremarkable. Straight leg raising did not produce pain, and there was a full range of motion in the left hip. Neurological examination revealed a flaccid monoparesis (MRC grade 2–3) of the left leg, involving both proximal and distal muscles. Deep tendon reflexes were absent in the left lower extremity. Sensory examination was normal. He had an antalgic gait, with associated left foot drop and a hip thrust to compensate for significant hip flexor weakness. The remainder of the examination was unremarkable.

Laboratory evaluation included the following normal tests: complete blood counts, metabolic panel, antinuclear antibody, serum immunoelectrophoresis, and HIV-1 western blot. Cerebrospinal fluid (CSF) analysis showed 22 white cells per mm^3 (80% lymphocytes), glucose 53 mg/dl, and protein 63 mg/dl. Electrodiagnostic studies of the affected limb were obtained 11 days after the onset of symptoms. These showed motor amplitudes reduced by 79–95% in the left lower extremity when compared with the right. Conduction velocities and sensory amplitudes were normal. Needle examination revealed fibrillations and positive sharp waves in the left tibialis anterior and medial gastrocnemius muscles. There was decreased recruitment and increased firing rate in these muscles, as well as the left quadriceps muscle. Needle examination of the left and right paraspinal muscles was normal. MRI of the lumbosacral spine showed intradural nerve root enhancement greater on the left, affecting L1–S1 (fig 1). Serum tested positive for WNV IgM antibody by enzyme immunoassay, and CSF results were reported as equivocal (exact titres are not provided by the Illinois Department of Public Health).

Suspected aetiologies before the results of WNV testing included an infectious or post-infectious radiculitis, plexitis, or anterior myelitis. He was treated with three days of intravenous methylprednisolone. During his hospital course, he had complete resolution of his hip pain and mild improvement in strength. Deep tendon reflexes returned within two days, and he was discharged home.

Comment

Decreased muscle strength can occur in up to one third of patients infected with WNV, and complete flaccid paralysis is seen in up to 10%.[1] In the cases described, however, weakness was usually associated with an encephalitis or aseptic meningitis, and the pathology appeared to be localised to the peripheral nerve. Recent reports, including ours, describe an isolated acute flaccid monoparesis in which the electrodiagnostic findings are consistent with either motor axon or anterior horn cell pathology.[3 4] Our report is further differentiated by radiographic evidence which confirmed asymmetrical nerve root involvement with good clinical correlation. The absence of sensory findings can be explained by relative sparing of the dorsal roots on both electrodiagnostic testing and MRI. Finally, the simultaneous onset of constitutional symptoms, hip pain, and leg weakness in our case suggests that the WNV infection can cause motor weakness during the initial viraemia, rather than there being a postviral autoimmune aetiology for the weakness.

The mechanism of weakness associated with WNV infection continues to be unclear. It has been hypothesised that it is similar to poliovirus, causing an acute flaccid paralysis in humans by attacking motor neurones directly.[3 4] This theory has been supported pathologically, as WNV has been isolated in the spinal cords of birds and horses, causing a similar paralytic syndrome.[5 6] However, MRI studies of acute poliovirus infection have shown increased signal in the anterior horn,[7] whereas the most recent cases of WNV associated weakness have not had any of these MRI

abnormalities.[4] Further, the EMG findings in all reported cases do not differentiate between a motor axonopathy and anterior horn cell pathology, making either location possible as a cause of weakness.

To our knowledge, this is the first case to present MRI findings supporting ventral root involvement in a case of flaccid paralysis associated with WNV. We propose that anterior radiculopathy should be considered in addition to motor neurone pathology when assessing pure motor weakness caused by WNV.

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A case of possible autoimmune bilateral vestibulopathy treated with steroids

Bilateral vestibulopathy can have various causes: ototoxicity (mainly caused by aminoglycosides), meningitis, bilateral tumours, neuropathies, bilateral sequential vestibular neuritis, or Menière's disease. Some types of bilateral vestibulopathy seem to arise from systemic autoimmune processes—for example, systemic lupus erythematosus, polychondritis, Cogan's syndrome, or rheumatoid arthritis. About 20% of cases of bilateral vestibulopathy, however, remain "idiopathic" despite extensive diagnostic workup.[1] Prompted by studies on immune mediated sensorineural hearing loss,[2 3] we previously demonstrated IgG antibodies against the membranous labyrinth (ampulla, semicircular canal, saccule, and utricle) in sera from eight of 12 patients with "idiopathic" bilateral vestibulopathy, compared with one of 22 healthy controls and none of six patients with systemic autoimmune disease.[4] Although the pathogenicity of these antibodies remains unclear, their appearance seems to indicate organ specific immune dysregulation.

Here we report a patient with a possible autoimmune bilateral vestibulopathy without hearing problems who recovered after steroid treatment. The recovery correlated with the disappearance of serum autoantibodies against inner ear structures.

