Central pontine myelinolysis temporarily related to hypophosphataemia

Central pontine myelinolysis (CPM) is known to be associated with the rapid correction of severe hypophosphataemia. However, there have been case reports of CPM occurring in normonatraemic patients. 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 44 year old woman was admitted with a 7 day history of difficulty in walking, and a spastic movement disorder such that two months after admission she was unable to walk unaided. Her neurological deterioration was precipitated by a 24 hour period of profound hyponatraemia during which sodium concentration dropped from 136 mmol/l to 122 mmol/l. Potassium concentration dropped from 4.2 mmol/l to 3.4 mmol/l. Her 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 hypophosphataemia is frequently implicated as a causative factor, but CPM has been reported in the presence of normonatraemia. Hypokalaemia, and hypophosphataemia. In these cases a hypothesis based on osmotic trauma must be questioned.

Recently an apoptotic hypothesis has been proposed. 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. Furthermore, the serum sodium concentrations in two of the patients remained normal from the onset of symptoms to the time of death.

The two patients presented here showed acrose 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 tonicity. 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 it would seem prudent to perform a low serum phosphate concentration 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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**References**


**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, increased tendon reflexes without circumduction of the patient to stretch") caused by exaggerated reflexes, leading to the spastic movement disorder.

This concept was based on animal experiments (for example, in the active muscle to dcate" 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. Problems occurred in pathology between the clinical signs of spasticity and the spastic movement disorder which hampers the patient were not considered.

The new concept Early clinical observations and studies in the 1980s on spastic movement disorders clearly fail to support the traditional concept. In the subsequent 20 years an increasing number of studies using different technological approaches with electromyographic (EMG) and EMG recordings on the relation between muscle EMG and reflex activity and muscle tone during various functional and clinical activities, respectively, has been reported. All these studies suggest that spasticity (reviewed in several articles) is a functional movement disorder. The 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 long 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 and active muscles.

The scientific consequence of this is that the physical signs observed 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 consequences. 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 implies—antispastic drugs should not generally be used—make the doctor somewhat sourceless.

- 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, 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 clinical program 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 spasticity 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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References

Intracranial hypotension after chiropractic manipulation of the cervical spine

The aetiology of intracranial hypotension is not fully understood, but CSF leakage from a meningeal dural venous sinus 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 doctor 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 received the same treatment and vision and presented to the neurological 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 mm3 and raised lactate. The second working diagnosis was basal tuberculous meningitis and treatment with a antituberculogous 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 hospita for surgical evacuation and leptomeningeal biopsy.

On examination there were no signs of meningeal 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.

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 microfibrillaropathy in the context of a connective tissue disorder. Jersey 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.7

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 Yoursy et al.,8 that CSF loss from another site in the dural sac may be followed by a CSF isodense effusion. 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.9 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 spinal 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 antibiotics may be avoided by considering this syndrome in the differential diagnosis.

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References


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.9 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,9 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 adrenocorticotropic 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 severely 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 examination...
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 latency = 166.0/159.6 ms.
- **brain stem auditory evoked response**: A; 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 decreased 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 improved 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).

**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. The demyelinative 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.1 No patients with X-linked adrenoleukodystrophy appear to have spontaneous remissions. 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.2,3 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 adrenoleukodystrophy is warranted.

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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.4 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 etiology.5 More recently, involvement of the anterior horn cell was implicated in several cases of WNV poliomyelitis, as localised by electrodiagnostic studies.4,6 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...
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 returned absent in the left lower extremity, with preserved reflexes in the right side. Needle examination of the left and right paraspinal muscles, as well as the left quadriceps muscle, revealed fibrillations and positive sharp waves with normal conduction velocities and sensory amplitudes. 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 postviral cause. The electrodiagnostic findings are consistent with either motor axon or anterior horn cell pathology. 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 sides of the spinal cord. Needle examination revealed asymmetrical nerve root enhancement on the left, consistent with an isolated acute flaccid monoparesis in which the electrodiagnostic findings are consistent with either motor axon or anterior horn cell pathology. 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 sides of the spinal cord. Needle examination revealed asymmetrical nerve root enhancement on the left, consistent with an isolated acute flaccid monoparesis in which the electrodiagnostic findings are consistent with either motor axon or anterior horn cell pathology.

