Central pontine myelinolysis temporarily 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. 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 sodium concentration of 136 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. Twenty four hour phosphate was immediately given and phosphate 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 dystarhria 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 dystarhria, 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 dystarhria 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, 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 acalosis 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 a 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.

A W Michell, D J Burn, P J Reading
Regional Neurosciences Centre, Newcastle-upon-Tyne, UK

Correspondence to: Dr Michell; awmichell@hotmail.com

References

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 myelinolysis.

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 muscle-dependent resistance to a particular stretch) caused by exaggerated reflexes, leading to the spastic movement disorder. This concept was based on animal experiments (for example, the snipped decerebrate cat) 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 and studies in the 1980s on spastic movement disorders 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 clinical approaches with electromyographic (EMG) and clinical techniques (that is, during movement) the presence of exaggerated tendon tap reflexes is associated with a loss of the functionally essential polysynaptic loop. These reflexes, which is the 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) compromise 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 (that is, 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. The scientific 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 may benefit from the use of antispastic drugs will lead to the development of new forms of therapy.

References


Intracranial hypertension after chiropractic manipulation of the cervical spine
The aetiology of intracranial hypertension is not fully understood, but CSF leakage from the subarachnoid space may be involved. In the majority of patients without a history of mechanical opening of the dura the cause of intracranial hypertension is unknown and the syndrome is termed “spontaneous” intracranial hypertension. We report a case of intracranial hypertension 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 chiropractor 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 a 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

www.jnnp.com
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 meningeal signs and apart from an incomplete right sixth nerve palsy the cranial nerves were intact. Neuropsychologically she was fully oriented but with slowed reactions. In 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 manifestations 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 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 microfibrillogenesis in the context of a connective tissue disorder. 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.

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 Yousr et al., that CSF loss from another site in the dural sac may be followed by a CSF isodense effusion at the C1–C2 region, caused by extravasation or transudation from the para-sagittal venous plexus.

In a series of 30 patients with intracranial hypotension, Chung et al reported one who had also undergone spinal chiropractic manipulation. 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.

J Beck, A Raabe, V Seifert
Department of Neurosurgery Johann Wolfgang Goethe-University, Frankfurt am Main 60528, Germany
E Dettmann
Department of Neuroradiology, Johann Wolfgang Goethe-University
Correspondence to: Dr Jürgen Beck;
j.beck@em.uni-frankfurt.de

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. 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, 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 1983, 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 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 skin folds. On neurological...
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; II–V absent; AD, wave I, 1.94 ms; II, 2.88 ms, III–V absent.
- **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, L = 8.64/9.44 ms, P27 = 54.60 ms (delayed)/absent;
- **Median somatosensory evoked response:** 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 reduced interpeak latencies from the somatosensory evoked response and the brain stem auditory evoked response, with nearly normal or normal amplitudes, reflect demyelination. The improved interpeak latencies from the brain stem auditory evoked response and the peroneal somatosensory evoked response after treatment indicate remyelination. No patients with X-linked adrenoleucodystrophy 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. 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

We thank Dr Gerald Raymond from the Kennedy-Krieger Institute for his comments and Diane Petryk from Buffalo VA Medical Center for her excellent technical support. The investigators were supported in part by grant RR00052 from the United States Public Health Service (HWM), National Institutes of Health (NIH-NINDS) K23 NS42379-01 (RT), and local funds from the Department of Veterans Affairs, Medical Center, Buffalo, New York (EF).

**References**


**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. Although electrophysiological 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 1997 case report, suggesting acute anterior myelitis as the aetiology. More recently, involvement of the anterior horn cell was implicated in several cases of WNV poliomyelitis, as localised by electrodiagnostic studies. 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 were absent in the left lower extremity, with good clinical correlation. 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

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%. 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. 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.

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).
abnormalities. 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 rior radiculopathy should be considered in addition to motor neurone pathology when assessing pure motor weakness caused by WNV.