Case report

A 55 year old man was admitted to the hospital with recurrent sudden monosymptomatic attacks of rotational vertigo lasting for 30 to 60 seconds over three years. For one year he had experienced unsteadiness of gait, particularly in the dark and on uneven ground, as well as blurred vision during head movement or when walking. He reported no disturbances of hearing. His medical history was otherwise normal; in particular there was no evidence of other neurological, otological, or rheumatological disorders, nor had there been any previous treatment with ototoxic drugs.

Clinical examination showed that the head impulse test (Halmagyi and Curthoys) was pathological on both sides. There was no evidence of oculomotor, central vestibular, or cerebellar disorders. Hearing function was also normal. Caloric irrigation (30°C and 44°C) showed a peak slow phase velocity of horizontal nystagmus of < 5°/s on both sides. The per- and postrotatory nystagmus lasted less than five seconds. An audiogram was normal. High resolution magnetic resonance imaging of the brain stem and computed tomography of the temporal bones were also normal. Testing for serum autoantibodies (determined as described previously[4]) against the inner ear structures, the semicircular canals, and otolith organs was positive (titre $> 1:100$). No antinuclear, anticytoplasmic, or antineural antibodies were detected.

On the assumption that an immune dysregulation caused the bilateral vestibular dysfunction, the patient was treated with steroids for six weeks, beginning with 100 mg/day methylprednisolone, and tapering the dose every third day by 20 mg/day until the patient was receiving only 20 mg/day for a duration of four weeks. Follow up examination at the end of this treatment showed that vestibular function had improved on both sides, with a peak slow phase velocity of 14°/s after caloric irrigation with warm water (44°C), and 12°/s on the right and 10°/s on the left with cold water (30°C). At that time serum autoantibodies remained positive.

Two years later the patient was seen again for follow up examination. The head impulse test was normal. Caloric vestibular testing showed a complete recovery of vestibular function with a peak slow phase velocity of > 25°/s (30°C/44°C) on both sides. Per- and postrotatory nystagmus were longer than 50 seconds on both sides. Serum autoantibodies against the vestibular organ had disappeared.

Comment

Immune mediated inner ear disease is characterised by sensorineural hearing loss that is most often rapidly progressive and bilateral, and may be accompanied by vestibular symptoms. Diagnosis of autoimmune inner ear disorders, however, is problematic as there is no universally accepted set of diagnostic criteria or diagnostic test.[5] Our patient had only isolated vestibular signs and symptoms, typical of a bilateral vestibulopathy (the reported recurrent attacks of vertigo at the beginning of the disease are often found in this condition[1]). An autoimmunological aetiology was likely, as other causes had been excluded and raised titres of inner ear specific antibodies were detected. These decreased in parallel with clinical improvement after immunomodulatory treatment.

The treatment trials on autoimmune inner ear disorders that have so far been published have focused only on hearing loss.[2] This single case shows that isolated vestibular dysfunction may also be improved by steroids.

We had hypothesised in our earlier study[4] that some of the so called idiopathic vestibulopathies might be caused by autoimmune inner ear disorders. From the clinical course and response of this patient, we conclude that a short course of steroids may have an effect in patients with incomplete autoimmune induced bilateral vestibulopathy. We therefore recommend that inner ear autoantibodies be determined in bilateral vestibulopathy, and if there is evidence of an autoimmune disorder and vestibular failure is not complete, a short term treatment trial should be started to preserve or even improve vestibular function. This, however, needs to be further evaluated in a prospective study on a large group of patients.

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An Italian family affected by Nasu-Hakola disease with a novel genetic mutation in the TREM2 gene

Polycystic lipomembranous osteodysplasia with sclerosing leucoencephalopathy (PLOSL; MIM 221770), also known as Nasu-Hakola disease, is a recessively inherited disorder characterised by systemic bone cysts and progressive presenile dementia associated with sclerosing leucoencephalopathy.[1] The onset usually occurs in the third decade of life with pathological fractures; later on, symptoms of frontal lobe dysfunction appear, with upper motor neurone involvement and epileptic seizures. Some patients, however, do not have clinically manifest osseous problems despite the radiological demonstration of cystic bone lesions. The disease leads to death before the age of 50.[1]

The disease is characterised by genetic heterogeneity: mutations in two genes (TYROBP and TREM2) encoding different subunits of a membrane receptor complex in natural killer and myeloid cells have been associated with the disease.[2 3]

This rare disorder was initially described in Finland and Japan but is now recognised to have a worldwide distribution.[1] In particular, sporadic cases have been described in Italy,[4 5] and a homozygous mutation in the splice donor consensus site at intron 3 of TREM2 has been identified in two affected siblings.[3]

We report here the clinical and genetic analysis of an Italian family in which two siblings are affected by PLOSL.

