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

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

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A case of possible autoimmune bilateral vestibulopathy treated with steroids

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

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

Case report

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

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

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

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

Comment

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

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

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

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

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

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

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

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

Methods

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

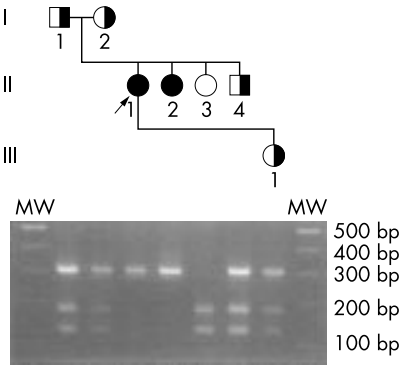

Figure 1 Family pedigree. Black symbols denote affected individuals, white symbols denote unaffected individuals, and half black symbols denote carriers. The arrow indicates the proposita. Segregation of the mutation in exon 2 of TREM 2 gene (191 C→T) was analysed by Pst I site digestion. The mutation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

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

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

Case histories

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

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

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

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

Genetic analyses

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

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

Comment

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

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

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