M Park, J S Hui, R E Bartt
Cook County Hospital and Rush-Presbyterian-St Luke’s Medical Center, 1725 West Harrison Street. Suite 1118, Chicago, IL 60612, USA

Correspondence to: Dr Margaret Park; margaret.rush@ruh

References

A case of possible autoimmune bilateral vestibulopathy treated with steroids

Bilateral vestibulopathy can have various causes: ototoxicity (mainly caused by aminoglycosides), meningitis, bilateral vestibulopathy treated with steroids. A case of possible autoimmune bilateral vestibulopathy treated with steroids.

Case report

A 53 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 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° and 44°C) showed a peak slow phase velocity 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) against the inner ear structures, the semicircular canals, and otolith organs was positive (titre > 1:100). No antinuclear, anticytoplasmic, or antineuronal 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) 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 rapid 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. The onset of inner ear disease 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 oseous problems despite the radiological demonstration of cystic bone lesions. The disease leads to death before the age of 50.

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.

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

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

Methods

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

References


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

Polycystic lipomembranous osteodysplasia with sclerosing leucocencephalopathy (PLOS; 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 leucencephalopathy. The onset of the disease 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 oseous problems despite the radiological demonstration of cystic bone lesions. The disease leads to death before the age of 50.

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.

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

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

Linkage analysis identified a homozygous C to T mutation at position 191 (191 C→T) in exon 2 of 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 analyse segregation of the mutation in the family.

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).

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. Segregation of the mutation in the proposita. 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 characterized 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. 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.

D Soragna, R Tupler
Department of General Biology and Medical Genetics, University of Pavia, Pavia, Italy

M T Ratti, L Montalbetti
Neurological Institute “C Mondino” IRCCS, Department of Neurological Sciences, University of Pavia, Via Paolo 3, 27100 Pavia, Italy

L Papi, R Sestini
Medical Genetics Unit, Department of Clinical Pathophysiology, University of Firenze, Firenze, Italy

Competing interests: none declared

Correspondence to: Professor Lorenza Montalbetti; lmontalb@unipv.it

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.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."2 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.3 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. 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 negative and positive 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 such comparisons—that high titres 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.

C H Polman
Department of Neurology, VU Medical Centre, 1007 MB Amsterdam, Netherlands

L Kappos
Department of Neurology, University Hospitals, Basel, Switzerland

J Petkau
Department of Statistics, University of British Columbia, Vancouver, Canada

A Thompson
Institute of Neurology, University College London, UK

Correspondence to: Professor C H Polman; ch.polman@vumc.nl

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.

C Ortenzi
Department of Molecular, Cellular and Animal Biology, University of Cambridge, 62/322 Camerino, Italy; claudio.ortenzi@tin.it

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.7 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 months 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 3–4.8 In the pivotal IFNβ-1b study an effect on relapse rate was only observed in the 19–24 and 25–30 month epochs.1 Hence we would argue that these comparative studies1 are simply too short, and in the case of the INCOMIN trial underpowered (n = 188)4 to demonstrate an effect of neutralising antibodies on clinical efficacy. It is therefore impossible to extrapolate the significant short term differences observed 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.11 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 4.5%).4,11 Similarly, in the IFNβ-1b study7 the mean rate of NAB+ patients is identical to patients on placebo (1.08 v 1.06). In the IFNβ-1a (Avonex®) trial,1 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 study...
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. 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,32 in contrast to a conservative approach by applying the results from the trial,21,28 and assuming that NAB+ patients behave like the NAB-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 (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,21 which if taken into account would seem reasonable if there is any power of the subanalysis. Polman and colleagues further reduce the power of the subanalyses by limiting the longitudinal study to “switchers”—that is, clinical responses are compared within individual patients during NAB− and NAB+ periods.32 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; 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.

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.33 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.4 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.5 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 recommendation.6

We disagree with Polman and colleagues’ statement that “the clinical impact of neutralising antibodies to interferon β during treatment of multiple sclerosis may be limited and may not be as important as suggested in the editorial.” Short to intermediate term data (< 4 years) from the relapsing multiple sclerosis studies discussed above 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 impact of neutralising antibodies, particularly in view of the phenomenon of transient high titre neutralising antibodies. Many neuromuscular conditions are described by autoantibodies (1965–2000) unexplained weakness and sensory disturbance.5–9 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.3 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 and also disagrees with another less systematic review of older studies (covering 100 subjects, 13 publications and 6 authors between 1885–1937).1 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.