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. This theory has been supported pathologically, as WNV has been isolated in the spinal cords of birds and horses, causing a similar paralytic syndrome. However, MRI studies of acute poliovirus infection have shown increased signal in the anterior horn, whereas the most recent cases of WNV associated weakness have not had any of these MRI findings.
A case of possible autoimmune bilateral vestibulopathy treated with steroids

Bilateral vestibulopathy can have various causes: ototoxicity (mainly caused by aminoglycosides), meningitis, other neurological or rheumatological abnormalities. Some types of bilateral vestibulopathy seem to arise from a systemic autoimmune process—for example, systemic lupus erythematosus, polychondritis, Cogan’s syndrome, or rheumatoid arthritis. At least 20% of cases of bilateral vestibulopathy seem to arise with autoimmune phenomena. A novel genetic mutation in the TREM2 gene has been associated with the disease.

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

Polyclonal lipomembranous osteodysplasia with sclerosis (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 leuconecephalopathy. The disease results from a point mutation in TREM2, a member of the immunoglobulin superfamily.

Methods

After giving their informed consent, all the family members were submitted to neurological examination, psychological interview,
ment. She had been in good health until aged 50. 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 PLOS1 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 investigate a possible change in enzymatic restriction sites introduced by the mutation, we investigated a possible change of the TREM2 gene. The mutation changes glutamine 33 to a stop codon (Q33X).

Mutations in two genes encoding different subunits of a receptor signaling complex result in different disease phenotypes. Mutations in different components of a single signalling pathway may lead to the same clinical condition.

In conclusion, in Italy PLOS1 is explained by different mutations in TREM2 gene. 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.

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References


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. 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. 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. 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 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 SPSM 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. 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.

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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References

Neutralising antibodies to interferon β

I read the editorial by Dr G Giovannoni and colleagues’ 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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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.

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 months and six month 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 after years 3–4. In the pivotal IFNβ-1b study an effect on relapse rate was only observed in the 19–24 and 25–30 month epochs. Hence we would argue that these comparative studies are simply too short, and in the case of the INCOMIN trial underpowered (n = 188), to demonstrate an effect of neutralising antibodies on clinical efficacy. It is therefore impossible to extrapolate the significant short term differences in annualised relapse rate 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. 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%). Similarly, in the IFNβ-1b study the annualised relapse rate of NAB+ patients is identical to patients on placebo (1.08 v 1.06). In the IFNβ-1a (Avonex®) trial, 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 up, as the study was terminated prematurely. It is these data from the pivotal relapsing multiple sclerosis clinical
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. 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; however, a conservative approach by applying the results from the trial,13 and assuming that 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, it would only have a 35% chance of detecting a significant difference between NAB+ and NAB− patients (Fishers exact test). Compare this to a power of 80% used in the design of the original study. This prior calculation is an overestimate as it ignores the therapeutic effect observed before the development of neutralising antibodies, as evidenced in this study,22 which if taken into account 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 toward 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 visit22; 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.22

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. Similarly, the higher doses may be responsible for inducing high dose tolerability 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 misrepresented our recommendations. 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. 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.

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 not as evident as suggested in the editorial.” Short to intermediate term data (≤4 years) from the relapsing multiple sclerosis studies discussed above22 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 also needed to support 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 dating from 1908 with a related question.

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.1 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 time1 and also disagrees with another less systematic review of older studies (covering 100 subjects, 13 publications and 6 authors between 1885–1937). 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., 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 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 evidence. The patient remained in the psychiatric unit for seven months during which time she was heavily sedated. The nursing staff reported that the patient was diagnosed with HSE; diagnosis was confirmed with a positive PCR test for herpes simplex in the CSF. Despite the absence of any EEG abnormalities in our case, it showed a similar favourable response to carbamazepine. We believe that any patient with unmitigated 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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References

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 severe temporal 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 psychoses2,3 and major depression.4 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.5 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.6

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.7 Carbamazepine responsive psychosis 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.8 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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References

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 for the 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 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 for the 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 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 for the 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 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 for the 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 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 for the 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 realism...
“fooled” 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. 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. 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.

The precepts of informed consent require that participants in a randomised controlled be informed of all the consequences and potential complications of a procedure. Numness in the territory of the third occipital is an unavoidable side effect of third occipital nerve 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 unmasked. 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 Frieh 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 deviates 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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References

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 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 obtained 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. 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.

In the neurological picture of the June issue (Komotar JR, Clatterbuck RE. Cocidiomycosis 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 Komotor BJ.

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, I Montalbetti.

The ordering of the authors in the letter by De Tiège, Laureys, Goldman, et al in the July issue (Regional cerebral glucose metabolism inakinetic 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 Cabgl 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 4×10⁴ and 4×10⁵ 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.)