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Case Report

Regression of Motor Skills in an Eight Years Old Boy

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Abstract

The classical late-infantile form is the most common presentation of Metachromatic leukodystrophy (MLD).

An 8 years old boy showed dysphagia, recurrent urinary and stools retention. He has past history of easy fall down and psychomotor regression since 18 months of age.

Brain MRI revealed diffusely abnormal signal of white matter of the brain bilaterally, that may count into demyelinating disease. Blood test revealed slightly low leukocyte arylsulfatase A (ARSA) activity (20% of normal activity). Next Generation Sequencing (NGS) genes panel testing identified compound heterozygous c.178C>Tp.(Arg60Trp) and c.93 G>Ap.(Gly31 1 Ser) variants in ARSA gene. Bone marrow transplantation is not recommended in this form. The prognosis of the patient is poor and is most cases, mortality appear 1 to 7 years after the diagnosis.

Keywords: *Psychomotor Regression; Dysphagia; Urinary and Stool Retention; Ataxia; Spasticity; Dystonia; Metachromatic Leukodystrophy*

Introduction

Metachromatic leukodystrophy (MLD) is panethnic, with reported incidences ranging between 1 in 40,000 and 1 in 170,000, except in specific ethnic groups with higher frequency.

The classical late-infantile form is the most common. The inheritance of this disease is autosomal recessive. The symptoms start between 10 and 25 months (before 30 months) and is progressive to death in 1 to 7 years. The first manifestations are loss of acquired motor skills, especially walking, which becomes unsteady. Examination at this time reveals hypotonia and genu recurvatum. Deep tendon reflexes are diminished or even absent and severe spasticity develops. Delay or deterioration in walking, optic atrophy and grayish discoloration of the retina, symmetrical decrease in the density of cerebral white matter and elevated cerebrospinal fluid protein. Arylsulphatase A activity is severely impaired; excretion of sulphatides is increased. The latter can differentiate between true arylsulphatase A deficiency and pseudodeficiency that occurs in 7 - 15% of the general population.

The age at onset of the juvenile form ranges between 3 and 14 years. May present with psychiatric symptoms. Failure in school, behavioral problems or disturbance of cognitive function may precede motor abnormalities, especially in patients with a later onset (> 6 years). Progressive difficulties in walking, with pyramidal signs and peripheral neuropathy, together with cerebellar ataxia constitute the most

common presentation, but various other symptoms can occur, such as hemiplegia, dystonia and choreoathetosis. Seizures may develop. If done before neurologic symptoms develop, bone marrow transplantation is a successful treatment, at least for some patients. Magnetic resonance imaging (MRI) shows involvement of the posterior central white matter with sparing of the subcortical areas; the posterior part of the corpus callosum is also usually involved. Hagberg has viewed the progression of the disease in four stages, the initial picture representing stage I. In stage II the patient is no longer able to stand but can sit. There is ataxia and truncal titubation. Speech deteriorates and is dysarthric or aphasic, and mental function regresses. Muscle tone is increased in the legs, and deep tendon reflexes are exaggerated. Ocular nystagmus develops, and ophthalmoscopy reveals optic atrophy. In stage III, the patient develops spastic quadriplegia and is confined to bed. There may be decerebrate or decorticate rigidity or dystonic movements. Seizures develop in about a third of patients. Pharyngeal muscle coordination is lost, and there is difficult with feeding and with the airway. Mental deterioration continues, and speech is lost. The child may continue to respond to parents and smile. In stage IV contact is lost. The patient is blind and cannot swallow. Tube feeding is required. Death results usually from pneumonia.

Two distinct types of adult MLD have been identified. In the first group, patients have predominant motor disease, with pyramidal and cerebellar signs, dystonia and peripheral neuropathy, or isolated peripheral neuropathy. In the second group, behavioural and psychiatric problems (often confused with schizophrenia) are the presenting symptoms, followed by dementia and spastic paresis. Adult MLD refers to patients presenting after puberty. Onset may be as young as 15 years-of-age or as late as 62. Survival may be for five or 10 years or longer.

The clinical laboratory evaluation of patients with established MLD is notable for elevation of the concentration of protein in the cerebrospinal fluid. The level may be normal early in infantile disease, but it rises progressively to levels of 100 mg/dL or higher. This is true also for the younger-onset juvenile patients; while later-onset juvenile and adult-onset patients usually have normal levels of protein, though there have been a few with elevated concentrations. The electroencephalograph (EEG) may be abnormal, especially in those with seizures. There may be diffuse slowing or spike discharges, often focal. The EEG tends to be normal in the adult-onset patient. Motor nerve conduction is slowed.