Methods

After giving their informed consent, all the family members were submitted to neurological examination, psychological interview,

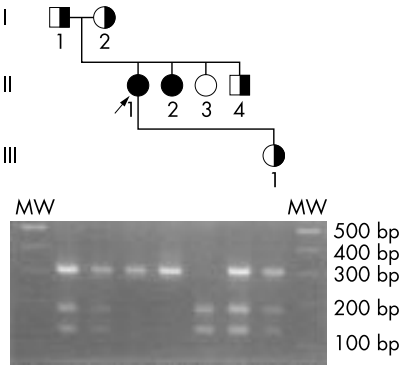

Figure 1 Family pedigree. Black symbols denote affected individuals, white symbols denote unaffected individuals, and half black symbols denote carriers. The arrow indicates the proposita. Segregation of the mutation in exon 2 of TREM 2 gene (191 C→T) was analysed by Pst I site digestion. The mutation abolished the Pst I site.

bone radiographs, and brain computed tomography (CT) or magnetic resonance imaging (MRI). Genomic DNA was extracted from whole blood by standard methods. The entire coding sequences and the intron–exon boundaries of TYROBP and TREM2 genes were amplified from the DNA of each patient. After purification with a QIAquick PCR purification kit (Quiagen, Milan, Italy), polymerase chain reaction (PCR) products were directly sequenced on both strands using the Big Dye terminator kit (Applied Biosystems, Milan, Italy) and a model 310 automated sequencer (Applied Biosystems).

Linkage analysis was undertaken using the microsatellite markers D19S608, D19S610, and D19S876. The order on chromosome 19 is as follows: centromere – D19S610 – TYROBP – D19S876 – D19S608 – telomere. Briefly, primers specific for each locus were used to amplify the repeat sequences in template DNA by PCR. The forward primers were labelled by 6-carboxyfluorescein, and PCR products were analysed by a model 310 automated sequencer (Applied Biosystems).

Case histories

The family pedigree is shown in fig 1. The family originated from a restricted area of northern Italy (Piacenza) and pedigree analysis seems to exclude consanguinity in the last five generations.

The proposita (II,1) is a 46 year old woman. She was of normal psychomotor development. She had been in good health until aged 23 years, when pathological fractures of both extremities started to occur, with radiological evidence of multiple cystic lesions in the distal bones. At the age of 30 she began to have insidious personality changes, depression of mood with suicidal ideas, and loss of social inhibition and judgment. Aged 40, psychological assessment suggested frontal dysfunction, and neurological examination showed the presence of primitive reflexes, mild apraxia, dyscalculia, and spatial and temporal disorientation. An EEG showed theta and delta activity dominating in the frontal areas, and brain CT showed a marked and diffuse cerebral atrophy with calcification in the basal ganglia. The disease progressed, with marked worsening of cognitive and motor functions, cerebral ictal events and epileptic seizures, leading finally to a vegetative state.

The affected sister (II,2) is 35 years old. At the age of 30 she began showing progressive loss of judgment, depressed mood, changes of personality, and uninhibited attitudes. No pathological fractures occurred, but *x* ray imaging showed cystic bone lesions in the metatarsal bones. Neuropsychological assessment revealed deterioration of intellectual function with frontal signs, dyscalculia, and dysgraphia. Cerebral MRI showed severe diffuse cerebral atrophy with basal ganglia calcification.

Neither cystic bone alterations nor pathological cerebral signs were found in the relatives.

Genetic analyses

Sequencing analyses did not detect any mutation in the five exons and in the intron–exon boundaries of TYROBP gene. Microsatellite analysis was undertaken with molecular markers spanning 120 kb of the genomic region containing the TYROBP gene. Although only marker D19S610 was fully informative, the linkage analysis excluded any association between the presence of the disease in our family and the PLOSL locus on chromosome 19.

In the two affected sisters, sequencing analysis identified a homozygous C to T mutation at position 191 (191 C→T) in exon 2 of the TREM2 gene. The mutation changes glutamine 33 to a stop codon (Q33X). To screen the family members for the identified mutation, we investigated a possible change in enzymatic restriction sites introduced by the mutation. The mutation abolished a Pst I site. This allowed us to propose a simple test to screen the family members: the parents (I,1; I,2), the proposita's daughter (III,1), and the brother (II,4) were found to be heterozygous carriers of the mutated allele, while the other sister (II,3) was homozygous for the wild type allele (fig 1).

Comment

The clinical features of our cases are typical of PLOSL, but this family presents a novel homozygous mutation in exon 2 of TREM2. This mutation generates a premature stop codon and it is unlikely to be a polymorphism. Our findings confirm that PLOSL is characterised by a remarkable genetic heterogeneity, showing that mutations in different components of a single signalling pathway may lead to the same clinical condition.

