

# Atypical clinical course in juvenile metachromatic leukodystrophy involving novel arylsulfatase A gene mutations

**Banu Anlar\*** MD, Hacettepe University Faculty of Medicine, Department of Paediatric Neurology, Ankara, Turkey.

**John S Wayne** PhD, Department of Pathology and Molecular Medicine, McMaster University;

**Barry Eng** BSc, Molecular Diagnostic Genetics, Hamilton Regional Laboratory Medicine Program, McMaster University Medical Centre, Hamilton, Ontario, Canada.

**Kader Karli Oguz** MD, Hacettepe University Faculty of Medicine, Department of Radiology, Ankara, Turkey.

\*Correspondence to first author at Hacettepe University Faculty of Medicine, Department of Paediatric Neurology, Ankara, Turkey 06100.

E-mail: banlar@hacettepe.edu.tr

A male and female with juvenile metachromatic leukodystrophy (MLD) with unusual manifestations are presented, each involving a novel arylsulfatase A gene mutation. One patient demonstrated acute intermittent encephalopathic episodes for 1 year after having received the diagnosis of MLD at the age of 6 years. The other patient presented at the age of 5 years with acute hemiparesis, which was diagnosed as acute disseminated encephalomyelitis and resolved in 3 weeks. After 2 years of remission he started to show progressive neurological deterioration. The episodic manifestations in both patients were associated with acute, resolving cerebral lesions on magnetic resonance imaging accompanying or preceding the classical demyelinating lesions of MLD. The diagnosis of MLD was based on arylsulfatase A enzyme activity levels and genetic analysis, and after the exclusion of neurological conditions such as encephalitis, vasculopathy, or mitochondrial disorders. The pathogenesis of this previously undescribed finding in MLD is unknown but might be related to a susceptibility of myelin to acute damage.

Metachromatic leukodystrophy (MLD) follows an invariably progressive course after onset. We present two cases of juvenile MLD with acute, resolving cerebral lesions in addition to the classical demyelinating lesions of MLD, and discuss possible underlying mechanisms.

## Case report

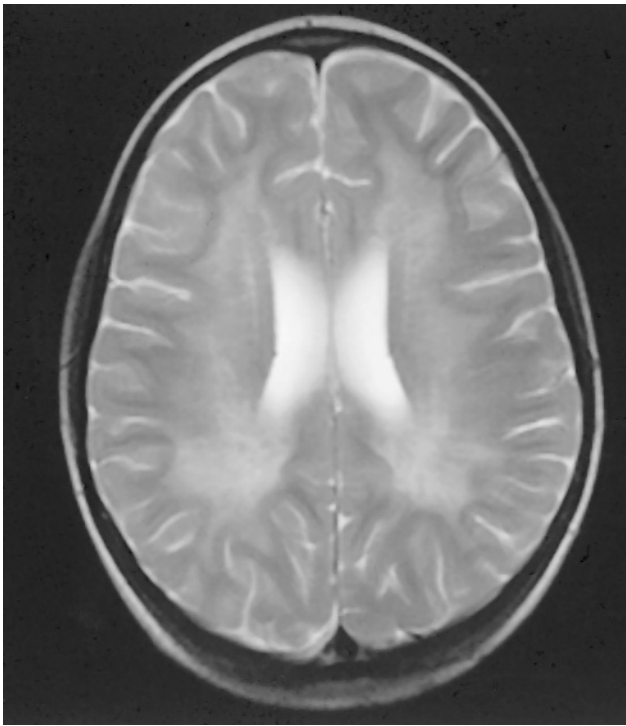
### PATIENT 1

A previously healthy 6-year-old female, single child of non-consanguineous parents, presented with gait disturbance of 45 days. A wide-based gait, diminished patella and ankle reflexes, extensor plantar responses, and slight tremor on finger-to-nose test were observed. Nerve conduction velocity was diminished on electroneuromyography. Cerebrospinal fluid (CSF) contained elevated protein but no cells. Arylsulfatase A (ARSA) activity was 9nmol/s/mg protein (normal range 50–990nmol/s/mg protein). Magnetic resonance imaging (MRI) showed symmetrical T2 hyperintensities involving the periventricular and deep white matter and corpus callosum representing demyelination, and T2 hypointense stripes within the abnormal white matter, representing preserved areas (Fig. 1).

The symptoms showed little progression for 1 year. She then started to experience relapses and remissions, beginning with left focal seizures associated with right frontotemporal discharges on electroencephalogram. CSF findings were

See end of paper for list of abbreviations.

unchanged. MRI showed a right, contrast-enhancing occipital lesion involving cortex and subcortical white matter (Fig. 2).

