Where Leukodystrophy and Storage Disorder Meet: A Rare Cause of Neurodegeneration

Dear Editor,

Multiple sulfatase deficiency (MSD) is an important leukodystrophy that should be considered in any child with clinical features of a storage disorder and neuroimaging showing white matter involvement. Ichthyosis and cherry-red spot lesions in the eye are important clinical clues to the diagnosis of MSD. We present here an interesting case to highlight this point and review the cases described from India (n = 7, including the index case).

A 4-year-old boy presented with global developmental delay and skin lesions noted in early infancy. At 18 months of age, he was able to sit and walk with support, wave bye-bye, and speak 6–7 words. By the second year of life, he gradually developed autistic features, language regression, progressive motor impairment, and recurrent head drops. With treatment, the head drops remitted by the third year of life. Electroencephalograph at that time showed frequent bilateral fronto-central inter-ictal discharges. Currently, he could sit with support, had tightness of lower limbs, limited vocalization, impaired vision, and abnormal skin with hyperpigmentation over the limbs and the trunk.

On examination, he had poor visual fixation and following restricted interaction with the mother, incomprehensible sounds, microcephaly (head circumference 47 cm), coarse facial features, and generalized ichthyosis over trunk and limbs [Figure 1], generalized spasticity, bilateral ankle contractures and hyperreflexia. There was no organomegaly. Fundus showed healed cherry-red spot. Skeletal survey showed anterior beaking in one lumbar vertebra, and widened distal metaphysis of left ulna with mild irregularity. Electroencephalogram was normal. Magnetic resonance imaging (MRI) of the brain revealed bilateral symmetrical hyperintensities in periventricular white matter suggestive of a leukodystrophy [Figure 2a-h]. Skin biopsy showed orthokeratosis with follicular plugging in epidermis and scanty lymphomononuclear inflammatory infiltrates in the dermis consistent with ichthyosis. Nerve conduction study did not show peripheral neuropathy. A clinical diagnosis of leukodystrophy with

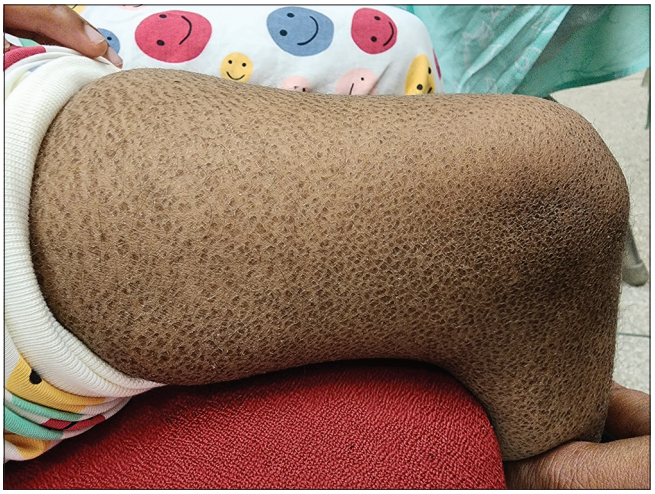

Figure 1: (a) Clinical photograph showing ichthyosis (fish-like scales) in the index case

