Child Neurology: Sjögren-Larsson syndrome

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Sjögren-Larsson syndrome (SLS), an autosomal recessive disorder of lipid metabolism, was first described in Vasterbotten County, Sweden.[1] The worldwide prevalence is not known, but in Sweden, the estimated prevalence is only 0.4 per 100,000 population.[1] Deficiency of fatty acid aldehyde dehydrogenase (FALDH) causes an accumulation of fatty alcohols and fatty aldehydes, leading to altered cell-membrane integrity and an increase in biologically active lipids, and primarily affects skin, eyes, and the CNS.[2] The clinical triad consists of congenital ichthyosis, spastic diplegia, and intellectual disability.[2] Focused research has unraveled biochemical pathways and genetic abnormalities underlying the pathogenesis of this disorder, paving the way for novel treatment strategies.[2] We describe an infant with genetically established SLS and discuss clinical, radiologic, genetic, and biochemical features of this rare disorder.

CLINICAL CASE This 4-year-old boy from the south Indian state of Kerala, born to nonconsanguineous parents presented with global developmental delay. Antenatally, labor was threatened at 24 weeks of gestation. However, pregnancy continued, and he was born by normal vaginal delivery at 34 weeks. His birth weight was 2.8 kg, and he had neonatal jaundice and sepsis. His skin was dry and scaly from birth. Between 10 months and 3 years of age, he had 4 episodes of febrile seizures. From 3 years of age, he developed unprovoked generalized tonic-clonic seizures every 1 to 2 months. His milestones at 4 years included standing with support, babbling, and recognizing parents.

On examination, he was conscious and dull and had intermittent smile, drooling, and generalized ichthyosis (figure, A–C). Hair and nails were normal. He had photophobia but could fix and track light and respond to sound. Ocular fundi and extraocular movements were normal. Generalized spasticity, exaggerated stretch reflexes, and extensor plantars were noted. At 6 years of age, he developed increased spasticity and contractures at the knees and ankles and became bed-bound. The frequency of generalized tonic-clonic seizures was reduced with sodium valproate, but he developed frequent myoclonic jerks.

Hemogram, hepatic, renal, and thyroid function tests; lipid profile; and calcium, phosphorus, alkaline phosphatase, creatine kinase, lactate, uric acid, and homocysteine were normal. Tandem mass spectrometry screening for amino acidemias, organic acidemias, and disorders of fatty acid oxidation was normal. Urine screening did not reveal abnormal metabolites. Echocardiogram, ECG, and nerve conduction studies were normal. EEG showed slowing of background. Brain MRI at 1 year of age showed mild diffuse leukoencephalopathy (figure, D and E). Repeat brain MRI at 4 years showed progression of white matter changes without enhancement or restriction (figure, F–M). Brainstem and cerebellum were spared. Magnetic resonance spectroscopy (MRS) showed a prominent lipid peak at 1.3 ppm and another smaller lipid peak at 0.9 ppm (figure, N).

Targeted exome sequencing of *ALDH3A2* showed a heterozygous nonsense mutation in exon 4 (c.529C>T), resulting in a stop codon and premature truncation of protein at codon 177, and another heterozygous single base pair deletion in exon 1 (c.126delG), resulting in frameshift and premature truncation of protein and 64 amino acids downstream to codon 43. This was validated by Sanger sequencing. His father was heterozygous carrier of a c.529C>T variant, while his mother was heterozygous for c.126delG. The clinical features and course were consistent with SLS and are further supported by compound heterozygous mutation in *ALDH3A2*.

