

Homozygote for mutation c. 1204 + 1G > A of the ARSA gene presents with a late-infantile form of metachromatic leukodystrophy and a rare MRI white matter lesion type

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Abstract. The metachromatic leukodystrophy (MLD) – causing mutation c. 1204 + 1G > A damages an intron-exon splice site recognition sequence. This results in a complete loss of enzymatic activity of arylsulfatase A (ARSA) protein molecules. We have found a late-infantile type MLD-patient to be homozygous for this mutation, which was not reported earlier, but is consistent with previous suggestions. Interestingly, the cerebral magnetic resonance imaging (MRI) in this patient displayed linear or punctuate structures radiating in the demyelinated white matter, which resembled the patterns described in Pelizaeus-Merzbacher disease. It should be emphasised that whenever a cerebral MRI demonstrates the ‘tigroid’ or ‘leopard-skin’ demyelination pattern not only Pelizaeus-Merzbacher disease, but also metachromatic leukodystrophy diagnosis should be considered; this suggests the necessity of ARSA activity estimations in patients with such specific MRI patterns.

Key words: arylsulfatase A, lysosomal disorder, metachromatic leukodystrophy, magnetic resonance imaging.

Deficiency of a lysosomal enzyme – arylsulfatase A (ARSA; EC 3.1.6.8) causes metachromatic leukodystrophy (MLD; OMIM 250 100) – a severe metabolic, neurodegenerative disorder, inherited as an autosomal recessive trait. Storage of ARSA substrates, above all – sulfatide (galactosylceramide-3-O-sulfate) leads to demyelination in the central and peripheral nervous systems and in consequence to clinical manifestations. Three main clinical types of MLD are distinguished according to age of onset and clinical course: late-infantile (severe, 0–2 years), juvenile – with subtypes of early (4–6 years) and late juvenile

(8–16 years), and adult (mild, with onset after puberty) (von Figura et al. 2001).

The patient, a boy, is one of three children in a family with no history of neurological disorders. His parents are consanguineous (a common great grandfather). The pregnancy and labour progressed without complications. The child developed normally through the age of 14 months, when first symptoms of developmental regression were observed and the boy started to scramble. When he was 18 months old, symptoms of speech worsening and spasticity in lower limbs were noted. In 25th month of life he was disabled to

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walk. At the age of 3 years he developed rotatory horizontal nystagmus, hypotonia, muscle weakness, areflexia in all limbs. No abdominal reflexes, a positive Babinski reflex, a positive Rossolimo reflex, pseudobulbar palsy followed by progressive quadriplegia with spastic and flaccid characteristics were seen. Currently, when he is 6 years old, the patient is no longer able to sit without support. His contact with the environment is limited to smiling and single syllables. After informed consent neurological, biochemical and molecular examinations were performed.

ARSA activity in isolated peripheral blood leukocytes (Lee-Vaupel and Conzelmann 1987) measured at 37°C was 11.7 nmol mg⁻¹ protein/hr, at 0°C it was 4.5 nmol mg⁻¹ protein/18 hr (control values: 105–30 nmol mg⁻¹ protein/hr at 37°C; 262–80 nmol mg⁻¹ protein/18 hr at 0°C). Thin layer chromatography revealed huge amounts of sulfatide in urine (qualitative assay) (Ługowska et al. 1997).

The genomic DNA was obtained from leukocytes and tests for eight most common MLD-causing mutations were performed by means of PCR-RFLP methods: c. 459 + 1G > A, p.P426L, p.I179S, p.A212V, p.R84Q, p.S96F, c. 1204 + 1G > A, 1401_1411del11bp, and for

strated abundant, diffused, hyperintensive lesions in the white matter of brain hemispheres and corpus callosum. These changes, displaying the character of demyelination, were localised symmetrically (Figure 1).

The above findings confirmed the diagnosis of late-infantile type MLD in the investigated patient.

To our knowledge this is the first MLD patient homozygous for c. 1204 + 1G > A reported so far. This mutation was found by Fluharty in a late juvenile patient in heterozygosity with mutation p.I179S, and also described in another three out of 100 MLD patients in heterozygosity with other MLD-causing mutations accounting for 2% of prevalence (Fluharty et al. 1991). We have identified this mutation in another two out of 39 unrelated MLD patients from Poland: in one late-infantile patient in heterozygosity with an unidentified MLD-causing mutation, and in one late juvenile MLD patient – in heterozygosity with mutation p.I179S. This gives the 4/78 i.e. 5% prevalence of c. 1204 + 1G > A in the examined Polish MLD patients (data not shown), which is higher than that described earlier by Fluharty et al. Mutation c. 1204 + 1G > A damages an intron-exon splice site recognition sequence,

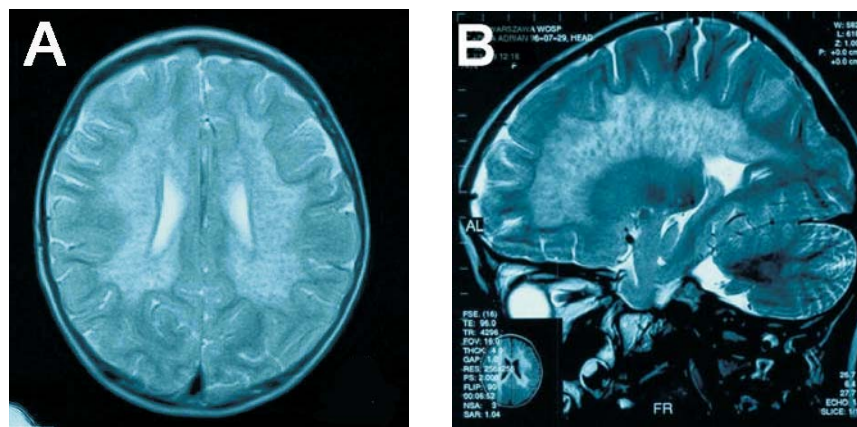


Figure 1. T2-weighted MR image demonstrates the punctuate ('leopard skin') and a radiating ('tigroid') pattern: A – axial appearance, B – sagittal appearance

the ARSA-pseudodeficiency allele (Berger et al. 1997; Gieselmann et al. 1991). This analysis has shown the presence of mutation c.1204 + 1G > A in homozygosity and the absence of the ARSA-pseudodeficiency allele in the proband.

On electrophysiological examination of peripheral nerves a decreased motor nerve conduction velocity was found, visual and auditory evoked potentials (VEP, BAEP) results were abnormal, indicating a demyelinating neuropathy of senso-motoric character. Cerebral MRI demon-

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resembled the patterns described in Pelizaeus-Merzbacher disease, which is often diagnosed on the basis of MRI appearance and clinical course (molecular analysis, as well as the estimation of N-acetylaspartylglutamate in urine or the cerebrospinal fluid is rather rare) (Burlina et al. 2001). The so-called 'tigroid' or 'leopard-skin' appearances have been reported only twice in MLD-patients suffering from different types of the disorder and it seems that these specific MRI white matter lesions are not frequently found in MLD-patients (Faerber et al. 1999; Kim et al. 1997).

It cannot be excluded that the peculiar MRI phenotype depends on other genetic or epigenetic factors. It should be emphasised, however, that whenever a cerebral MRI demonstrates the 'tigroid' or 'leopard-skin' demyelination pattern, not only Pelizaeus-Merzbacher disease, but also metachromatic leukodystrophy diagnosis should be considered; this suggests the necessity of ARSA activity estimations in patients with such a specific MRI pattern.

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