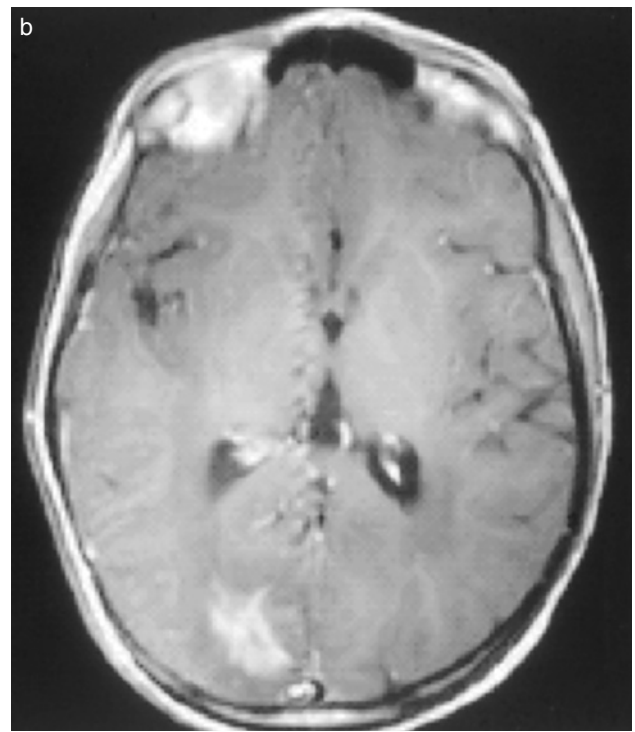
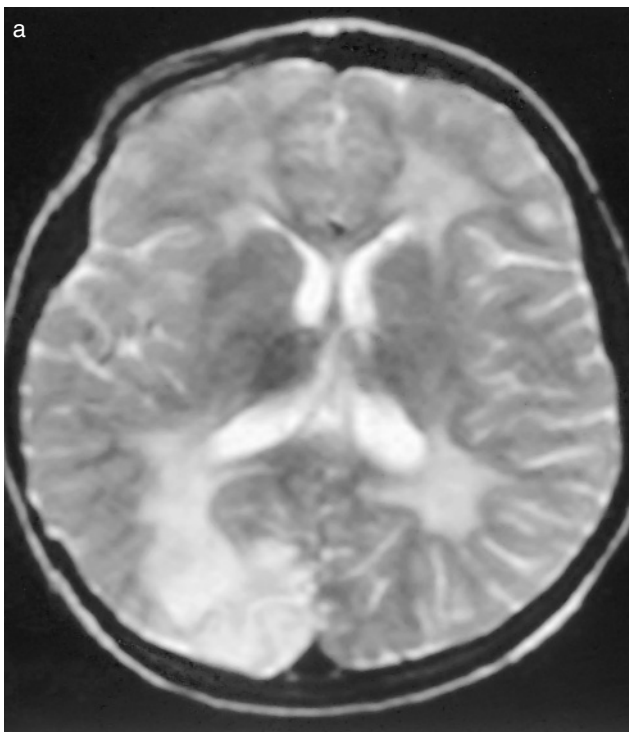


**Figure 1:** Bilateral hyperintense cerebral white matter on transverse  $T_2$ -weighted turbo spin-echo (TR/TE; 5170/115ms) image. TR, time to repeat; TE, time of echo.

She was treated with acyclovir for a presumed diagnosis of encephalitis and recovered in 10 days. However, 2 days later she was readmitted with diplopia, headache, and vertigo, followed by loss of consciousness and anisocoria within 12 hours. On cranial MRI the right occipital lesion had disappeared; instead, the pons, red nuclei, and pyramidal tract in the mesencephalon had increased T2 signal intensity (Fig. 3a) with intense contrast enhancement (Fig. 3b). Routine laboratory investigations, CSF and serum cultures, and viral antibody titres were negative except for high CSF protein (178mg/dl). She was treated with anticonvulsant and antiviral drugs, and returned to her clinical baseline in 42 days.

Three episodes of vomiting, ataxia, tremor, or left hemiparesis, each lasting 1 to 2 weeks, occurred within 1 year, with no intercurrent infection, medication, or other systemic factors. Further metabolic tests, including serum and CSF lactate levels, urinary organic acids, and mutation analyses for mitochondrial diseases, were negative. On the next MRI obtained 5 months after the first episode, red nuclei abnormalities of previous MRI had disappeared, but swelling and T2 hyperintensity localized to the right cerebral peduncle, together with new T2 hyperintensities in the right thalamus, posterior limb of the internal capsule, and basal ganglia had appeared. These recent lesions resolved again with partial clinical recovery. MRI findings were consistent with MLD: T2 signal abnormalities with stripes in periventricular white matter, centrum semiovale, and corpus callosum remained unchanged during a further 2-year follow-up.