DISCUSSION The salient features in our patient are preterm delivery, ichthyosis, developmental delay, photophobia, seizures, spasticity, progressive loss of motor function, and compound heterozygous mutation in *ALDH3A2*. A wide variety of mutations, e.g., missense, deletion, and rarely insertion mutations, in *ALDH3A2* have been reported in SLS. Mutations are homozygous or compound heterozygous affecting both alleles of *ALDH3A2* and result in loss of enzyme activity.[1] Among patients of European descent, 943C→T and
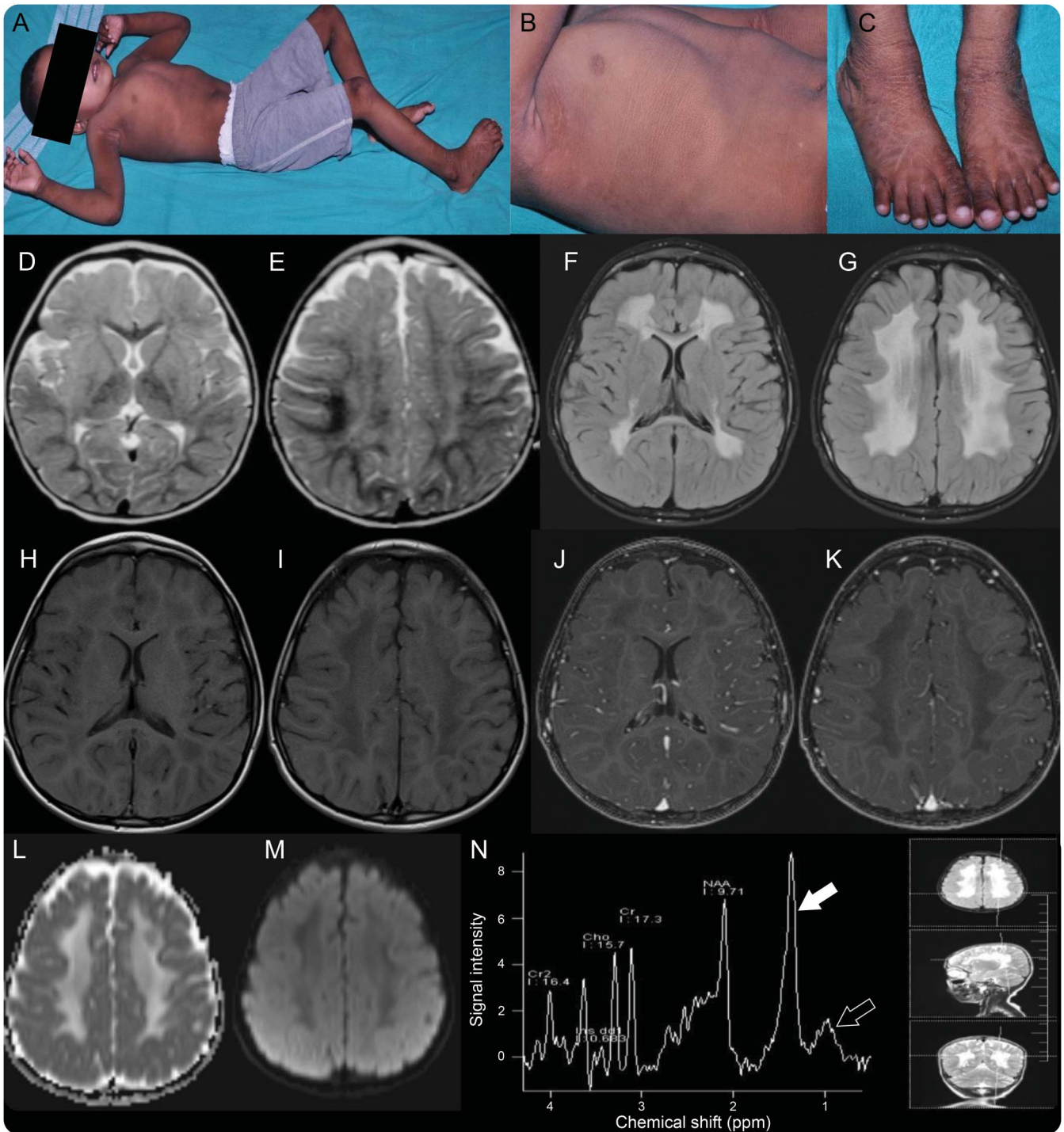
Clinical features at 6 years of age (A–C). The patient is bed-bound and has generalized ichthyosis sparing the face, spasticity, and contractures at the knee and ankle (A). Note the brownish scaly lesions over the trunk (B) and distal extremities (C). Axial sections of the brain (D–M). Mild hyperintensity is seen in supratentorial white matter in T2-weighted sequences at 1 year of age (D and E). Increase in white matter involvement at 4 years of age with hyperintensity involving the inner fibers of the corpus callosum and posterior limb of the internal capsule (F) and white matter in the periventricular and lobar white matter (F and G) in fluid-attenuated inversion recovery sequences. These areas are hypointense in axial T1-weighted sequences (H and I) and do not enhance in postcontrast sequences (J and K). Apparent diffusion coefficient (L) and diffusion-weighted imaging (M) show facilitated diffusion of affected regions. Magnetic resonance spectroscopy (N) reveals a prominent lipid peak at 1.3 ppm (solid arrow) and another smaller peak of lipid at 0.9 ppm (open arrow).

