LETTERS

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.1 Here we describe two patients in whom chronic alcohol abuse led to profound hypophosphataemia that was closely temporally related to the development of CPM.

Case 1

A 29 year old woman was admitted for investigation of painless jaundice of 10 days’ duration. She had consumed 100–140 units of alcohol a week for the preceding 18 months and had been noted to have mildly deranged serum transaminase levels one year previously. On admission she was fully oriented with normal speech and gait. She had a mild postural tremor but no asterixis. A plasma biochemical profile showed her sodium to be 122 mmol/l, potassium 2.1 mmol/l, and urea 5.9 mmol/l. Serum creatinine was 182 μmol/l, phosphate 0.65 mmol/l, magnesium 0.59 mmol/l, and total corrected calcium 2.18 mmol/l. A peripheral venous cannula was immediately given parenteral phospha- tium and magnesium supplements, chlo- ridiazepoxide, and intravenous vitamins including vitamin K and thiamine.

Three days after admission she developed a Sapii aureus septicaemia secondary to a peripheral venous cannula infection. This required treatment with intravenous cefuro- xime and flucloxacillin. She subsequently became drowsy and by day 10 had developed a severe spastic dysarthria and profound spastic tetraparesis. There was a bilateral lower motor neurone pattern of facial weakness and gaze evoked nystagmus. The clinical 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 immunohisto- chemistry, an imbalance was shown between apoptosis and antia apoptotic factors in glial cells with the appearance of oligodendro- cytes. Furthermore the serum sodium concentrations in two of the patients remained normal from the onset of symptoms to the time of death.

Sodium concentration of 136 mmol/l and potassium of 3.4 mmol/l. The serum phospha- tium was profoundly low at 0.13 mmol/l. T2 weighted and FLAIR se- quence 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, multi- vitamins, and minerals including phosphate. She made a rapid improvement such that her dysarthria had resolved and gait improved sufficiently for her to be discharged 11 days after admission.

Comment

The pathophysiology of CPM is not well understood. Rapid correction of severe hypo- natraemia is frequently implicated as a causa- tive factor, but CPM has been reported in the presence of normonatraemia,2 hypokalaemia,3 and hypophosphataemia.4 In these cases a hypothesis based on osmotic trauma must be questioned.

Recently an apoptotic hypothesis has been proposed.5 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 immunohisto- chemistry, an imbalance was shown between proapoptotic and antiapoptotic factors in glial cells with the appearance of oligodendro- cytes. 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 acrle 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 trig- gered apoptosis and CPM. The temporal association of neurological deterioration with the rapid correction of profound hypophos- phataemia in case 1 is unlikely to relate to osmotic stress in view of the small contribu- tion of phosphate towards tonicity. The rapid change in plasma phosphate may, however, increase cellular stress, contributing to eventual apoptosis.

Both patients described here made good recoveries with phosphate replacement and supportive care. This suggests that wide- spread apoptosis had not occurred. In these patients the speed and degree of recovery might reflect the resolution of pontine oedema that could account for less wide- spread 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 mortality4 it would seem prudent to check and treat low serum phosphate concen- trations in susceptible patients. This particu- larly refers to alcohol abusers or malnour- ished 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

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

One expects that convincing research results would have an impact on clinical practice. However, whether or not a new concept becomes transferred to an application in clinical practice is dependent on the medical
field and on the therapeutic consequences. The issue discussed here concerns spasticity, a common motor disorder in, for example, patients who have had a stroke or a spinal cord injury.

The traditional concept

Over many years it was widely accepted that spasticity consists of muscle hypertonia (that is, increased resistance of a muscle to stretch) caused by exaggerated reflexes, leading to the spastic movement disorder. This concept was based on animal experiments (for example, in the de cerebrate 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) recordings have provided evidence on the relation between muscle EMG and reflex activity and muscle tone during various functional and clinical conditions. All these studies fused into a new concept of spasticity (reviewed in several articles[4–9]). This concept has never been questioned in its basic aspects.