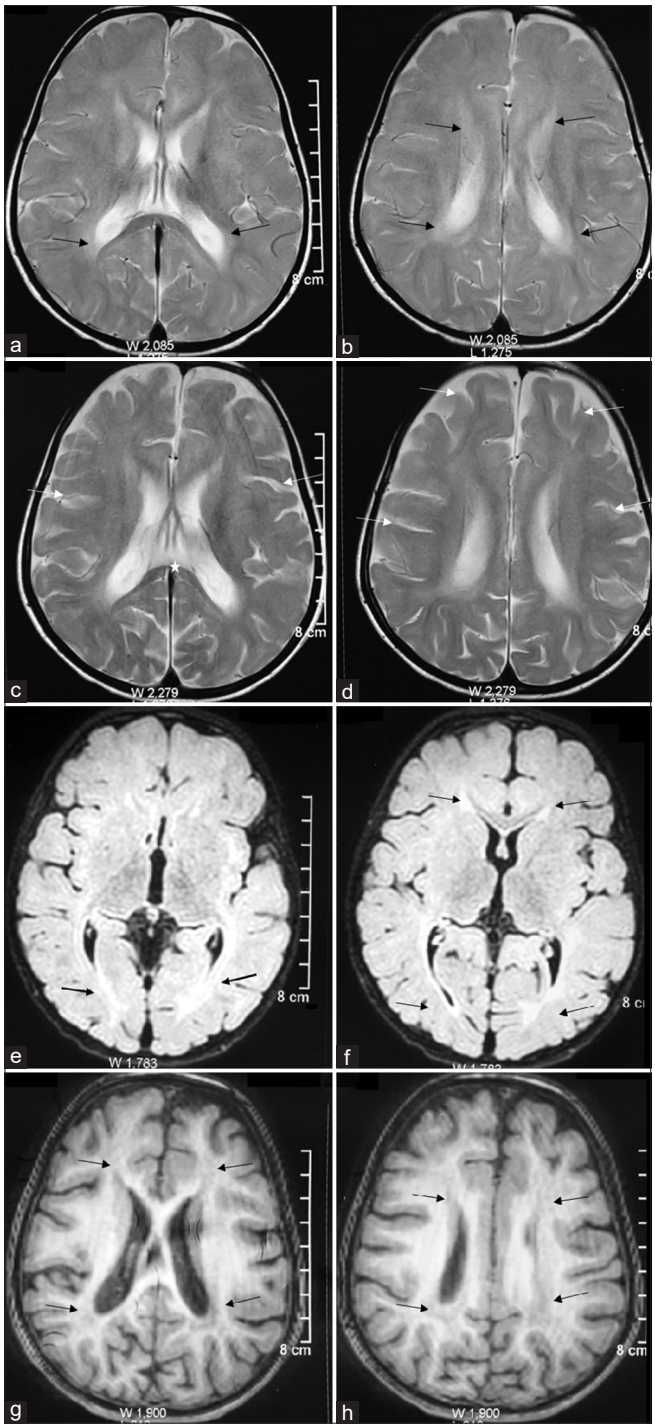

Figure 2: (a-h) Serial MRI scans of the brain (a-b) Axial T2w images show presence of T2w hyperintensities in bilateral periventricular region (black arrows), mild diffuse cerebral atrophy, and thinning of corpus callosum. Three-year follow-up MRI with axial T2w images (c-d) show progression of bilateral symmetrical hyperintensity in periventricular white matter, widened sulcal spaces (white arrows) with corpus collosum volume loss (star) suggestive of brain atrophic changes. The corresponding T2-FLAIR images (e-f) show similar hyperintensities in the white matter (arrows) and the same areas are hypointense on axial T1w images (g-h)

ichthyosis such as Sjögren-Larsson syndrome and MSD was considered. Genetic sequencing showed compound heterozygous variation in the sulfatase modifying factor 1 (*SUMF1*) gene at exon 3 (c.451A > G, p. Lys151Glu) and exon 5 (c.691dup p.Trp231LeufsTer11) confirming the diagnosis of MSD.