J Stone, C Warlow
Division of Clinical Neurosciences, School of Molecular and Clinical Medicine, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK

References

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) 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.3 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 and also disagrees with another less systematic review of older studies (covering 100 subjects, 13 publications and 6 authors between 1885–1937).1 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.

J Stone, C Warlow
Division of Clinical Neurosciences, School of Molecular and Clinical Medicine, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK
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 overlook 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 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. An EEG 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; Holkken et al. found that psychiatric problems are the main cause of long-term disability in these patients. Despite the fact that clinical relapse of HSE is well documented, cognitive and psychiatric problems are usually already in place in the acute stage and further deterioration or relapse is uncommon. 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. The patient responded to carbamazepine, 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 carbamazepine. We feel that any patient with unaccommodated behavioural or psychiatric symptoms after HSE should have a therapeutic trial of carbamazepine, even in the absence of any clinical or neuropsychological evidence of seizure activity.

T A Z K Gaber, M Eshiett
Intermediate Rehabilitation Unit, Leigh Infirmary, Greater Manchester, UK

Correspondence to: Dr T Gaber; t_gaber@mailcity.com

References

Radiofrequency neurotomy

In reading the study by Govind and colleagues, 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 means of treatment for third-occipital headache. Presumably they are prepared, given the apparently impressive numbers of respondents, to forego the usual practice of placebo controlled trials. 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. That a single trial of radiofrequency neurotomy in 24 so-called “whiplash patients” is sufficient basis for the current authors to abandon validation with a double blind method seems absurd, especially when closer inspection of that trial lays it in a less positive light. 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 work.

A Carson, M Sharpe
Division of Psychiatry, School of Molecular and Clinical Medicine, University of Edinburgh, Royal Edinburgh Hospital, Morningside Park, Edinburgh EH10 5HF, UK

Correspondence to Dr Stone; jstone@skull.dcn.ed.ac.uk

References
The precepts of informed consent require that participants in a randomised controlled trial be informed of all the consequences and potential complications of a procedure. Number in the territory of the third occipital is an unavoidable side effect of third occipital nerve 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. They 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 obtained, 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 the pain is real, and the patients there is nothing we can do for you.

N Bogduk, J Govind, W King
Royal Newcastle Hospital, Australia

Correspondence to: Professor N Bogduk, Department of Clinical Research, Royal Newcastle Hospital, Newcastle, NSW 2300, Australia

Reference

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 prove not 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.

The 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.

O Kwan, J Friel
Correspondence to: Dr O Kwan, 207, 10708–97 Street, Edmonton, Alberta, Canada T5H 2L8; oliverkwan@shaw.ca

References

In the neurological picture of the June issue (Komotar JR, Clattenburg RE. Coccidiodymo-
sis 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 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, 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, J 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, Dalbusti 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 4×10^4 and 4×10^5 CFU). Lane 10 water. Lane 12 DNA molecular weight marker (XIV, 100 bp ladder, Roche Diagnostics). (Correction to J Neurol Neurosurg Psychiatry 2003;74:756–9.)
Psychoneuroendocrinology; the scientific basis of clinical practice


In the last two decades a wealth of information has been gathered regarding the potent influences of our endocrine hormones on the brain and behaviour, giving rise to the discipline of psychoneuroendocrinology. By calling upon leading authorities in their subjects, Wolkowitz and Rothschild have produced this timely volume that explores, with great clarity and success, what might be the clinical significance of the empirical scientific findings in this emerging field and how this may underpin breakthroughs in the treatment of behavioural and affective disorders. Essentially, each contributor considers how hormonal changes observed in primary psychiatric illness, the psychiatric sequelae of hormonal dysregulation in primary endocrinological illness, and the potential for exogenously administered hormones, or hormone antagonists to influence behaviour and affect.