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

The scientific consequence of this is that the physical signs obtained during clinical examination are an epiphenomenon rather than the cause of the functional condition (which impairs the patient). During movement, essential reflex mechanisms are involved which cannot usually be assessed by clinical testing. Consequently, the clinical examination required for diagnostic purposes has to be separated from functional testing, which should determine the therapeutic approach. For example, motor function can be assessed by a walking index, such as WISCI. 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 could be associated with an accentuation of the disability, with a performance of functional movements. Consequently, spastic muscle tone is required so that a patient can walk again after a stroke.

Facts and consequences

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

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

- The old concept was simple to understand and had a clear therapeutic consequence: the prescription of antispastic drugs. It is seemingly logical that exaggerated reflexes cause muscle hypertonia. The new concept is more coherent and has therapeutic implications—that antispastic drugs should not generally be used—make the doctor somewhat resourceless.
- It is not rewarding for a neurologist to take care of patients after a stroke and to have to explain that there are limited therapeutic options (that it will be impossible to restore normal function, and that physical exercises will be more helpful than drug treatment).
- It is, of course, of no interest for companies producing antispastic drugs to support graduate medical education in this new concept, with its limited opportunities for drug treatment.
- The consequences of this experience should be as follows. First, scientific research results should be translated into an understandable and pragmatic format, to convince doctors and patients of the superiority of the new concept. Second, such a novel concept should initiate the development of new forms of treatment (for example, in the field of active physiotherapy); at very least it should be associated with a well-structured physical treatment programme which allows the doctor to become involved. Third, the concept should emphasise that immobilised patients may benefit from the use of antispastic drugs (for example, in the management of spastics and for easier nursing); this would make the concept more acceptable to the drug companies. Finally, the concept should include perspectives and limitations of any possible achievements.

V Dietz
ParaCare, Institute for Rehabilitation and Research, University Hospital Balgrist, Forchstr 340, 8008 Zurich, Switzerland

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Corresponding interests to: Professor Dr V Dietz; dietz@balgrist.unizh.ch

References


Intracranial hypotension after chiropractic manipulation of the cervical spine

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

Case report

A 40 year old woman underwent a spinal chiropractic manipulation. The patient grabbed 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
working diagnosis was encapsulating arachnoiditis and steroids were given. Six days later a repeat lumbar puncture showed 60 cells per mm³ and raised lactate. The second working diagnosis was basal tuberculous meningitis and treatment with a antituberculotic regimen was started. Another MRI was performed, and now showed bilateral subdural effusions. At this point blood leucocytosis was found and a subdural empyema was postulated as the third working diagnosis. The patient was referred to our neurosurgical university hospital for surgical evacuation and leptomeningeal biopsy.

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

The diagnosis of intracranial hypotension was established by the typical clinical and radiological signs and antibiotics were stopped. On MRI a suspected CSF leak at the level of C1–C2 could be identified, with a CSF isodense fluid accumulation in the paravertebral soft tissue and musculature (fig 1). MRI of the cervical spine 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 did not longer show 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 pathological 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 microfrillodgraphy 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 Yousry and colleagues, that CSF loss from another site in the dural sac may be followed by a CSF isodense fluid accumulation (arrows) in the dorsal perivertebral space around the dural sac. The subarachnoid space around the myelon is flattened. The level of maximum extradural CSF isodense fluid accumulation was at C1/C2; no other site of spinal CSF leakage could be detected.

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

In July 2000, he presented to the Buffalo VA Medical Center with complaints of leg stiffness and balance problems. Physical examination showed mild hyperpigmentation, especially in the palmar skinfolds. On neurological...
examination there was increased tone and decreased vibratory and positional sensation in the lower extremities only. His gait was spastic, with hyperactive deep tendon reflexes and extensor plantar responses.