The ARSA gene was analyzed by using allele-specific amplification refractory mutation system (ARMS) assays for several common MLD alleles and the pseudodeficiency (PD) allele, followed by nucleotide sequence analysis of the exons and



**Figure 2:** A hyperintense lesion. (a)  $T_2$ -weighted turbo spin-echo (TR/TE; 4000/100ms) image; (b) contrast enhancement on  $T_1$ -weighted spin-echo (TR/TE; 550/15ms) image on right occipital cortex. TR, time to repeat; TE, time of echo.



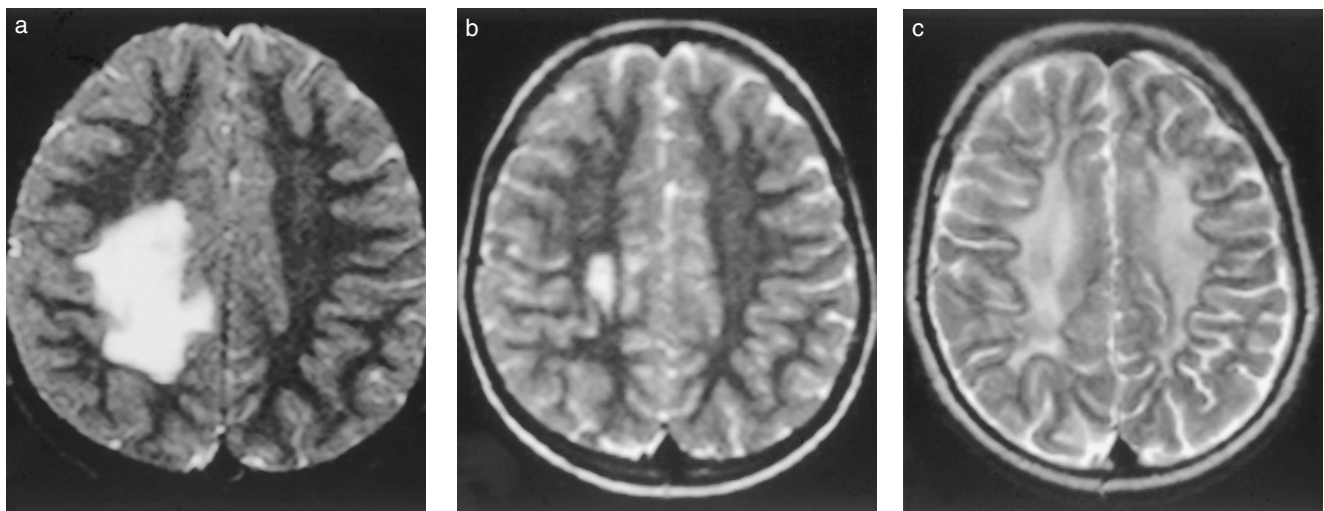
alteration would reduce or abolish ARSA activity. This is a conserved domain within which several other missense mutations have been reported in patients with MLD, including p.Pro426Leu (Polten et al. 1991), p.Leu428Pro (Regis et al. 1997), p.Pro425Thr (Marcão et al. 1999), and p.Tyr429Ser (Eng et al. 2003).

PATIENT 2

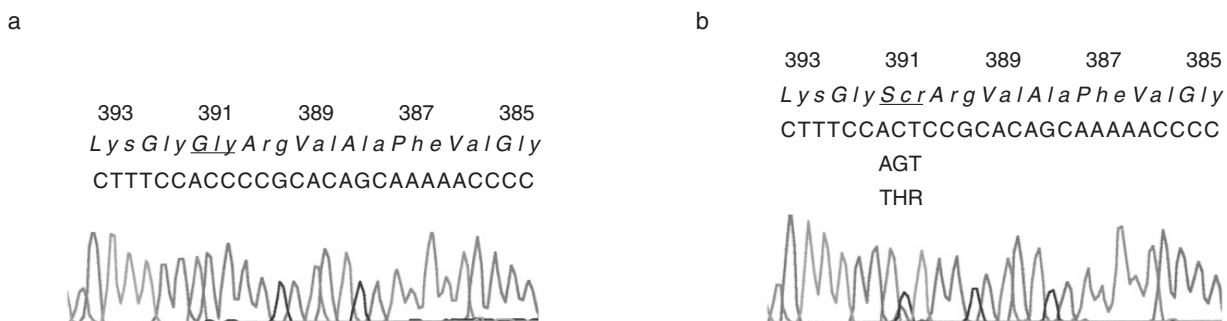
Patient 2, a male currently 11 years old, presented at the age of 5 years with a 1-day history of left hemiparesis. Cranial MRI showed a T<sub>2</sub>-hyperintense, non-enhancing edematous lesion in the right centrum semiovale (Fig. 5a) that resolved significantly 3 weeks later (Fig. 5b) and was interpreted as being compatible with an acute demyelinating lesion, probably acute disseminated encephalomyelitis (ADEM). He was discharged with complete resolution of hemiparesis. Preschool psychometric evaluation with the Stanford–Binet test revealed normal IQ. Attention deficit, hyperactivity, impaired

