

## Clinical Notes

### Juvenile metachromatic leukodystrophy in a boy with epilepsy

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Metachromatic leukodystrophy (MLD) is an autosomal recessive disorder, caused by deficiency of arylsulfatase A (cerebroside sulfatase A, ASA), which results in accumulation of sulfatides, mainly in the brain and peripheral nerves. The estimated frequency of MLD from previous reports is 1 in 40,000 cases. The deficiency in ASA activity is caused by mutations in the ASA gene. The deficiency is systemic and affects other organs, in addition to the nervous system.<sup>1</sup> Metachromatic leukodystrophy presents with progressive mental retardation, behavioral abnormalities, and recurrent seizures. We report a case of juvenile MLD, in a young boy, presenting with epilepsy, and mental subnormality. It is one of the rare metabolic disorders, occurring with epilepsy in this patient, diagnosed in the late stage of the illness.

We present a 14-year-old Pakistani boy, of non-consanguineous parents, of full term normal delivery, with normal early developmental milestones, studied up to the first preliminary class. At the age of 7, he developed declined higher mental function, with slowness in school performance. He developed recurrent abdominal pain, with loss of appetite. He lost weight and had generalized muscle wasting. At the age of 12, he developed recurrent generalized tonic clonic convulsions. Later, he developed generalized tiredness and weakness, with difficulty in walking and developed unsteadiness of gait. Clinical examination showed a generalized thin body mass, with skin and bony appearance, with gross muscles wasting. He had microcephaly with a head circumference of 51 cm, and jerky horizontal nystagmus. He had bilateral pyramidal signs with mild to moderate motor weakness of all 4 limbs. No organomegaly was seen. Laboratory results revealed pancytopenia and megaloblastic anemia, with normal serum vitamin B12, folate levels, and serum arylsulfatase A level of 39 units (normal range: 55-80). Serum very long chain fatty acid level, CSF study, and abdominal ultrasound were normal. Bone marrow biopsy revealed megaloblastic anemia, with no evidence of leukemia or infiltration. The EEG showed abnormal record due to slow and irregular basic activity, with sharp and slow epileptiform discharges, in the fronto-central areas bilaterally. Nerve conduction study showed predominantly demyelinating sensory motor polyneuropathy. Sural nerve biopsy: light microscopy showed focal myelin degeneration of the peripheral nerves and occasional cells, containing metachromatic granules. The electron microscopic study showed focal myelin degeneration of large myelinated fibers, with occasional



**Figure 1** - Axial T2 image at the ventricular level, demonstrates high signal intensity abnormalities (shown by arrows) in the frontal and occipital periventricular white matter. Loss of hemispherical brain tissue is also noted.

cells containing intracytoplasmic lipid globules, as well as lamellar inclusions, and endoneurial fibrosis. These features are of lipid storage disorder, consistent with MLD. An MRI brain showed microcephaly and severe parenchymal loss, with diffuse confluent high signal, white matter changes in the frontal, occipital, and periventricular areas, suggestive of demyelination, consistent with MLD (Figure 1). The clinical picture, physical findings, laboratory results, and radiological appearances were consistent with the diagnosis of MLD. He was treated with anticonvulsants, general supportive care, and other symptomatic treatment. However, his neurological deficits and neuromuscular condition, slowly progressed to severe muscle wasting and he was unable to walk, and confined to a wheelchair in due course. The more specific therapy for MLD, bone marrow transplantation was considered, but due to advanced staging of the illness and his very poor general condition, we could not carry out the special treatment. Due to recurrent intercurrent infections, progressive liver failure and systemic infection, leading to septicemia, unfortunately, he succumbed to death 2 years after the diagnosis. In the presented case, the onset of symptoms was at the age of 7, therefore making it possible to classify this as the Juvenile type of MLD.

We have described the clinical picture, characteristic radiological appearances, enzymatic deficiency, and the various clinical presentations of juvenile MLD. Mental deterioration is often the first symptom. It appears in boys or girls, around 16 years of age. Poor school performances and recurrent school failures are common. Neurological symptoms, ataxia, cognitive, or psychiatric features are misdiagnosed as multiple sclerosis or spinocerebellar heredo-ataxia. Pyramidal and cerebellar symptoms with altered speech will occur. Central and

peripheral neurological symptoms are very characteristic of MLD.<sup>1</sup> Seizures may occur, which in some cases can be the early symptoms, associated with mental deterioration, as seen in our patient. Recurrent seizures are common in MLD and may occur at any stage of the disease, particularly in patients with Juvenile onset. Generalized seizures are more common in patients with late infantile onset, where as partial seizures are more common in those with juvenile onset disease. Although in our patient with juvenile onset MLD, generalized seizures were reported early and difficult to control by monotherapy. Diazepam and nitrazepam are the best anticonvulsants, due to excellent activity against all types of seizures and spasticity.<sup>2</sup> Up to 5 years ago, the radiological diagnosis of leukodystrophy was based on CT scan. Symmetrical involvement of the corticospinal tracts, known as Wallerian degeneration, is better seen on MRI and can be missed on CT scan. More recently, MRI has been used to study the pathology of the white matter diseases, with great success. An MRI seems to be superior in visualizing the extent of the lesions, their precise anatomical localization, and any involvement of the brainstem and cerebellum. In MLD, there are symmetrical confluent areas of hypo intensity in the periventricular white matter and sparing of the arcuate fibers in the beginning. There is no contrast enhancement in this type of leukodystrophy. In some patients, the thalamus, the posterior limb of internal capsule, the cerebellum, and the quadrigeminal plate, show the signal changes.<sup>3</sup> Bone marrow transplantation (BMT) has been advocated as a treatment in an attempt to correct the enzyme deficiency. Such a transplant was performed in 1991, in a 16-year-old girl, with a form of late onset Juvenile MLD, caused by a homozygous P426L mutation in the ASA gene, engraftment was prompted and resulted in constant enzymatic normalization of circulating lymphocytes. During a 6-year follow up period, her condition was subject to major fluctuations, but on the whole, findings show slow neurologic and neurophysiological deterioration.<sup>4</sup> Kidd et al,<sup>5</sup> reported long term stabilization after BMT in Juvenile MLD. Bone marrow transplant was carried out in a 16-year-old boy with juvenile MLD followed for 8 years; he showed no increase in symptoms, no progression of neurological signs, and no neurophysiological deterioration. Brain levels of ASA increased enough to prevent further deterioration.<sup>5</sup> After several decades of research, there was no suitable therapy available for this metabolic disease. Allogenic hemopoietic cell transplantation (HCT) when performed at an early stage of the disease,

may improve some cases. Successful developments of ASA deficient mice models reminiscent of human MLD, have been used in various therapeutic trials such as enzyme replacement, hematopoietic stem cell-based gene therapy and direct injection of ASA expressing viral vectors, into the brain.<sup>6</sup> A recombinant human Arylsulfatase A (rh ARSA) enzyme is available under trial in UK. Oligodendroglial cell therapy in a mouse model is also under trial.

Our report highlights the importance of early diagnosis, in a rare metabolic disorder with the typical radiological appearances and enzymatic deficiency. When a young patient presents with mental retardation and epilepsy, as initial symptoms, MLD should be considered, and it is mandatory to get careful history, clinical examination, appropriate specific biochemical tests; an MRI brain scan should be performed, to obtain an early diagnosis, and avoid morbidity and mortality. Bone marrow transplantation appears to be a feasible treatment in the early stage of the disease. However, there are limitations to recent therapeutic measures, such as gene therapy, BMT, and enzyme replacement therapy.

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