Late onset MLD with normal nerve conduction associated with two novel missense mutations in the ASA gene

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Metachromatic leukodystrophy (MLD) rarely has its clinical onset in young adults, with a combination of cognitive and behavioural symptoms and peripheral neuropathy. Here we present an exceptional case with very late onset at 42 years of age and no clinical or neurophysiological sign of peripheral neuropathy. Molecular analysis revealed compound heterozygosity for two novel missense mutations affecting conserved residues in the arylsulphatase A (ASA) sulphatase and carboxyterminal domains, resulting in an 89% loss of enzymatic activity. This case indicates that MLD needs to be considered in the differential diagnosis of very late onset white matter diseases, even if not accompanied by peripheral nerve involvement.

METHODS

Patient

A 47 year old male of northern Italian origin, born of non-consanguineous parents, was evaluated for a progressive demyelinating illness started at the age of 42 years. The first symptoms consisted of unpredictable and inappropriate behaviour with bursts of aggressiveness. Occasional loss of spatial orientation heralded a progressive cognitive deterioration. Informed consent was obtained for molecular genetic studies.
RESULTS

Case report

The patient was hospitalised at 46 years of age for diagnostic investigation. Brain magnetic resonance imaging (MRI) showed a diffusely increased T2 signal in the white matter, most prominent in the frontal lobes and near the ventricles, and a thin corpus callosum (fig 1). Electromyography and nerve conduction studies did not reveal any abnormality (table 1). Multimodal evoked potentials (visual, auditory, and somatosensory) also were within normal limits. The electroencephalogram showed widespread epileptiform activity. Based on the above clinical findings, a screening for adult onset leukodystrophies was carried out. Plasma aminoacids, urinary organic acids, very long chain fatty acids, and beta-galactocerebrosidase were all within normal limits. ASA activity in leukocytes was 11.3% of the mean of the controls. A positive essay for urinary sulphatides confirmed the diagnosis of MLD.

At the age of 47 years, the patient was examined by one of the authors (MP). He was quiet and collaborating, but disoriented in time and space. A severe concentration and attention deficit, lack of motor persistence, and lack of perseveration were evident. In addition to these signs of frontal lobe involvement, a moderate memory deficit, acalculia, anosognosia, visuospatial deficits, and a mild comprehension deficit associated with poor verbal output indicated a more global brain dysfunction. There was no ataxia and no focal motor or sensory deficit. Tendon reflexes were symmetrically increased in the four limbs and a bilateral Babinski sign was present.

Molecular genetic studies

The patient was found to be a compound heterozygote for two novel missense mutations in ASA, G293D in exon 5, and C489G mutation in exon 8, and heterozygous for the N350S pseudodeficiency polymorphism in exon 6. The G293D
mutation is localised to the ASA sulphatase domain, in a position that is conserved in other sulphatases and in alkaline phosphatase. The C489G mutation involves a highly conserved cysteine residue near the carboxyl terminus. Analysis of the patient’s mother and maternal uncle revealed both the G293D mutation and the N350S polymorphism, showing that they occurred in a cis configuration. Using PCR amplification of specific alleles, the paternal uncle was not found to carry the C489G mutation. Neither mutation was found in more than 100 unrelated healthy controls from the same region of northern Italy.

**DISCUSSION**

The clinical presentation of our patient was remarkable because of the absence of detectable peripheral nervous system involvement and because of the exceptionally late onset of symptoms in the fifth decade of life. Onset with psychiatric symptoms was otherwise typical for adult onset MLD. Behavioural and cognitive abnormalities still dominated the clinical picture 5 years after onset. At this stage the patient was clearly demented, with global neuropsychological deficits, although the most severe deficits involved frontal lobe functions. Motor deficits and ataxia were markedly absent. The clinical picture was in agreement with the MRI finding of a diffuse leukencephalopathy predominantly affecting the frontal lobes and the periventricular white matter, but not sparing any part of the brain.

The absence of peripheral nervous system involvement is very unusual in adult onset MLD. Two among the 14 cases described by Kappler et al 10 had no detectable peripheral nerve involvement in the very early symptomatic stage of the disease, but only the patients reported by Seidel et al 11 (one case), 12 Brion et al (one case), 13 and Cengiz et al (three cases in one family) 14 continued to have no detectable neuropathy several years into the clinical course.

To our knowledge, our patient is the first case of adult MLD without neuropathy for whom the causative mutations in the ASA gene have been identified. The presence of the pseudodeficiency polymorphism confounded the interpretation of the biochemical analysis of our patient and his family, a situation that has been previously reported. 15 We could in any case demonstrate that our patient has the biochemical abnormality of MLD by showing an increased urinary excretion of sulphatides.

Microdeletions and point mutations in ASA may cause MLD. Milder cases usually have missense mutations that allow some residual enzyme activity. The pathological nature of the two novel missense mutations we identified in our patient was supported by the non-conservative amino acid changes, by the involvement of conserved residues in the ASA protein and by their absence in more than 100 controls from the same population. However, a straightforward genotype–phenotype correlation remains difficult. Despite the confounding effect of the associated pseudodeficiency, it is clear that the patient’s missense mutations led to a less severe enzyme defect than in typical infantile MLD. 16 Accordingly, urinary excretion of sulphatides is also less important, as evaluated by a semi-quantitative essay. However, mild disease can only be part of the explanation for this peculiar phenotype. Intriguingly, the opposite phenotype of exclusive peripheral nerve involvement has also been reported in cases of mild late onset MLD. 17 18 The causative mutation, a homozygous aminoacid change (T286P), was determined for one of these patients. 19

Our observation further extends the phenotype of adult onset MLD. This condition should be tested in all adult patients presenting with an otherwise unexplained leukencephalopathy, particularly if the frontal lobes are most affected, even when onset is as late as the fifth decade and there is no detectable peripheral nerve involvement.

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