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Original article

Peripheral neuropathy as the sole initial finding in three children with infantile metachromatic leukodystrophy

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ABSTRACT

Metachromatic leukodystrophy (MLD) is a progressive white matter disease caused by arylsulfatase A deficiency. Demyelination in the nervous system is detected by cerebral magnetic resonance imaging (MRI) and neurophysiological studies.

We present three children with infantile MLD, who had difficulties in standing and walking with absent reflexes. Protein levels in cerebral spinal fluid (CSF) were elevated and nerve conduction studies revealed slowing down of motor nerve conduction velocity. Initial cerebral MRIs showed no white matter changes. Consecutively, all three children developed clinical symptoms of neurodegenerative disease. Follow-up MRI and arylsulfatase A testing led to diagnosis of MLD.

We conclude, that in young children who present with an acute/subacute demyelinating polyneuropathy, MLD is a differential diagnosis.

1. Introduction

Metachromatic leukodystrophy (MLD) is an autosomal recessively inherited progressive white matter disease caused by arylsulfatase A deficiency.[1] In MLD, sphingolipid sulfatide accumulates in lysosomes leading to progressive demyelination of peripheral and central nervous systems (CNS). In CNS, lipid storage affects both oligodendrocytes and neurons causing astrogliosis and activation of microglia.[1] Demyelination is recognized by cerebral magnet resonance imaging (MRI).[2] There is no ''disease-modifying'' causal therapy, although intrathecal infusion of arylsulfatase A, restriction of vitamin A (cofactor of sulfatide synthesis), bone marrow and stem cell transplantation have been attempted.[1,3]

Different types of MLD according to onset and clinical progression exist. The late-infantile form is the most common (1:40.000). After normal development, symptoms start with weakness in lower extremities, difficulty in walking and the

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absence of deep tendon reflexes, indicating peripheral neuropathy. Regression of motor and cognitive abilities, bulbar paralysis, sudden changes of motor tone with screaming attacks usually follow.[1]

Initial clinical presentation without any abnormal radiological CNS findings is very unusual. We report three patients with MLD who presented with a demyelinating polyneuropathy in the absence of white matter changes in the MRI.

2. Case reports

2.1. *Patient 1*

Development was normal up to 14 months, when difficulties in standing and walking appeared with muscular hypotonia and the absence of deep tendon reflexes. No cognitive impairment was noted. Slowing of motor nerve conduction velocity (NCV) indicated demyelinating peripheral polyneuropathy. Nerve and muscle biopsy at 2 years showed a mixed axonal and demyelinating neuropathy of unknown origin.

At 2 years and 9 months the boy was unable to stand. Cerebral spinal fluid (CSF) revealed an increased protein level 110 mg/dl without cells. MRI scan of the brain and spine was normal. Presumed diagnosis was chronic inflammatory polyneuropathy (CIPD). Subsequently, he was treated with prednisolone with improvement of symptoms. Unfortunately, he was lost to follow-up until the age of 8 years – he had severe dystrophy, tetraparesis, swallowing problems and bilateral opticus atrophy. Cerebral computer tomography (cCT) showed brain atrophy with periventricular hypodense areas. The diagnosis of MLD was established by arylsulfatase A deficiency in leukocytes. At the age of 10 years aspiration pneumonia caused death.

2.2. *Patient 2*

After normal development, the girl showed weakness of lower extremities at 18 months. She had muscle atrophy with reduced deep tendon reflexes in lower extremities. Cerebral MRI was normal (Fig. 1a and b). Spinal MRI showed a thickening of cauda equina and nerve roots as seen in CIDP. Protein was increased in CSF (1242 mg/l (normal: 150–450 mg/l)) but no cells. Electrophysiological studies showed slowing of sensory and motor NCV. Muscle/nerve biopsy showed neuropathic changes and signs of subacute de- and remyelination without inflammatory infiltrates suspicious of hereditary motor and sensory neuropathy (HMSN) type I (Charcot-Marie-Tooth), which was not confirmed by molecular studies. Due to clinical deterioration and diagnosis of CIDP two courses of intravenous immunglobuline (0.5 g/kg for 5 days every 4 weeks) were given without clinical improvement. Subsequently, the patient showed complete loss of speech and ambulation. Cranial MRI showed prominent leukodystrophy (Fig. 2a and b). Arylsulfatase A level was deficient in lymphocytes. MLD was also confirmed by genetic testing. Pneumonia caused death at the age of 43 months.

2.3. *Patient 3*

After a normal development, the boy at the age of 14 months showed unstable gait with frequent falls. Neurological evaluation with 23 months revealed loss of deep tendon reflexes in the lower extremities. Cerebral and spinal MRI was normal. Neurometabolic work-up (organic acids in plasma, CSF and urine; lactate, pyruvate in plasma and CSF, isoelectric focussing of transferrin, long-chain fatty acids, acylcarnitine, carnitine) revealed no abnormalities. CSF showed elevation of protein concentration (112 mg/dl), electrophysiological studies slowing of sensory and motor NCV. Congenital

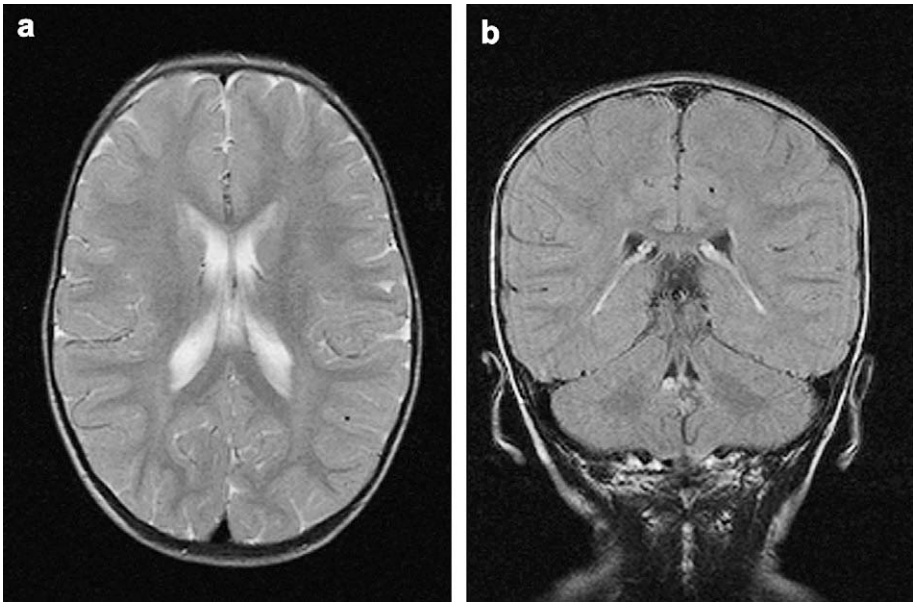

Fig. 1 – cMRI of Patient 2 at the age of 24 months shows no abnormal findings (a) axial T_2-weighted image (b) coronal flair weighted image.