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LATE INFANTILE TYPE OF METACHROMATIC LEUKODYSTROPHY CAUSED BY NOVEL COMBINATION OF HETEROZYGOUS ARSA MUTATIONS

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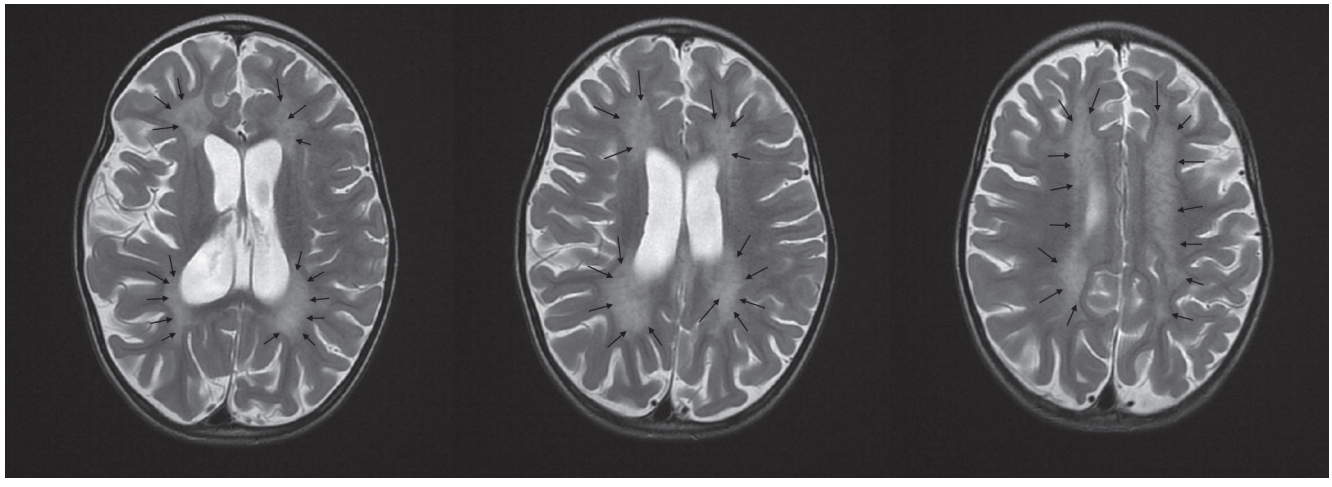

Figure 1. MRI of endocranium revealed bilaterally symmetric, increased signal intensity of the white matter. Tigroid pattern of the white matter with linear normal intensity was present within the white matter that has been spared from the demyelination.

Key words: metachromatic leukodystrophy, magnetic resonance imaging, arylsulfatase A, mutation analysis, genotype-phenotype correlations.

We describe a 3-year-old girl who was diagnosed with metachromatic leucodystrophy by genetic mutation analysis. She was born at the end of a full term pregnancy that had no complications. Her parents were healthy and non-consanguineous. BW 3950 g, BL 52 cm, HC 35 cm, AS 9/10. Early development was uneventful. Nevertheless, in the 2nd year, she developed deterioration of mental function. She had rapid speech regression, became weak, and was unable to stand and walk. During the next 6 months disorder progressive worsened, muscle tone generally increased to the rigidity. She deteriorated to profound psychomotor retardation. MRI revealed a bilateral periventricular leukoencephalopathy with cerebral atrophy (Fig. 1). Mutation analysis of the arylsulfatase A gene (ARSA) encoding enzyme arylsulfatase A revealed a compound heterozygosity. The first mutation is splicing c.684+1G>A; p.? in intron 3 and the second one is missense mutation c.827C>T; p.Thr276Met in exon 4 in ARSA gene each in heterozygous state.

Metachromatic leucodystrophy is a rare autosomal recessive lysosomal storage disease caused by mutations at the locus 22q13.33. Specifically, mutations result in arylsulfatase A deficiencies. This enzyme normally functions within lysosomes, degrading newly synthesized cerebroside- 3-sulfate into cerebroside and sulfate. Intralysosomal accumulation of cerebroside- 3-sulfate leads to progressive demyelination of white matter throughout the central and peripheral nervous system. The prevalence of MLD was estimated to be 1-9/1.000.000. Approximately 50-60% of patients have the late infantile form. Both of the mutations have been reported as disease-causing mutations previously, but not in the form of compound heterozygosity. According to our best knowledge, this combination of ARSA mutations has been revealed for the first time. This report expands clinical variability of MLD and may have implications for genotype-phenotype correlation in MLD.

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