Journal of the Neurological Sciences 338 (2014) 214–217

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Short communication

A homozygote for the c.459+1G>A mutation in the *ARSA* gene presents with cerebellar ataxia as the only first clinical sign of metachromatic leukodystrophy

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ARTICLE INFO

Article history:
Received 4 September 2013
Received in revised form 3 December 2013
Accepted 19 December 2013
Available online 31 December 2013

Keywords:
Cerebellar ataxia
Metachromatic leukodystrophy
Arylsulfatase A
Magnetic resonance imaging
Lysosomal storage disease
Neurometabolic disease

ABSTRACT

Metachromatic leukodystrophy (MLD) is a rare lysosomal disorder caused by deficient activity of arylsulfatase A or the lack of saposin B, which results in the accumulation of sulfatide in the oligodendrocytes and in the Schwann cells. Three main clinical types of MLD can be distinguished according to the age of onset and the dynamics of clinical outcome: late infantile, juvenile, and adult. We report on a case of late infantile MLD presenting with cerebellar ataxia as the only first clinical sign preceding even changes in white matter visible in MR imaging. The diagnosis was made on the basis of successive MRI, characteristic of demyelination, which developed in the course of the disease, and on the results of the following biochemical and molecular analyses. Very low residual activity of arylsulfatase A was demonstrated in blood leukocytes and the patient was a homozygote for a common mutation c.459+1G>A in the *ARSA* gene. Since cerebellar ataxia is a relatively common but unspecific neurological symptom in toddlers, it is recommended that MLD be considered as part of the differential diagnosis even if the initial neuroimaging studies are normal and ataxia is the only clinical symptom of the disease.
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1. Introduction

Lysosomal storage diseases are a group of genetically inherited metabolic disorders caused by pathological changes in the lysosomal apparatus. Metachromatic leukodystrophy (MLD) belongs to the group of sphingolipidoses and is caused mainly by the storage of sulfatide due to deficient activity of arylsulfatase A (ARSA) or a sphingolipid activator protein — saposin B. Sulfatide accumulates most intensively in oligodendrocytes and in Schwann cells, leading to the demyelinating process of the central and peripheral nervous systems. Excess of sulfatide is excreted in urine and bile (for a review see [1]).

Three clinical types of MLD can be distinguished based on clinical outcome and the dynamics of disease progression. In the late infantile form, symptoms appear between the 12th and 30th months of age. Typically, first clinical signs include weakness, hypotonia, clumsiness, frequent falls, toe walking, and slurred speech. As the disease progresses, inability to stand, difficulty with speech, deterioration of mental function, increased muscle tone, pain in the arms and legs, generalized or partial seizures, compromised vision and hearing, and peripheral neuropathy are frequent. The onset of juvenile form MLD is between 4 and 14 years. Decrease of school performance and behavioral problems are followed by clumsiness, gait problems, slurred speech, and incontinence. Seizures may also occur. Progression is similar to but slower than the late-infantile form. In adult patients first clinical signs are problems in school or job performance, personality changes or neurologic symptoms (weakness and loss of coordination progressing to spasticity and incontinence) are observed. Seizures predominate initially and peripheral neuropathy is common. The disease course is variable and may last over two to three decades. The final stages of all three forms of the disease are similar (for a review see [2]). All clinical symptoms result from progressing demyelinating processes.