In conclusion, in Italy PLOSL is explained by two different mutations in TREM2 gene.[3] Its prevalence is undetermined because the disease is likely to go unrecognised. We believe that if physicians were more aware of this disease and were able to identify more cases, this would lead to a better clinical and genetic understanding of the condition.

Acknowledgements

We are grateful to the family who participated in this study and to the "Associazione Laura Fossati ONLUS". A special thank you to Dr Ileana Ranzini for her secretarial support.

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PostScript

CORRESPONDENCE

Neutralising antibodies to interferon β during the treatment of multiple sclerosis

Giovannoni and colleagues are to be commended for their detailed analysis of the impact of neutralising antibodies (NAB) to interferon β (IFNβ) during the treatment of multiple sclerosis.[1] We are in general agreement with many of their statements and conclusions, but a few points should be discussed in a wider context.

With respect to the clinical significance of neutralising antibodies to IFNβ, the authors state that "IFNβ has little if any clinical and MRI efficacy in the presence of neutralising antibodies." We think it is appropriate to be more circumspect, as most published studies suggest that in NAB positive patients, clinical (and MRI) efficacy of interferon treatment is present when compared to placebo, and that there is some evidence that more immunogenic higher dose treatment can be more effective than less immunogenic lower dose treatment.[2] Giovannoni *et al* appear to base their statement on the increase in T2 burden of disease in the NAB positive group in the PRISMS extension study, but they do not mention similar comparisons which, if interpreted in the same way, would indicate that the NAB positive group does better than the placebo group.[3] For example, the relapse rate in placebo patients was 1.3/year in years one to two, whereas it was 0.81 and 0.50 in NAB positive and NAB negative high dose patients in years three to four. We recognise that this specific comparison is fraught with difficulties owing to time trends in the relapse data, but these potential difficulties are present in all such comparisons. In a recent paper we report—in probably the largest study of neutralising antibodies in multiple sclerosis, describing 100 NAB positive patients in the European SPMS study—that high titres of neutralising antibodies do have a clinical impact, but that this impact is rather limited, and that on both clinical and MRI measures patients on active treatment who develop neutralising antibodies continue to do consistently better than those on placebo.[4] The main conclusions of this paper are based on longitudinal analyses of the data on those patients who switched from NAB negative to NAB positive status; this is the only statistical approach that allows a direct assessment of whether the change from NAB negative to NAB positive status is associated with diminished efficacy of a treatment. Cross sectional comparisons are not fully reliable for establishing the impact of neutralising antibody positivity, as NAB positive and negative subgroups may differ on baseline variables (maybe unobserved) that are predictive of both neutralising antibody formation and diminished clinical response.

Giovannoni *et al* also state that during continued treatment "in the case of IFNβ-1b some NAB positive patients revert to NAB negative status over two to five years of follow up" and that "patients with high titres of neutralising antibodies seldom revert to being negative." In the European study of IFNβ-1b in secondary progressive multiple sclerosis the proportion of treated patients who have been NAB positive and subsequently revert back to being NAB negative is about 40% after a treatment duration up to three years (without convincing evidence that patients with higher titres revert less frequently), whereas in the study by Rice *et al* this percentage is close to 80% after a mean treatment duration of more than eight years.[4 5]

In our opinion, these data suggest that the clinical impact of neutralising antibodies to IFNβ during the treatment of multiple sclerosis may be more limited and more transient than suggested in the editorial, and that the development of neutralising antibodies in itself does not provide justification for switching treatments or for considering (aggressive) strategies to reduce or revert the development of neutralising antibodies. Given the current rather uncertain state of knowledge concerning the impact of neutralising antibodies, we advocate that treatment decisions should be based on clinical grounds rather than on neutralising antibody titres.

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Neutralising antibodies to interferon β

I read the editorial by Dr G Giovannoni and colleagues[1] with great interest. I have, however, to report a minor error concerning the list of the excipients of the Rebif reported in their table 1. In the table the authors reported the following excipients: mannitol, HSA, sodium acetate, acetic acid, *sodium chloride*. Actually, as you can check in the summary of product characteristics published from EMEA (www.emea.eu.int) on 29 March 1999, in the list of excipients sodium chloride is absent, whereas *sodium hydroxide* is present.

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1 **Giovannoni G**, Munschauer FE, Deisenhammer F. Neutralising antibodies to interferon β during treatment of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2002;**73**:465–9.