The main text begins with a delightful account of the historical roots of psychoneuroendocrinology, dating back to the ancient philosophers, and the recent rapid development of this discipline. There is then an exhaustive coverage of central nervous system neuropeptides and hypothalamic releasing factors, which addresses the controversial question of whether alterations in their secretion contribute secondarily to or are causative of aspects of psychiatric illness. There is also a balanced view of the potential use of melatonin and its analogues as therapeutic drugs, and a review of the psychiatric manifestations of endocrinopathies—including diabetes mellitus and those affecting secretion of prolactin, growth hormone, and parathyroid hormone. There follows next a section each on glucocorticoid hormones, gonadal hormones, and thyroid hormones, considering conditions of over- and/or undersecretion, which can produce behavioural symptoms closely resembling signs of primary psychiatric illness. The penultimate section is devoted to the use and interpretation laboratory testing in clinical psychoneuroendocrinology to improve accuracy of diagnosis and treatment. The volume ends with an updating of Hans Selye’s original exposition of the general adaptation syndrome that occurs in response to stressors—both exogenous and endogenous. Although mounted to protect the host, the stress response itself may become harmful—both emotionally and physically—if allowed to proceed unchecked.

This comprehensive work clearly demonstrates the importance of crossing the traditional boundaries of endocrinology, neurosciences, and psychiatry, and represents an approachable and informative text that should be of value not only to clinicians from many disciplines, but also to basic scientists, teachers, and the educated public.

P E M Smith

Clinical neurology, 3rd edn


Clinical neurology is now into its third edition since first appearing in 1989 under the original editors Fowler and the late David Marsden, an indication of its popularity in a congested market of similar titles. It provides excellent value as a comprehensive introduction to neurology for medical students, MRCP candidates, other junior doctors, and physicians of all specialties, but does not pretend to have the depth of detail required by more senior neurologists in training or in practice. On looking up a few topics with which medical SHOs’ (and their bosses) always seem to have difficulty, I found dysphasia clearly covered, eye movement disorders well described and illustrated, and lateral medullary syndrome mentioned in the text but not in the index. Cord compression, coma, and confusion are each presented well, and there are good overviews of common (and rare) neurological syndromes pitched at just the right level for the readership. Chapters on intracranial pressure, cerebrovascular disease, epilepsy, infection, spinal disease, and many other topics guide the neurological novice confidently through diagnosis and management. The book is substantially updated from the second (1998) edition, and although there are many new illustrations and information, these are only minor caveats in a textbook whose uniformly British contributors have done such a good job. Clinical neurology will continue in this edition as a firm favourite for MRCP trainees, in the GP surgery library, and to inform and stimulate the undergraduate neurology curriculum.

P K Newman

Behavioral medicine in primary care—a practical guide


It is well known that a large proportion of consultations in primary care have their origins in the psychological wellbeing of the patient. There is clearly a need for a reference book in this area that strikes the right balance in presentation, ease of use, and usefulness, without being overbearing. With this in mind, is this book of use to a primary care physician with limited training in behavioral medicine? The early chapters go back to basics and focus on the doctor–patient relationship. The reader not so keen on this approach may be lost by the wayside in these chapters. However, for those prepared to re-value the patient interview, the chapters presented will be very insightful. Because this is a quick reference book, if the reader is so inclined, the early chapters can be skipped, but the reader may miss out on the central message of the book, which is the understanding of the doctor–patient relationship. Further thumbing through the book will reveal comprehensive backgrounds and practical approaches to psychiatric, medical, and behavioural disorders in primary care, including pharmacological treatments for psychiatric illnesses. The book is written for the US healthcare system but most treatment options suggested are available in the UK.

The presentation of information is stylish and cohesive, with the 35 chapters following a similar format including case illustrations. These illustrations are interesting but occasionally a little too simplistic. The book’s major achievement is its diversity, which is also its weakness, as some detail is lost. However, this is a minor criticism.
Overall, this is a well edited and presented book, which fulfils its aims as a practical reference book adequately. It offers a different approach to the behavioural and medical problems in the primary care setting. Although the book would be of limited use to trainees in psychiatry, due to its primary care focus, it would serve as a useful text to those in primary care, other healthcare professionals, and students.

G Price

Quantitative MRI of the brain—measuring changes caused by disease


We have waited for a long time for a comprehensive book on magnetic resonance (MR) techniques that will appeal to the neurologist/neuroradiologist as well as the physicist and researcher. A book that is right up to date and is relevant across the board for all who are interested in the technique and that deals with quantification.

