LETTERS

Central pontine myelinolysis temporally related to hypophosphataemia

Central pontine myelinolysis (CPM) is known to be associated with the rapid correction of severe hyponatraemia. However, there have been case reports of CPM occurring in normonatraemic patients. 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 132 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. Plasmapheresis was immediately given and potassium, sodium and magnesium supplements, chlorothiazide, and intravenous vitamins including vitamin K and thiamine.

Three days after admission she developed a Staph aureus septicemia secondary to a peripheral venous cannula infection. This required treatment with intravenous cefuroxime and flucloxacinil. 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 dystarhria, 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, dystarhria, 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 absence of normonatraemia, hypokalemia, and hypophosphataemia. In these cases a hypothesis based on osmotic trauma must be questioned.

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

The two patients presented here showed acrose temporal association between severe hypophosphataemia and the development of CPM. Both patients abused alcohol, and the first patient had moderate hyponatraemia with hypokalemia. 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 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 account for less widespread or incomplete apoptosis.

There are useful practical conclusions to be drawn from these 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 mortality1 it would seem prudent to check and treat low serum phosphate concentrations in susceptible patients. This particularly refers to alcohol abusers or malnourished patients treated with intravenous glucose, diuretics, and steroids which may lower serum phosphate concentrations.

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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 tone which resists active stretch and deviates the limb from a straight position, as indicated by legrésistance du cadre nerveux) 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. Physiological 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 methodical approaches with electromyographic (EMG) and biomechanical recordings focused on the relation between muscle EMG and reflex activity and muscle tone during various functional movements. EMG and functional movements: interaction between basic approaches with electromyographic recording and functional movements. Subsequently she complained of headaches and had a clear therapeutic consequence: physical therapy alone in patients with spasticity and use of stretch as a treatment of spastic hypertonia. Phys Med Rehabil Clin N Am 2001;12:747–68.

Intracranial hypertension after chiropractic manipulation of the cervical spine
The aetiology of intracranial hypertension is not fully understood, but CSF leakage from a dural meningeal diverticulum or meningeal sinus 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. 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. 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.
The diagnosis of intracranial hypotension was established by the typical clinical and radiological signs and no additional site of CSF leakage could be identified. If 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 main 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 microfrilloliosis in the context of a connective tissue disorder. 1

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

Before steroid treatment was begun, brain MRI and evoked potential testing were undertaken, as follows:
- **visual evoked response**: OS/OD, P100 = 166.0/159.6 ms
- **brain stem auditory evoked response**: AS, wave I, 2.00 ms; II–V absent; AD, wave I, 1.94 ms; II, 2.88 ms, III–V absent
- **peroneal nerve somatosensory evoked response**: left/right, L3 = 8.64/9.44 ms, P27 = 54.60 ms (delayed)/absent;
- **median somatosensory evoked response** and upper and lower extremity peripheral nerve conduction velocities: normal

Brain MRI showed mild to moderate confluent hypertense 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 neurological findings and history in this patient are typical of adrenomyeloneuropathy, and this diagnosis was confirmed by the abnormal 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 the visual radiations, which probably correlates with the initially abnormal visual evoked response.

Adrenocorticosteroid replacement therapy restored the plasma ACTH level to normal, improved the gait disturbance, and completely corrected the visual evoked response latencies.

Prolonged interpeak latencies of the somatosensory evoked response and the brain stem auditory evoked response, with nearly normal or normal amplitudes, reflect demyelination. The reduced interpeak latencies from the brain stem auditory evoked response and the peroneal somatosensory evoked response after treatment indicate remyelination. 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 neurologic 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 therapy suggests that a more systematic analysis of the neurologic effects of corticosteroid treatment in X-linked adrenoleucodystrophy is warranted.

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Acute anterior radiculitis associated with West Nile virus infection

Our knowledge of neurological syndromes associated with West Nile virus (WNV) infection continues to evolve. Recent reports during the 1999 outbreak in New York City have most commonly described an encephalitis and aseptic meningitis associated with the infection, but muscle weakness was also found to be an unexpected but prominent feature. 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. 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. Sensory examination was normal. He had an antalgic gait, with associated left foot drop and a hip thrust to compensate for significant hip flexor weakness. The remainder of the examination was unremarkable.