short-term memory, and visual perception noticed during his first years at school were interpreted as sequelae of ADEM. Two years later his parents complained about diminishing school performance. The Wechsler Intelligence Scale for Children–Revised revealed a total IQ score of 50. Cranial MRI at that time demonstrated bilateral symmetrical periventricular T<sub>2</sub> hyperintensities extending to centrum semiovale (Fig. 5c). ARSA activity was 1.5 nmol/s/mg protein, confirming the diagnosis of MLD. A more detailed family history revealed a degenerative disorder in a paternal uncle who had died at the age of 29 years. Parents were second cousins. The patient is currently being followed-up clinically and shows slow intellectual and motor deterioration.

Comprehensive sequence analysis demonstrated that the proband is homozygous for a missense mutation that alters amino acid residue 391 (Fig. 6). Position 391 is polymorphic in the normal population, with the two common alleles being Thr (ACT) and Ser (AGT; Polten et al. 1991). The mutation in



**Figure 5:** Large edematous lesion in right centrum semiovale. (a) T<sub>2</sub>-weighted turbo spin-echo (TR/TE; 3800/105ms) image; (b) T<sub>2</sub>-weighted images obtained 3 weeks later, in which lesion has resolved; (c) 4 years after first episode, T<sub>2</sub>-weighted imaging revealed diffuse demyelination of centrum semiovale.



**Figure 6:** (a) Reverse nucleotide sequence of patient 2 showing homozygosity for c.1071A>G mutation; (b) reverse nucleotide sequence of an unaffected individual who is heterozygous for common polymorphism at residue 391 (Ser or Thr). Sequence analysis confirmed that both parents of patient 2 are heterozygous for this mutation (not shown).

the proband changes residue 391 to Gly (GGT) and is most probably due to a single base change (c.1071A>G) on an allele having Ser at position 391. This mutation has not previously been reported in patients with MLD, nor have we observed it in normal healthy samples ( $n > 100$ ).

### Discussion

Juvenile MLD manifests between 4 and 12 years of age and, despite some phenotypic variation within and between families, shows a relentlessly progressive course (Haltia et al. 1980, MacFaul et al. 1982). Relapsing–remitting MLD has been reported in a 48-year-old patient but not in children (Sadeh et al. 1992). Certain leukodystrophies can present with acute symptoms and signs after infection or trauma; however, remissions are unexpected (McGuinness et al. 1996). Patient 1 had an unusual course, with exacerbations and remissions. The first exacerbation was interpreted as encephalitis, or an autoimmune reaction or metabolic decompensation triggered by an infection. Enhancing deep gray and white matter lesions were seen in another relapse for which no triggering factors were detected. Those additional findings were dynamic: they fluctuated in correlation with clinical status. The interpretation of MRI included a toxic–metabolic process; however, exogenous toxins were unlikely in view of the history and the protracted clinical course, and investigations for endogenous metabolic toxins or mitochondrial disorders were unrevealing.

Patient 2 showed an acute attack with well-documented resolution before classical findings were established. Again, MRI findings subsided with remission, to evolve to typical MLD lesions and clinical course. The first episode might have represented an initial manifestation of MLD; however, strict unilaterality and clinical and radiological remission contradict this possibility. In the absence of diagnostic tests for ADEM, this disorder cannot be eliminated for the first episode. It is unknown at present whether the myelin in a preclinical MLD patient is more susceptible to autoimmune attacks.

Our cases suggest that juvenile MLD may present with atypical, sometimes episodic, symptoms and findings. The relation between these clinical findings and the novel mutations remains to be confirmed in other patients.

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### List of abbreviations

ADEM	Acute disseminated encephalomyelitis
ARSA	Arylsulfatase A
CSF	Cerebrospinal fluid
MLD	Metachromatic leukodystrophy

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