Metachromatic leukodystrophy can be diagnosed by the measurement of ARSA activity in isolated blood leukocytes or cultured skin fibroblasts and by the detection of sulfatide excretion in urine sediment. For the correct diagnosis the presence of the ARSA pseudodeficiency (PD) allele must be checked. In individual homozygous for the ARSA pseudodeficiency allele (genotype PD/PD) or in compound heterozygotes for an MLD causing mutation in the *ARSA* gene and the pseudodeficiency allele (genotype MLD/PD), the activity of arylsulfatase A measured in vitro with an artificial substrate is low (10–30% of normal activity). Unlike MLD patients, these individuals do not develop any clinical symptoms of MLD [3,4]. Additionally, homozygotes for ARSA PD allele do not excrete elevated amounts of sulfatide. The ARSA

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0022-510X/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jns.2013.12.030

pseudodeficiency allele is a polymorphism in the *ARSA* gene caused by two A>G transitions at nt 1788 and nt 2723 of the *ARSA* gene, which result in the loss of the N-glycosylation site and loss of the poly-A signal. In rare cases, when ARSA activity is preserved but sulfatide excess is excreted, the saposin B deficiency must be excluded [1]. The purposes of this case study were to extend the knowledge about atypical MLD onset and to allow an accurate early diagnosis. Since MLD is inherited autosomally recessively, correct diagnosis permits detection of heterozygotes and genetic counseling for family members.

2. Case report

The boy was born as the first child to healthy, young, nonconsanguineous parents. As the newborn and an infant he developed normally until 18 months. He could walk independently when he was 13 months old and his gait was skilled. At the age of 20 months he was admitted to the Department of Neurology at the local hospital with signs of cerebellar ataxia associated with a febrile illness. On admission, neurological examination revealed gait unsteadiness, muscle hypotonia, nystagmoid eye movements, and intentional tremor of hands. Tendon reflexes were preserved. MR imaging in SE/T1-weighted, FSE/T2-weighted, FLAIR and DWI sequences showed no focal changes in the brain. As the infectious etiology of this state was suspected, investigations for antibodies against TORCH, adenoviruses and *Borrelia burgdorferi* were performed, all of which were negative. Vinpocetine was administered because of its properties to enhance cerebral blood-flow, neuroprotective effects, and potential anti-inflammatory activity and quick regression of clinical symptoms (e.g. retreat of nystagmus) was observed. Improvement of the patient's general condition and normal MRI led to a working diagnosis of parainfectious cerebellar ataxia. At that time, neither lumbar puncture nor other additional investigations were performed.

After two months, the patient was admitted to the Clinic of Neurology of Child and Adolescents, IMC (Warsaw, Poland) because of recurrent ataxia, nystagmus, paresis of lower limbs with hyperactive deep tendon reflexes, presence of the bilateral Babinski sign, and spasticity pronounced more in the left side of the body than the right. Additionally, a developmental decline was observed. He was no longer able to say several single words (like 'mom', 'dad', 'give') or to build simple phrases. He did not display any interest in the environment. His manual fine skills deteriorated. He also stopped understanding previously familiar situations or orders or to name body parts. When the boy was 23 months old, successive MR imaging detected widespread symmetrical demyelination of periventricular and central white matter of both cerebral hemispheres without brain atrophy. The U-fibers were spared. The corpus callosum was affected. There was no involvement of the posterior limbs of internal capsules (PLICs), brain stem and cerebellum. No contrast enhancement of the lesions was found. The tigroid pattern of white matter involvement was highly suggestive of metachromatic leukodystrophy (Fig. 1). The activity of arylsulfatase A in blood leukocytes was 11.8 nmol/mg protein/h (normal range 148 ± 52.2) at 37 °C and 16 nmol/mg protein/h at 0 °C (normal range 150 ± 65.7). The reaction was performed with the use of 4-nitrocatechol sulfate as the substrate [5]. The screening for four mutations in the *ARSA* gene, most common in the Polish population, was done by PCR-RFLP method [6]. The search for mutations c.459+1G>A, p.P426L, p.I179S, and c.1204+1G>A resulted in the detection of mutation c.459+1G>A in the homozygous state in proband and in heterozygous state in both of his parents. Mutation c.459+1G>A is of a severe type, leading to the loss of the splice donor site at the border of exon 2 and the following intron in the *ARSA* gene. Homozygotes for this mutation present with the late infantile form MLD. The presence of ARSA pseudodeficiency allele was excluded by means of a PCR-RFLP method [7]. Sulfatide excretion was not analyzed in this patient because of difficulties in obtaining the 24 h urine collection.