Paul Tofts has produced a book that is in the coffee table style, in the best sense of the concept, and in price; in the fact that the book invites you to pick a section at random and find that the information is immediately accessible and self-contained. The level of detail is impressive, as is the design of the presentation where information of different types is presented in boxes comprising summaries of opinions, and practical suggestions. The layout works well; chapters take you through theory to practical applications and mention problems and solutions along the way. It is clear that it has been written by people who have hands on experience of MR and who have had to deal with the issues associated with quantification in all forms of MR use (diffusion, magnetisation transfer, spectroscopy, contrast enhanced MRI, functional MRI, blood perfusion and volume estimation, and the various practicalities associated with analysing images, to mention just some of the topics covered).

The usual pitfalls of multiauthor books have been avoided as Paul Tofts is involved in the writing of many of the chapters and the book has the coherence of a single author book. The style of writing is occasionally poetic, for example: “the paradigm shift from qualitative picture-taking to objective measurement-making is taking place”, which elegantly summarises the theme of the book. I have to mention the introduction, which might have been written by Melvyn Bragg and at first seems a little out of place in a science textbook and more fitting to a book on the arts. It references Stravinsky, John Cleese, Bronowski, and Rachmaninov, among others, and speculates about the nature of creativity: “Sometimes I seemed to be witnessing the creation of perfection”, writes Paul Tofts. I smiled to myself when I first read this but having looked at this book in greater detail, I think he might have a point. If you are involved with MR imaging in any way I urge you to look at this book, and once you have, you will know that you need to have it and you will want it for its sheer comprehensiveness, and the knowledge that quantification in MR imaging is truly at the cutting edge.

M Maier

Neuroscience in medicine, 2nd edn


Neuroscience in medicine, second edition, is aimed primarily at medical students and seeks to explain the basic structure and function of the nervous system underlying medicine. It is arranged as a collection of essays by individual contributors, interspersed with short clinical chapters. Most of the chapters are written at a level appropriate for medical students but others (for example those on hypothalamus, muscle, and ion channels) carry detail more suited to a neuroscience undergraduate or even post-graduate student. While it is no bad thing to offer students more information than they strictly need, it does need careful management in order to avoid a fascinating subject becoming a daunting one.

In terms of coverage, it is refreshing that subjects such as sleep, cerebrospinal fluid, and neuroimmunology are dealt with individually, as these tend to be minimised or overlooked in some textbooks. However, there are also some serious omissions. There is no chapter explaining the structure and function of the autonomic nervous system, surely one of the topics most often misunderstood by medical students. Also, parts of the motor system are described in several chapters but no attempt is made to show how it all fits together. The order in which subjects are dealt with is unusual. For example, chapters on synaptic transmission and receptors come early in the book while neurotransmitters are covered in a chapter on spinal mechanisms for control of muscle is divorced from the other chapters dealing with either spinal cord or other motor functions, being placed between chapters on the thalamus and chemical messenger systems.

Perhaps the greatest disappointment is the illustrative material, which varies considerably from chapter to chapter. While some contain effective explanatory diagrams, others have figures of poor quality (apparently due to scanning at low resolution, as in the chapters on spinal cord and higher brain function). The chapter dealing with neuroanatomy relies on a few black and white photographs and histological sections—no diagrams or MRIs.

In summary, when compared to its many competitors, this book is unlikely to appeal to its intended audience. Sadly the generally high quality of the individual contributions is not sufficient to compensate for the poor organisation and variable illustration of this book.

M Lowrie

Local therapies for glioma: present status and future developments


This small book, which is a supplement of Acta Neurochirurgica, represents the proceedings of a meeting held in Milan in 2003. It is organised by the EANS Neuro-oncology Executive, which is chaired by Professor Westphal. The point of the meeting was to describe the concepts and status of local therapies for glioma. Owing to the inevitable failure of surgery, chemotherapy, and external beam radiotherapy to prolong life in gliomas, a great deal of effort and pharmaceutical effort has been put into developing local therapies for gliomas.