Authors' reply

We would like to thank Dr Ortenzi for pointing out our transcription error in relation to the excipients of Rebif® in table 1 of our editorial.[1]

We agree with Polman and colleagues that recent comparisons show that the more immunogenic higher dose interferon β (IFNβ) preparations are more efficacious than the lower dose less immunogenic preparations over 24 month[2] and six month[3] periods of observation. However, as discussed in our editorial, the development of neutralising antibodies and their effects on the clinical efficacy of IFNβ are delayed. In the PRISMS study the effect of neutralising antibodies on clinical efficacy only became apparent in years 3–4.[4] In the pivotal IFNβ-1b study an effect on relapse rate was only observed in the 19–24 and 25–30 month epochs.[5] Hence we would argue that these comparative studies[2 3] are simply too short, and in the case of the INCOMIN trial underpowered (n = 188),[2] to demonstrate an effect of neutralising antibodies on clinical efficacy. It is therefore impossible to extrapolate the significant short term differences shown in these studies beyond the periods of observation reported.

Because of regression to mean and the well documented tendency for the relapse rate to decrease with disease duration, it is not possible to draw any meaningful conclusions from a comparison of the relapse rate in years 1–2 and years 3–4 from the PRISMS extension study.[4 6] In addition to the impact of neutralising antibodies on relapse rate, the PRISMS extension study clearly shows—using the more objective T2 lesion volume or burden of disease—that the average annualised increase in lesion volume over four years in the neutralising antibody positive (NAB+) patients is similar to the increase in the annualised lesion volume in the placebo treated patients in the first two years of the study (NAB+ 4.4% *v* placebo 5.45%).[4 6] Similarly, in the IFNβ-1b study,[5] the annualised relapse rate of NAB+ patients is identical to patients on placebo (1.08 *v* 1.06). In the IFNβ-1a (Avonex®) trial,[7] the impact of neutralising antibodies was limited to MRI outcomes. The failure of neutralising antibodies to have an effect on disease progression and relapse rate in this study probably reflects the size and duration of follow u, as the study was terminated prematurely. It is these data from the pivotal relapsing multiple sclerosis clinical

trials, and other studies on in vivo markers of IFNβ activity discussed in our editorial, that we use to support our statement that "interferon β has little if any clinical and MRI efficacy in the presence of neutralising antibodies."

Data on the impact of neutralising antibodies in secondary progressive multiple sclerosis (SPMS) trials is less clear. This is to be expected, however, as the efficacy of IFNβ on disease progression—the primary outcome measure in SPMS trials—is limited and hence it would be difficult to demonstrate a significant impact on neutralising antibodies on the primary outcome measure when the actual therapeutic intervention itself is only marginally effective.[8 9] It would be very surprising if neutralising antibodies had a significant impact on disease progression, as none of the trials is powered to detect an effect of neutralising antibodies on this outcome. For example, in the European SPMS study, 100/360 (28%) of IFNβ-1b treated patients became NAB+ (titre > 20) over the course of the trial.[10] Taking a conservative approach by applying the results from the trial,[8 10] and assuming that NAB+ patients behave as if they are on placebo and NAB– patients behave like the original IFNβ-1b treated cohort, one would expect 49.8% of the 100 NAB+ patients to progress over three years, compared with 38.9% of the 260 NAB– patients. At the same level of significance (0.029) from the original study, a two sided test would only have a 35% chance of detecting a significant difference between NAB+ and NAB– patients (Fisher's exact test). Compare this to a power of 80% used in the design of the original study. This power calculation is an overestimate as it ignores the therapeutic effect observed before the development of neutralising antibodies, as evidenced in this study,[10] which if taken into account has the potential to further reduce the power of the subanalysis. Polman and colleagues further reduce the power of the subanalysis by limiting the longitudinal study to "switchers"—that is, clinical responses are compared within individual patients during NAB– and NAB+ periods.[10] This longitudinal approach reduces the number of patients available for analysis and potentially shortens the period of observation. A longitudinal approach would seem reasonable if there are no carryover therapeutic effects of IFNβ-1b treatment from the NAB– to NAB+ phase and if the follow up in the NAB+ phase is of sufficient duration to account for the delayed effects (24 to 48 months) of neutralising antibodies on clinical efficacy. In this study the mean follow up in the NAB+ phase would be on average too short (less than 24 months) for one to be confident of excluding a delayed effect of neutralising antibodies on disease progression. Despite the lack of power of these subanalyses, they produce some surprising results. In the cross sectional study there was a trend towards greater disease activity in the NAB+ group in the third year, and a significant percentage T2 volume change from baseline to year 1, year 2, and the last visit[10]; in the underpowered and potentially flawed longitudinal analysis there was no indication of an attenuation of treatment effects on disability progression but, surprisingly considering the lower relapse rate in secondary progressive multiple sclerosis, there was a robust effect on relapse rate.[10]

Another way of interpreting the European SPMS NAB data as presented by Polman and colleagues is that the much higher dose of IFNβ-1b (875 μg/week) given in that study, in comparison with the lower licensed doses of IFNβ-1a (30–132 μg/week), acted to quench some of the neutralising activity of the antibodies.[10] Similarly, the higher doses may be responsible for inducing high dose tolerance in a subset of the patients. These phenomena are well observed with other biologicals in which the read-outs are more objective than in multiple sclerosis—for example, coagulation in anti-factor VIII and glucose levels in anti-insulin antibody positive patients.