Laboratory evaluation included the following normal tests: complete blood counts, metabolic panel, antinuclear antibody, serum immunoelectrophoresis, and HIV-1 western blot. Cerebrospinal fluid (CSF) analysis showed 22 white cells per mm$^3$ (80% lymphocytes), glucose 53 mg/dl, and protein 63 mg/dl. Electrodiagnostic studies of the affected limb were obtained 11 days after the onset of symptoms. These showed motor amplitudes reduced by 79–95% in the left lower extremity when compared with the right. Conduction velocities and sensory amplitudes were normal. Needle examination revealed fibrillations and positive sharp waves in the left tibialis anterior and medial gastrocnemius muscles. There was decreased recruitment and increased firing rate in these muscles, as well as the left quadriceps muscle. Needle examination of the left and right paraspinal muscles was normal. MRI of the lumbosacral spine showed intradural nerve root enhancement greater on the left, affecting L1–S1 (fig 1).

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Suspected aetiologies before the results of WNV testing included an infectious or postinfectious 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.

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

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**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 faccids paralysis associated with WNV. We propose that anterior radiculopathy should be considered in addition to motor neurone pathology when assessing pure motor weakness caused by WNV.

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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, polyarthritis rheumatica, or systemic sarcoidosis. About 20% of cases of bilateral vestibulopathies, however, remain “idiopathic” despite extensive diagnostic workup. Prompted by studies on immune mediated sensorineural hearing loss, we previously demonstrated IgG antibodies against the membranous labyrinth (ampulla, semicircular canal, sacule, and utricle) in sera from eight of 12 patients with “idiopathic” bilateral vestibulopathy, compared with one of 22 healthy controls and none of six patients with “idiopathic” unilateral vestibulopathy, compared with one of 22 healthy controls and none of six patients with “idiopathic” unilateral vestibulopathy. Some of these patients 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 with warm water (44°C) did not cause asymmetry. 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, anticentoplastic, 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 rapidly progressive and bilateral, and may be accompanied by vestibular symptoms. Diagnosis of autoimmune inner ear disorders, however, is problematic as there is no universally accepted set of diagnostic criteria or diagnostic test. One patient had only isolated vestibular signs and symptoms, typical of a bilateral vestibulopathy (the reported recurrent attacks of vertigo at the beginning of the disease are often found in this condition). An autoimmune immunological profile was likely, as other causes had been excluded and raised titres of inner ear specific antibodies were detected. These decreased in parallel with clinical improvement after immunomodulatory treatment.

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

We had hypothesised in our earlier study that some of the so called idiopathic vestibulopathies might be caused by autoimmune inner ear disorders. From the clinical course and response of this patient, we conclude that 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 vestibular failure. If there is evidence of an autoimmune disorder and vestibular failure is not complete, a short term treatment trial should be started to preserve or even improve vestibular function. This, however, needs to be further evaluated in a prospective study on a large group of patients.

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References

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

Poly cystic lipomembranous osteodysplasia with sclerosis leucoencephalopathy (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 leucoencephalopathy. The onset of the clinical manifestations occurs in the third decade of life with focal pathological fractures; later on, symptoms of frontal lobe dysfunction appear, with upper motor neurone involvement and epileptic seizures. In 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 (TYROBP and TREM2) encoding different subunits of a membrane receptor complex in natural killer and myeloid cells have been associated with the disease.1,2 This rare disorder was initially described in Finland and Japan but is now recognised to have a worldwide distribution. In sporadic cases have been described in Italy,3 and a homozygous mutation in the splice donor consensus site at intron 3 of TREM2 has been identified in two affected siblings.4

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

Methods

After giving their informed consent, all the family members were submitted to neurologiological examination, psychological interview, and neuropsychological assessment. No history of alcohol or drug abuse was found in these patients. The parents were from the same geographical area and there was no history of consanguinity.

Genetic analysis

Genetic analysis was performed on the affected family members and controls. DNA was extracted from peripheral blood using standard methods. The only available patient DNA sample was a blood sample taken from the affected mother. The TREM2 gene was amplified by PCR, and the resulting fragments were sequenced using the Big Dye Terminator Kit and an ABI-377 automated sequencer (Applied Biosystems, Foster City, California, USA). The sequences were aligned using Sequencher software (Gene Codes Corp., Ann Arbor, Michigan, USA).

Results

DNA analysis revealed a novel heterozygous mutation (c.2281A>T) in exon 3 of the TREM2 gene, which resulted in a change of a neutral glycine residue in 134 of the protein (G134D). This mutation was not found in 50 normal controls.

Discussion

This is the first report of a familial case of Nasu-Hakola disease with a novel mutation in the TREM2 gene.
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 PLOS 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 TREM2 gene. The mutation changes glutamine 33 to a stop codon (Q33X). 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 PLOS L, 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 PLOS L 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 PLOS L is explained by two different mutations in TREM2 gene. Its prevalence is undetermined because the disease is likely to go unrecognized. 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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