The rationale for placing compounds or therapies in the cavity created following the resection of a glioma is best described by the editors’ preliminary remarks. Unfortunately, evaluating the effects of local therapies are also difficult because the therapy will induce radiological changes, which could be interpreted as reactivation of quiescent tumour. These difficulties in assessment are later discussed in a separate chapter. The first half dozen chapters cover current clinical investigation, management approaches, and assessment of gliomas with respect to state of the art technologies such as surgery incorporating image guided volumetric resection of gliomas, fluorescence guided resections, and experience with glioma surgery with intraoperative high field MRI, postoperative imaging after brain tumour resection, and the use of external beam conformal radiotherapy and interstitial stereotactic radiosurgery. These chapters are in a sense the ante parate, because they set the scene for the novel local therapeutic approaches. They provide a solid, practical background for the subsequent chapters. The article on awake craniotomy in particular has thoughtful and useful information for those interested in the technique.

A variety of local therapies are covered in subsequent chapters. Some of these are well known techniques that simply involve local deposition of a chemotherapeutic agent (for example implantable drug releasing biodegradable microspheres for local treatment of brain glioma and intracavity chemotherapy for glioblastoma, present status and further directions), which have already reached clinical practice after phase III trials. The particular difficulties with local gene therapy for gliomas are well covered in two succinct chapters, which are comprehensively referenced. Other chapters discuss new approaches using specific techniques (for example non-invasive transcranial high intensity focused ultrasound (HIFUS) under MRI thermometry and guidance for the treatment of brain metastases and intracranial radioimmunotherapy in the treatment of malignant glioma, clinical and experimental findings; radioimmunotherapy targeting fibronectin; and comparing monoclonal antibodies and small peptide hormones for local targeting of malignant gliomas). The use of convection enhanced delivery techniques are described for the delivery of IL4 pseudomonas exotoxin (NBI-3001) for treatment of patients with recurrent malignant glioma, together with interim findings from ongoing phase I studies of IL3-PE38QQR for treatment of the same condition.

The remaining chapters reflect the editors’ particular interest in glioma cell invasion, the potential use of anti-angiogenic therapies, and stem cells in neuro-oncology. Pathophysiological advances in these areas could provide the basis for novel local therapies in the future.

What does this book offer the neuro-oncologist interested in oncology? Firstly, there are some good overviews of the current state of treatments, their evidence base, and the ways in which surgery and radiotherapy are likely to change in the not too distant future. The second group of chapters on true local therapies for glioma.
Neuroepidemiology—from principles to practice


Everyone, at one time or another, feels misunderstood and unappreciated. Epidemiologists are no exception. They get fed up with hearing secondhand opinions that epidemiology is a blunt instrument or that epidemiological investigations don’t allow inferences to be drawn about aetiology. Their hearts sink when they encounter people who believe that its methodology amounts to little more than counting cases. Eventually, exasperation drives them to write a book explaining what their subject is really about. If this was the motive behind Neuroepidemiology—from principles to practice, I hope the authors and editors found the process of writing as therapeutic. Whether practicing neurologists, who are identified as a target readership in the preface, will find that it changes their view is another matter.

The book follows a conventional format. Individual chapters on methods are followed by accounts of specific neurological diseases. An attractive feature is the final section with descriptions of clinical trials, evidence-based medicine, and health service research as they apply in neurology. Evidence-based medicine, and health services’ research as they apply in neurology. All chapters are easy to read, well illustrated, and well referenced. For those interested in neuro-epidemiology it is a very useful reference source that covers a gamut of approaches. The overall has something for everyone interested in neuro-epidemiology. The editors are to be congratulated for their contributions, the selection of authors, focusing on this important and evolving area, and addressing it in a very practical, clinically orientated fashion.

I R Whittle

Neurosurgical re-engineering of the damaged brain and spinal cord


Katayama, on behalf of the Neurorehabilitation Committee of the World Federation of Neurological Societies, has brought together essays presented at a Neurorehabilitation Committee Meeting held in 2002.