Neuroimaging by computed tomography (CT) or magnetic resonance (MR) is consistent with loss of myelin and increase in water. Low density on CT and hyperintense T2 images on magnetic resonance imaging (MRI) are visible in periventricular white matter indicative of leukodystrophy. Later there is evident atrophy.

Treatment of patients with MLD has been largely supportive. Baclofen may be useful in reducing spasticity. Bone marrow transplantation has been employed in a number of patients. It appears most useful in pre-symptomatic or early symptomatic patients. It may even accelerate progression in rapidly deteriorating patients. Best results were in juvenile and adolescent forms [1-4].

Case Report

An 8 years old boy was admitted in the pediatric ward because of dysphagia, recurrent urinary and stools retention, easy fall down and psychomotor regression.

He started to walk alone at 12 months of age but at 18 months, he easily falls down. Physiotherapy was prescribed during a couple of months because he showed flat. Recently, around 6 months ago before admission, started to have constipation, urinary retention and dysphagia, with progressive worsening.

He is the elder son of an unrelated healthy couple. He born by normal delivery, 39 weeks of gestational age.

Birth weight: 2.880 kg. Apgar10/10/10. His 6 years old younger brother is healthy. On physical examination, we found in our patient, ataxia, left eye astigmatism, right eye refractive error, abdominal distention secondary to bladder retention, dystonia and spasticity. Rou-

tine blood test was unremarkable. Brain MRI revealed diffusely abnormal signal of white matter of the brain bilaterally, that may count into demyelinating disease. (Figure 1). All clinical and radiological features were consisting with MLD and some test were performed for confirmation. The results showed slightly low leukocyte arylsulfatase A (ARSA) activity (20% of normal activity). Next Generation Sequencing (NGS) genes panel testing identified compound heterozygous c.178C>Tp.(Arg60Trp) and c.93 G>A p.(Gly31 1 Ser) variants in ARSA gene. Sangers sequencing of exon 1 and exon 5 of ARSA revealed NM_00487.6:c[178C>T];[931G>A] NP_000478.3:p.[(Arg60Trp)];[(Gly31 1 Ser)]. The sangers sequencing confirms the result of NGS genes panel. Both parents are carriers. The younger brother is normal. Our patient started treatment with baclofen, keppra and clonazepam with support from physiotherapy.

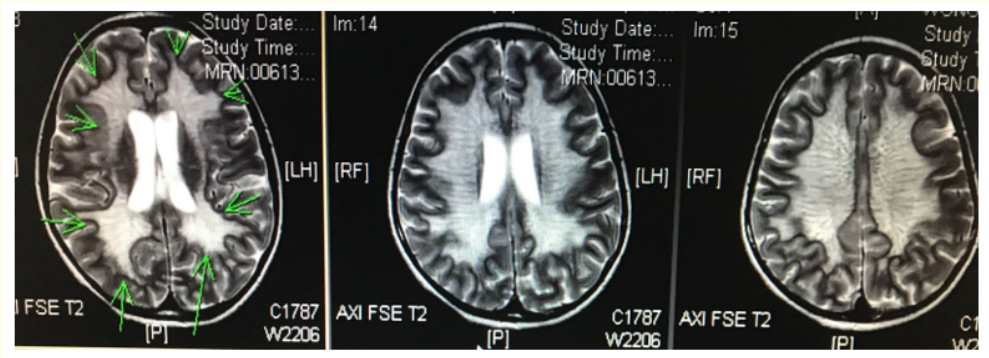

Figure 1: *Brain MRI revealed diffusely abnormal signal of white matter of the brain bilaterally, that may count into demyelinating disease.*

Discussion

Our case is compatible with late-infantile form, the most common presentation. The symptoms started at 18 months of age, with the patient fallen down in many occasions. The diagnosis was flat feet as a cause of this situation. With the evolution of the years, the psychomotor regression appeared and neurologic signs started, like ataxia, dystonia, spasticity and stools and urine retention become more frequent. Brain MRI showed typical signs of MLD. The enzyme and molecular studies confirmed the diagnosis. The treatment is direct to the symptoms. Bone marrow transplantation is not recommended in this form. The prognosis of the patient is poor and is most cases, mortality appear 1 to 7 years after the diagnosis. Prenatal diagnosis and genetic counselling are indicated for the next pregnancy [1,3].

Conclusion

Psychomotor regression in a child is part of the main symptoms of many Lysosomal Storage Diseases. When is associated with neurological signs, metachromatic leukodystrophy need to excluded. Brain MRI is an important examination to confirm leukodystrophy and the final diagnosis can be obtained by leucocyte arylsulfatase A (ARSA) activity and molecular study of ARSA gene.

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