Subsequently, the patient showed quick, progressive psychomotor regression. He developed spastic tetraparesis with the bilateral Babinski sign and hyperactive deep tendon reflexes.

3. Discussion

Cerebellar ataxia is a frequently observed but unspecific neurological symptom. The affected exhibit disturbances in balance, broad base gait, uncoordinated movements of extremities and eyes. Among numerous diseases which manifest with cerebellar ataxia [8], genetically inherited neurologic diseases, including inborn errors of metabolism, are distinguished. In this group, the following diseases should be considered: respiratory chain disorders, ataxia telangiectasia, abetalipoproteinemia, Refsum disease, gangliosidosis GM1, gangliosidosis GM2, metachromatic leukodystrophy, Krabbe disease (globoid leukodystrophy — GLD), Gaucher disease, sialidosis, and cerebrotendinous xanthomatosis.

Metachromatic leukodystrophy is among the rare neurometabolic disorders with a frequency of 1:40 000 to 1:120 000 live births. According to the results obtained in the Polish population it appears that MLD may be underdiagnosed, since the birth incidence was estimated at 1:24 390 live births on the basis of carrier frequency in the general population, whereas the incidence calculated from the number of cases of MLD diagnosed from 1975 to 2004 was 1:263 158 live births [9]. The clinical outcome of MLD is associated with pathological processes occurring in the white matter of central and peripheral nervous systems. Sulfatide, which accumulates in MLD, is a major component of the myelin sheet. It participates in the building of the lipid rafts which are a part of cell membranes. Lysosulfatide, a deacylated derivative of sulfatide, also accumulates in the tissues of MLD patients. Recently, a model has been proposed, where lysosulfatide should play a similar role as psychosine in lipid rafts disruption (psychosine is another cytotoxic compound and a lyso-lipid found in Krabbe disease). According to this model, the accumulation of lyso-lipids causes disorganization of myelin components, inflammation, synaptic dysfunction, and axonal defects [10,11]. So far, the pathomechanism of MLD is not elucidated but cerebellar ataxia is one of the leukodystrophy signs.

In the patient with the late infantile type MLD described here, the first and solely clinical symptoms in the form of cerebellar ataxia were present before any pathological lesions were seen on MRI. Additionally, his state improved temporarily during a few days, so that the parainfectious etiology of the disease was considered and the medical examination was stopped. A sudden relapse of the disease directed us to immediate further investigations, including MRIs, enabling the diagnosis. The tigroid pattern of white matter involvement that we found in our patient on the second MRI is typical of two entities: MLD and GLD. In GLD however PLICs are usually affected and cerebral atrophy is observed, which were not the case in our patient. GLD patients also show early involvement of the cerebellar white matter, hili of dentate nuclei and brain stem which were intact in our case [12]. The interesting finding was that the patient with cerebellar symptoms had no lesions in the cerebellum, while his supratentorial brain was affected. Similarly, Haberlandt described three children with infantile MLD, who had difficulties in standing and walking with absent reflexes. Initial cerebral MRIs showed no white matter changes, just as in our patient. Subsequently, all three children developed clinical symptoms of neurodegenerative disease. Follow-up MRI and ARSA testing led to the diagnosis of MLD [13]. Other authors also described isolated peripheral neuropathy, present as the sole, clinical symptom in adult MLD patients [14–16]. In all three MLD types, neuropathy may occur however spasticity and hyperactive reflexes are more often observed [17]. It should be also noted that in the late infantile form of MLD neuropathy is often an early presenting symptom with weakness presenting before ataxia or cognitive regression and spasticity may become more prominent later in the disease course.

We would like to emphasize that MLD, although rare, should be taken into consideration and simple enzymatic assay for ARSA activity

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