Polman and colleagues have misinterpreted our recommendations.[1] We do not recommend routine screening of neutralising antibodies at present, nor the switching of treatments in NAB+ patients unless clinically justified, nor aggressive strategies to reduce or reverse the development of neutralising antibodies.[1] We simply state that further research is necessary to assess whether these strategies are appropriate. Polman and colleagues' concluding statement that treatment decisions should be based on clinical grounds rather than on neutralising antibody titres is entirely in keeping with our recommendations.[1]

We disagree with Polman and colleagues' statement that "the clinical impact of neutralising antibodies to interferon β during treatment of multiple sclerosis may be more limited and more transient than suggested in the editorial." Short to intermediate term data (< 4 years) from the relapsing multiple sclerosis studies discussed above[4 5 7] do not support this claim, and long term clinical data (> 4 years) on the effects of transient neutralising antibodies on the therapeutic efficacy of IFNβ-1b do not exist to support the latter half of their claim. In addition, evidence is yet to surface on whether or not the phenomenon of transient high titre neutralising antibodies occurs to a similar degree in patients treated with IFNβ-1a; therefore the latter half of their statement, if true, may not be applicable to patients treated with IFNβ-1a.

In conclusion, clinicians cannot ignore the issue of neutralising antibodies, particularly in view of the evidence from other fields of medicine in which neutralising antibodies reduce or inhibit the efficacy of a wide range of biologicals, including type I interferons. Why should interferon treatment in multiple sclerosis be any different?

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A 1908 systematic review of the laterality of hysterical hemiplegia

Since the publication of our systematic review of the laterality of functional or medically unexplained weakness and sensory disturbance (1965–2000)[1] we have come across a study from 1908 with a similar aim.

Ernest Jones, later an eminent figure in the psychoanalytic movement, published his paper in French while working as an assistant physician at the London School of Medicine.[2] He reported on the cumulative analysis of 277 cases of hysterical hemiplegia described by 146 authors in 164 articles published between 1880 and 1908. Most of this material is in French and German and includes cases mentioned in doctoral theses and books.

There was no excess of left sided hemiplegia compared with right in hysteria in his analysis—54% had paralysis on the right side and 46% on the left. This was contrary to the prevailing opinion of the time[3 4] and also disagrees with another less systematic review of older studies (covering 100 subjects, 13 publications and 6 authors between 1885–1937).[5]

Jones' conclusions—that the laterality of hysterical hemiplegia has no diagnostic value—were the same as ours. His study has not been cited for at least 40 years (and probably much longer even than that). It has been neglected, like many other negative studies before and since, but it deserves recognition on this subject.

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Resolution of psychiatric symptoms secondary to herpes simplex encephalitis

We read with interest the editorial by Kennedy *et al*,[1] detailing the short-term treatment of herpes simplex encephalitis (HSE). We agree with the authors that we cannot overemphasise the seriousness of the neuropsychiatric symptoms that a number of these patients display in the long term.

We report a 55 year old woman who was diagnosed with HSE; diagnosis was confirmed with a positive PCR test for herpes simplex in the CSF and acyclovir was started the following day after presentation. After a few weeks the patient's recovery was almost complete and she was discharged home. Six months later, there was an abrupt change when the patient developed insomnia and would sit up all night watching children's videos; she also became hostile and confused. She was admitted to a psychiatric unit where she continued to be confused and agitated with episodes of extreme behaviour such as undressing or trying to attack staff.

MRI showed appearances consistent with severe encephalomalacia of the right temporal lobe with evidence of gliosis in the frontal and temporal lobes consistent with previous HSE. It was surprising that the EEG tracing was normal with no focal or epileptiform features.

The patient remained in the psychiatric unit for seven months during which time she failed to respond to different antipsychotic medications and she was heavily sedated. The nursing staff reported that the patient was generally confused but there were distinctive episodes where the patient would stare and then display abusive and disruptive behaviour for periods of up to an hour once or twice a day. Carbamezepine was started and when the patient reached a dose of 400 mg twice daily these episodes ceased completely and the patient's behaviour showed dramatic improvement. She continued to have mild cognitive impairment affecting mainly short-term memory.

Psychiatric problems after HSE are not uncommon; Hokkanen *et al* found that psychiatric problems are the main cause of long term disability in these patients.[2] Despite the fact that clinical relapse of HSE is well documented,[3] cognitive and psychiatric problems are usually already in place in the acute stage and further deterioration or relapse is uncommon.[2] In our case the comparatively long period between recovery and onset of behavioural and psychiatric symptoms seemed to cast doubt about the association with the HSE and uncertainty regarding the appropriate treatment

Vallini *et al* reported successful treatment of a HSE patient presenting with severe emotional liability and explosive emotional outbursts.[4] The patient responded to carbamezepine, which was started after his EEG showed seizure activity detected in temporal structures. Despite the absence of any EEG abnormalities in our case, it showed a similar favourable response to carbamezepine. We feel that any patient with intermittent behavioural or psychiatric symptoms after HSE should have a therapeutic trial of carbamazepine, even in the absence of any clinical or neurophysiological evidence of seizure activity.