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

- **Visual evoked response**: OS/OD, P100 = 166.0/159.6 ms; brain stem auditory evoked response: AS, wave I, 2.00 ms; II–V absent; AD, wave I, 1.94 ms; II, 2.88 ms, III–V absent;
- **peroneal nerve somatosensory evoked response**: left/right, L1 = 8.64/9.44 ms, P27 = 54.60 ms (delayed/absent);
- **median somatosensory evoked response** and upper and lower extremity peripheral nerve conduction velocities: normal.

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

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

**Comment**

The neurological findings and history in this patient are typical of adrenomyeloneuropathy, and this diagnosis was confirmed by the abnormally high plasma levels of very long chain fatty acids. In addition, brain MRI studies showed the presence of moderately severe cerebral inflammatory involvement, as occurs in approximately 30% of patients with adrenomyeloneuropathy. The demyelinating or inflammatory lesions affecting the spinal cord and brain stem long tracts that are characteristic of this disorder are the likely causes of the gait disturbance, the prolonged interpeak latencies of the peroneal somatosensory evoked response, and the abnormalities of brain stem auditory evoked response before prednisone treatment. The posterior periventricular lesion noted on MRI indicates that the patient had inflammation or demyelination in our patient. His visual evoked response latencies were unchanged. The visual evoked response became normal (OS/OD, P100 = 106.6/110.0 ms; fig 1). Brain stem auditory evoked response and the brain stem auditory evoked response, with nearly normal or normal amplitudes, reflect demyelination. The reduced interpeak latencies from the brain stem auditory evoked response and the peroneal somatosensory evoked response after treatment indicate remyelination.3 No patients with X-linked adrenoleucodystrophy appear to have spontaneous remissions.4 Therefore the clinical and evoked response improvement is likely to be attributable to prednisone treatment. Although two male patients with adrenomyeloneuropathy showed neurologic improvement after starting on prednisone, neither patient had simultaneous improvement in their evoked responses and MRI.5 Our findings are thus consistent with the hypothesis that steroid replacement therapy ameliorated the inflammation or demyelination in our patient. His improvement with prednisone replacement suggests that a more systematic analysis of the neurophysiological effects of corticosteroid treatment in X-linked adrenoleucodystrophy is warranted.

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LX Zhang, R Bakshi
Department of Neurology, State University of New York at Buffalo, Buffalo General Hospital, 100 High Street, Buffalo, NY 14203, USA

E Fine
Department of Neurology, VA Medical Centre, Buffalo, New York

H W Moser
Kennedy-Krieger Institute and Department of Neurology and Pediatrics, Johns Hopkins University, Baltimore, Maryland, USA

Correspondence to: Dr LiXin Zhang; zlixin@acsu.buffalo.edu

**References**


**Acute anterior radiulitis associated with West Nile virus infection**

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

**Case report**

A 29 year old right handed man with no significant past medical history reported...
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 associated left foot drop and a hip thrust to compensate for significant hip flexor weakness. Sensory examination was normal. He had experience weakness of his left leg, which caused him some difficulty in walking. Howev-er, 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.

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).

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%.$^3$ 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.$^4$ Our report is further differentiated by radiographic evidence which confirmed asymmetrical nerve root involvement with good clinical correlation. The absence of sensory findings can be explained by relative sparing of the dorsal roots on both electrodiagnostic testing and MRI. Finally, the simultaneous onset of constitutional symptoms, hip pain, and leg weakness in our case suggests that the WNV infection can cause motor weakness during the initial viraemia, rather than there being a postviral autoimmune aetiology for the weakness.