MSD is an uncommon, autosomal-recessive, neurodegenerative disorder of the lysosomal metabolism that shares clinical characteristics with sphingolipidosis, mucopolysaccharidosis, and other sulfatase deficiencies. The *SUMF1* gene encodes for the formylglycine-generating enzyme which helps in posttranslational activation of sulfatases.[1] Loss of sulfatase activity causes glycosaminoglycan and sulfatide storage in the lysosomes since the bulk of sulfatases is localized there. A common enzymatic deficiency affects numerous pathways, which causes a wide range of clinical manifestations forming the basis of the pathophysiology of MSD. The mutated formylglycine generating enzyme fails to activate sulfatases post-translationally, which causes variable clinical manifestations and increased excretion of glycosaminoglycans, oligosaccharides, and sulfatides in the urine. The lack of steroid sulfatase causes the typical ichthyosis in the skin. Clinically, MSD has three subtypes. The most severe type of MSD, known as neonatal MSD, begins in the neonatal period with severe cardiac valvular disease and dysostosis multiplex, which progresses quickly to death during the first 2 years of life. The most prevalent form, known as the infantile form, manifests as gradual neuromotor regression in the second year of life, as in the index case. The juvenile form is least common and presents with subacute and milder clinical presentation of psychomotor retardation and neurological deterioration.[2] Organomegaly, corneal clouding, retinopathy with vision loss, hearing loss, recurrent infections, gingival hypertrophy, joint stiffness, carpal tunnel syndrome, neuropathy, and leukodystrophy are additional symptoms of the infantile and juvenile types. Overall, <150 cases of MSD have been reported worldwide with very few cases of MSD from India (n = 7) which are summarized in Table 1. Treatment is mainly supportive and multidisciplinary.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Table 1: Review of children with MSD described from India (*n*=7)

Reference	No of patients	Case details	Genetic details
1. Index case, 2023	*n*=1, genetically confirmed	4-year-old boy with global developmental delay followed by neuroregression, ichthyosis, autistic features, epilepsy, visual impairment, microcephaly, coarse facial features, spasticity, ankle contractures, and hyperreflexia, healed cherry-red spot and dysostosis multiplex, leukodystrophy and absence of organomegaly	- *SUMF*1 gene - Compound heterozygous - Exon 3 (c.451A>G, p. Lys151Glu) and exon 5 (c.691dup p.Trp231LeufsTer11)
2. Sheth *et al*., 2023[3]	*n*=2, one case was genetically confirmed, second case confirmed by enzymatic assay.	Case 1: 6-year-old male with ichthyosis, irritability, poor social response, thinning of corpus callosum and, speech regression. Case 2: 2.5-year-old male with ichthyosis, leukodystrophy, and facial dysmorphism	- *SUMF*1 gene - Homozygous - Missense variant - Exon 7 (c.860A>T, p.Asn287Ile)
3. Gandhi *et al*., 2022[4]	*n*=1, genetically confirmed	An 11-month-old girl with neonatal presentation: intrauterine growth restriction, dysmorphism, intermittent breathing and feeding difficulty, failure to thrive, microcephaly, laryngomalacia, global developmental delay, generalized hypotonia, hemivertebrae, and butterfly vertebra	- *SUMF*1 gene - Homozygous - Missense variant - Exon 9, (c.1043C>T, p.A348V)
4. Nalini and Christopher, 2004[2]	*n*=1, confirmed by enzymatic analysis	A male child with myoclonic jerks, global developmental delay followed by cognitive decline, microcephaly, ichthyosis, hepatomegaly, spasticity, and ataxia, and diffuse cerebral and cerebellar atrophy. increased urinary excretion of mucopolysaccharide	--
5. Christopher and Nalini, 2002[5]	*n*=1, same case as reference[2] above by the same authors	A male child with myoclonic jerks, global developmental delay followed by cognitive decline, microcephaly, ichthyosis, hepatomegaly, spasticity, and ataxia, and diffuse cerebral and cerebellar atrophy, and increased urinary excretion of mucopolysaccharide	--
6. Bharucha *et al*., 1984[6]	*n*=2, confirmed by enzymatic assay	Case 1: 6-year-old boy with neuroregression, spasticity, microcephaly, ichthyosis, pectus excavatum, growth retardation and hepatomegaly, absent deep reflexes, and presence of metachromatic granules in myelin sheath in sural nerve Case 2: 2.5-year-old boy with neuroregression, growth retardation, microcephaly, pectus carinatum, hepatomegaly, ichthyosis, hypotonia, reduced deep tendon reflexes, and presence of metachromatic granules in myelin sheath in sural nerve	--

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