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Authors' reply

Gaber and Eshiett report an interesting case of carbamazepine responsive neuropsychiatric syndrome after herpes simplex encephalitis (HSE). Neuropsychiatric symptoms after HSE are well recognised.[1] The frontotemporal and limbic lesions in HSE are particularly likely to cause behavioural and psychiatric symptoms. Retrospective studies have previously implicated HSE in the delayed syndromes of violent psychoses[2] and major depression.[3] However, psychiatric disorders are also common after non-herpes virus encephalitis. Hunter and others had emphasised the importance of considering encephalitic antecedents, even if clinically unapparent, in the differential diagnosis of psychiatric patients.[4] Long term follow up data from the National Childhood Encephalopathy study have shown more recently that 20% of the affected children developed epilepsy and a similar proportion had behavioural problems, hyperactivity or unsociable behaviour.[5]

Besides being a first line antiepileptic, carbamazepine is also recognised to possess considerable therapeutic value in certain psychoses and is an effective long term treatment for bipolar disorder in some cases.[6] Carbamazepine responsiveness in this particular case may not, therefore, imply that the psychiatric symptoms were epileptic in origin. However, EEG signatures of epilepsy are often absent interictally, and the presence of psychoses is known to normalise EEG changes ("forced normalisation") in epilepsy patients.[7] In this particular case, we certainly concur with the authors' use of carbamazepine and were delighted to learn of the favourable response.

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Radiofrequency neurotomy

In reading the study by Govind and colleagues,[1] in which they report the findings of an unblinded, uncontrolled, non-randomised trial of radiofrequency neurotomy for the treatment of third occipital headache, we are surprised that the authors advocate this therapy.

The last statement of the abstract is: "No other form of treatment has been validated for this common form of headache". This implies that Govind *et al* believe they have validated radiofrequency neurotomy as a form of treatment of third occipital headache. Presumably they are prepared, given the apparently impressive numbers of responders, to forego the usual practice of placebo controlled trial.

We do not understand how the authors can expect this treatment to be realistically adopted in clinical practice with no attempt to validate it the way treatments are meant to be validated, through randomised, placebo controlled trials. The statement in their final paragraph that "some practitioners may be averse to implementing a treatment that requires repetition" could perhaps more appropriately state that "some practitioners may be averse to implementing a treatment that remains unvalidated".

The authors state that one reason they did not do a placebo controlled study is that a previous study has already validated this technique in other patients.[2] That a single trial of radiofrequency neurotomy in 24 so-called "whiplash patients" is sufficient basis for the current authors to abandon validation with traditional methods seems absurd, especially when closer inspection of that trial lays it in a less positive light.[3] We do not accept an argument that it was impossible to blind these subjects. It would be entirely reasonable to see just how often a placebo procedure *does* indeed

"fool" the patient. Govind *et al* seem to have already decided that this is not possible, a convenient assumption.

Further, we are concerned that Govind *et al* state categorically that "among patients with whiplash injuries, third occipital headache is common". The study group from which they determine this prevalence has been reviewed elsewhere, and is wholly inappropriate for a prevalence estimate, being best described as an unusual, highly select, and heterogeneous group of subjects.[3]

It is of note that, in regard to validated therapies for whiplash patients, the current study would have been rejected by the criteria of the Quebec Task Force on Whiplash Associated Disorders.[4] We suggest that an invasive procedure should not be advocated until it has been subjected to proper study. Fortunately, we are aware that others are undertaking a properly controlled trial of this form of therapy.

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Authors' reply

Our study reported an audit of outcomes for a treatment of a condition for which there is no other treatment available. It showed what proportion of patients obtained complete relief of pain, and for how long. Readers who wish to adopt this treatment for their patients can do so. If not, they should explain to their patients that they, personally, cannot offer them any treatment that is known to work; but they should not claim that there is no treatment. Our study shows that there is an option.

A placebo controlled trial would not prove that this treatment does not work. The outcomes should be the same as the benchmark established by our study, unless the operators perform the procedure poorly. A placebo controlled study could only show that all or part of the outcome is attributable to non-specific effects.

We consider this to be an unlikely outcome for we have never encountered in any of our own studies, nor in the literature, results showing that 86% of patients obtain complete relief of spinal pain following a sham procedure. Radiofrequency neurotomy has been shown to be associated with placebo responses in only a small proportion of patients, and for a limited duration.[1] They claim that responses to third occipital neurotomy is only a conjecture. In principle it is worthy of testing, but in practice it cannot be tested.