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

References

A case of possible autoimmune bilateral vestibulopathy treated with steroids

Bilateral vestibulopathy can have various causes: ototoxicity (mainly caused by aminoglycosides), meningitis, bilateral tumours, neuropathies, bilateral sequential vestibular neuritis, or Menière’s disease. Some types of bilateral vestibulopathy seem to arise from systemic autoimmune processes—for example, systemic lupus erythematosus, poly-chondritis, Cogan’s syndrome, or rheumatoid arthritis. About 20% of cases of bilateral vestibulopathy seem to arise from systemic autoimmune processes—for example, systemic lupus erythematosus, poly-chondritis, Cogan’s syndrome, or rheumatoid arthritis. About 20% of cases of bilateral vestibulopathy seem to arise from systemic autoimmune processes—for example, systemic lupus erythematosus, poly-chondritis, Cogan’s syndrome, or rheumatoid arthritis. About 20% of cases of bilateral vestibulopathy seem to arise from systemic autoimmune processes—for example, systemic lupus erythematosus, poly-chondritis, Cogan’s syndrome, or rheumatoid arthritis. About 20% of cases of bilateral vestibulopathy seem to arise from systemic autoimmune processes—for example, systemic lupus erythematosus, poly-chondritis, Cogan’s syndrome, or rheumatoid arthritis. About 20% of cases of bilateral vestibulopathy seem to arise from systemic autoimmune processes—for example, systemic lupus erythematosus, poly-chondritis, Cogan’s syndrome, or rheumatoid arthritis. About 20% of cases of bilateral vestibulopathy seem to arise from systemic autoimmune processes—for example, systemic lupus erythematosus, poly-chondritis, Cogan’s syndrome, or rheumatoid arthritis. About 20% of cases of bilateral vestibulopathy seem to arise from systemic autoimmune processes—for example, systemic lupus erythematosus, poly-chondritis, Cogan’s syndrome, or rheumatoid arthritis. About 20% of cases of bilateral vestibulopathy seem to arise from systemic autoimmune processes—for example, systemic lupus erythematosus, poly-chondritis, Cogan’s syndrome, or rheumatoid arthritis.

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

Case report

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

Clinical examination showed that the head impulse test (Halmagyi and Curratf) was pathological on both sides. There was no evidence of oculomotor, central vestibular, or cerebellar disturbances. Hearing function was also normal. Caloric irrigation (30° and 44°C) showed a peak slow phase velocity of 4°/s on both sides. The per- and postrotatory nystagmus lasted less than five seconds. An audiogram was normal. High resolution imagistic 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, anticyttoplasmic, or antineuronal antibodies were detected.

On the assumption that an immune dys-
regulation caused the bilateral vestibular dys-
function, 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 autoanti-
bodies 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 charac-
terised by sensorineural hearing loss that is most often rapidly progressive and bilateral, and may be accompanied by vestibular symp-
toms. Diagnosis of autoimmune inner ear dis-
orders, however, is problematic as there is no universally accepted set of diagnostic criteria or diagnostic test.° Our patient had only isolated vestibular signs and symptoms, typi-
cal of a bilateral vestibulopathy (the reported 
clinical presentation). An immunological antedate was likely, as other causes had been excluded and raised titres of inner ear specific antibod-
ies were detected. These decreased in parallel with clinical improvement after immuno-
modulatory therapy.

The treatment trials on autoimmune inner ear disorders that have so far been published have focussed only on hearing loss. A single case shows that isolated vestibular dysfunc-
tion may also be improved by steroids.

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

O Schüler, M Strupp, V Arbousw, T Brandt
Department of Neurology, Ludwig-Maximillians University, Klinikum Grosshadern, Marchioninistrasse 15, D-81366 Munich, Germany
Correspondence to: Dr Michael Strupp; mstrupp@neuro.med.uni-muenchen.de

References

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

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

The disease is characterised by genetic heterogeneity: mutations in two genes (TY-
ROBP and TREM2) encoding different sub-
units 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. Initially sporadic cases have been described in Italy, and a homozgyous 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 two sib-
plings are affected by PLOS.

Methods

After giving their informed consent, all the family members were submitted to neurologi-
cal examination, psychological interview,
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 (Qiagen, 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, D19S607, 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.

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Comment

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

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

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D Soragno, 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 Palestro 3, 27100 Pavia, Italy

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

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

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