Each chapter represents multi-author presentations largely derived from Japan. The manuscript consists of nine subsections addressing aspects of coma, restorative neurosurgery, early rehabilitation, functioning, imaging, neurological intervention, pain control, and neural transplantation. The editors have achieved a comfortable balance between scientific and clinical presentation. For example, the first section on monoaminergic and cholinergic pathologies for sleep and wakefulness in the rat model demonstrates elegant physiology, followed by clinical papers that explore median nerve stimulation effects on conscious levels in comatose patients. Both address mechanisms relevant to the reticular activating system. Novel methods for functional imaging of brain abnormalities are well represented, with particular reference to modern MRI sequencing. Specific surgical procedures to reconstruct nerve damage and therapeutic lesioning and muscular grafting for cerebral palsy are also covered.

Finally, there are a number of papers relating to various deep brain stimulators for the control of dystonia, pain, and other movement disorders. From a surgical perspective this is an interesting area showing expansion and considerable promise.

In summary, this volume represents a collection of mostly Japanese papers exploring different aspects of surgical manoeuvres which promise to improve outcome for a variety of brain and spine injured individuals. I recommend this book to those involved in the chronic rehabilitation of central nervous injured individuals and those neurosurgeons who seek subspecialisation in this area.

P J Kirkpatrick

Biopsychosocial approaches in neurorehabilitation—assessment and management of neuropsychiatric, mood and behaviour disorders


As the title implies, this book is ambitious in its remit, encompassing the complexity of brain injury outcome for the sufferer and the wider community. The acknowledged aim is to highlight the “interaction of biological, psychological and social forces on affect and behaviour” (p 2) by presenting a compilation of information from several research fields to provide a focus for the development of clinical practice.

The 17 papers are grouped into five sections covering assessment, mood and anxiety, behavioural health, relationships, and community services. There is no formal division between sections and, inevitably, there is some overlap. However, cross-referencing between papers is good. Perhaps not surprisingly, the overwhelming emphasis is on outcome after traumatic brain injury (TBI), but depression after stroke and psychosocial effects of aphasia are both covered.

Among the contributions, Tate presents a comprehensive overview of attempts to tease out the respective influence of pre- and post-morbid factors on outcome and draws the conclusion that personality changes are largely independent of premorbid personality. She reminds us that psychosocial factors characterising the TBI population also characterise the age group in which TBI is most prevalent. A review of literature on substance misuse (Taylor et al) identifies the importance of inter-disciplinary collaboration, noting that rehabilitation professionals may lack specific expertise in substance misuse and its treatment. Zasler and Martelli present a useful paper on the effects of mild traumatic brain injury, which are still poorly understood despite their prevalence, but which might have been strengthened by acknowledgment of recent UK work findings (for example King, 1996). In the final paper, Judd presents telling statistics to illustrate the mismatch that still exists, even in developed countries, between prevalence of traumatic brain injury and provision of adequate diagnostic and rehabilitation facilities.

Although quite expensive at £59.95, this compilation of papers serves to emphasise the multi-faceted role of modern neurorehabilitation and largely succeeds in its aim of providing a comprehensive information resource.

J Cockburn

Reference


CORRECTIONS

doi: 10.1136/jnnp.2003.026278corr1

In the Letter by Deschauer et al (J Neurol Neurosurg Psychiatry 2004;75:1204–5) the order of authorship is incorrect and should be: M Deschauer, P F Chinnery, S Shanske, S DiMauro, K Majamaa, E Wilichowski, D R Thorburn, S Zierz, A M Schaefer, D M Turnbull, R W Taylor.

doi: 10.1136/jnnp.2003.031262corr1

Soragna D, Papi L, Ratti M T, et al. An Italian family affected by Nasu-Hakola disease with a novel genetic mutation in TREM2 gene (J Neurol Neurosurg Psychiatry 2003;74:825–6). The correction in this paper regards the number of the nucleotide of the TREM2 mutation. In the paper the authors wrote that the mutation was at position 191 (191 C→T) in exon 2 of the TREM2 gene. The correct mutation is at position 97 (97 C→T) in exon 2 of the TREM2 gene. The mutation changes glutamine 33 to a stop codon (Q33X); this change is correctly reported in the paper. The authors apologise for the error.