The precepts of informed consent require that participants in a randomised controlled be informed of all the consequences and potential complications of a procedure. Numbness in the territory of the third occipital is an unavoidable side effect of third occipital neurotomy. It is a sign that the target nerve has been coagulated. It is an essential requirement for the procedure to work. The numbness lasts as long as the pain relief lasts. In a double blind trial this side effect cannot be masked. Therefore, patients who underwent a sham procedure would automatically know that they did not have the real treatment. Thereby the patients would be unblinded. Any placebo controlled trial which suffered unblinding would be fatally flawed and, therefore, unacceptable.

Any study that used a control short of a sham procedure would also be flawed, and would not escape criticism. Pundits would argue that patients would recognise that simply blocking the nerve, or simply inserting the electrode without mimicking the two hour procedure assiduously, is an obvious sham, and that any patient so treated would exhibit a nocebo effect.

For these reasons we did not venture to conduct a placebo controlled trial. If Dr Kwan and Dr Friel can show that a sham procedure on the third occipital nerve succeeds in achieving complete relief of pain in 86% of their patients we will gladly convert to their sham procedure.

We recognise it as a pity that our study would not be accepted by systematic reviews; but that is a problem for those who rely on reviews as the only source of evidence. In that regard we stand in good company. Were we to rely only on systematic reviews, radiofrequency neurotomy for trigeminal neuralgia would not be an accepted treatment; nor would we be allowed to perform appendicectomies.

While others are satisfied to deny care to patients while they engage in purist debates about levels of evidence, we are rewarded with patients grateful for the relief that they obtain, and who report: "you must repeat the procedure because I am never going back to suffering headaches again". If someone devises a better treatment for third occipital headache, we will adopt it. In the meantime we feel it would be dishonest of us to tell our patients there is nothing we can do for you.

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CORRECTIONS

In the neurological picture of the June issue (Komotar JR, Clatterbuck RE. Coccidiomycosis of the brain, mimicking en plaque meningioma. *J Neurol Neurosurg Psychiatry* 2003;**74**:806) the initials of the first author were reversed; his name should read as Komotar RJ.

The ordering of the authors in the letter by Soragna D, Tupler R, Ratti *et al* in the June issue (An Italian family affected by Nasu-Hakola disease with a novel genetic mutation in the TREM2 gene. *J Neurol Neurosurg Psychiatry* 2003;**74**:825–6) is incorrect, it should be as follows: D Soragna, L Papi, MT Ratti, R Sestini, R Tupler, L Montalbetti.

The ordering of the authors in the letter by De Tiège, Laureys, Goldman, *et al* in the July issue (Regional cerebral glucose metabolism in akinetic catatonia and after remission. *J Neurol Neurosurg Psychiatry* 2003;**74**:1003–4) is incorrect, it should read as follows: X De Tiège, JC Bier, I Massat, S Laureys, F Lotstra, J Berré, J Mendlewicz, S Goldman.

In the June issue of JNNP fig 1 of the paper by Cagli S, Oktar N, Dalbasti T, *et al* (Failure to detect *Chlamydia pneumoniae* DNA in cerebral aneurysmal sac tissue with two different polymerase chain reaction methods. *J Neurol Neurosurg Psychiatry* 2003;**74**:756–9) was incorrect. The following figure is the correct image that should have been published.

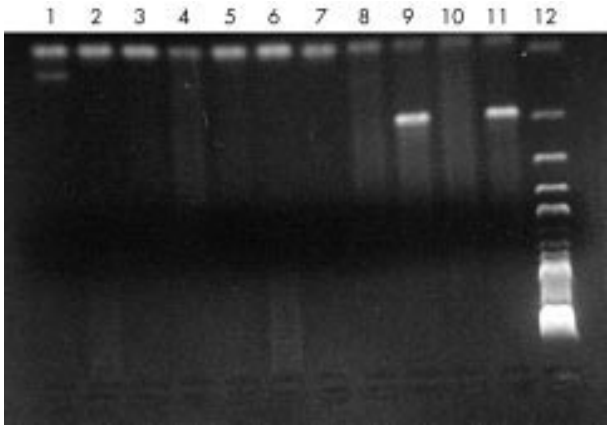

Figure 1 *C pneumoniae* TETR PCR of clinical samples. Lanes 1 to 3, 5 to 7 clinical samples. Lanes 4 and 8 negative control (water). Lanes 9 and 11 positive control (C pneumoniae 4×10^{-1} and 4×10^{-2} CFU). Lane 10 water. Lane 12 DNA molecular weight marker (XIV; 100 bp ladder, Roche Diagnostics). (Correction to *J Neuro Neurosurg Psychiatry* 2003;**74**:756–9.)