1297-1298delGA have the highest prevalence.[1,3] Our patient had compound heterozygous mutation in *ALDH3A2*; one of the mutations, c.529C>T, has previously been reported,[4] while the other mutation, c.126delG, is novel. Genetic heterogeneity contrasts with the fairly uniform clinical phenotype.

Mutations in *ALDH3A2* result in deficiency of FALDH, a member of the aldehyde dehydrogenase

family, which are a group of enzymes involved in oxidizing aldehydes to their corresponding carboxylic acids, depending on their subcellular location and tissue distribution. FALDH located in human microsomes catalyzes oxidation of medium- and long-chain fatty aldehydes. FALDH has highly conserved regions in humans and other species. All clinical manifestations, e.g., ichthyosis, retinal changes, and abnormalities on brain MRI, are linked to abnormal accumulation of fatty alcohols and fatty aldehydes secondary to FALDH deficiency. Furthermore, FALDH also plays a role in metabolism of leukotriene B4 (LTB4). It is hypothesized that increased urinary excretion of LTB4 by the fetus in amniotic fluid may trigger premature labor by inducing inflammatory response; however, definite evidence for the same is lacking.[2] Accumulation of LTB4 in the skin is thought to cause pruritus. However, Zileuton, a leukotriene antagonist, does not consistently improve pruritus, and the actual cause of pruritus is unknown.[5]

Normal lipid metabolism is essential for normal structure and function of the stratum corneum. In SLS, skin becomes ichthyotic in an attempt to restore normal barrier function.[2] Skin histology shows hyperkeratosis, acanthosis, and papillomatosis. Differential diagnoses of congenital ichthyosis are trichothiodystrophy, neutral lipid storage disease, Conradi-Hünermann-Happle syndrome, Gaucher disease, keratitis-ichthyosis-deafness syndrome, and Netherton syndrome, among others.[6] Ichthyosis in SLS is diffuse and occurs at birth, and skin appears erythrodermic in the neonatal period. Skin appears lichenified and yellowish–dark brown, particularly in the flexures.[2] Hypohidrosis may lead to heat intolerance.[2]

Retinal abnormalities are common, manifest after 3 years of age, and include perifoveal glistening crystalline deposits in ganglion cell layer and inner plexiform layer, microcysts in fovea, and markedly reduced macular pigment.[7] These changes, secondary to Mueller cell degeneration and deficiency of retinal carotenoids, are associated with impaired vision and photophobia.[2]

CNS involvement manifests as spasticity and intellectual disability. As noted in our patient, progressive spasticity limits motor function and leads to contractures and loss of independent ambulation.[1,8] Cognitive functions are stable, unlike other neurometabolic disorders.[1,2] Pseudobulbar dysarthria may be severe enough to cause anarthria.[9] Orofacial dysfunction occurs, but severe dysphagia is rare.[9] Epilepsy is noted in only a small fraction of patients.[2] Our patient initially had febrile seizures but subsequently had unprovoked seizures. EEG shows slowing of background when recorded in the interictal period.[1]

Brain MRI changes include delayed myelination and leukoencephalopathy. Subcortical white matter is unmyelinated even in adulthood. Periventricular white matter is hyperintense on T2-weighted and isointense or slightly hypointense in T1-weighted sequences. These changes may be patchy but are more often confluent. The parieto-occipital region is most commonly affected, although an occasional patient may have predominant involvement of frontal white matter. Corpus callosum is involved in some patients. The subcortical white matter is unaffected, and the spared zone is distinct from the unmyelinated U fibers. These changes develop during the first 2 or 3 years of life, commensurate with the myelination process, and do not progress thereafter. The brainstem and cerebellum are always spared.[10]

The periventricular white matter demonstrates a prominent, narrow peak at 1.3 ppm in proton MRS at all echo times (20, 30, and 135 milliseconds) and another smaller peak at 0.8 to 0.9 ppm.[10] These lipid peaks are a reflection of abnormal accumulation of lipids probably rich in fatty alcohols and fatty aldehydes; however, biochemical studies on brain parenchyma in SLS are lacking. Abnormal lipid peaks are also seen in multiple sclerosis, Niemann-Pick disease type C, dihydroxyacetone phosphate acyltransferase deficiency, and other peroxisomal disorders. In these conditions, lipid peaks are broad and less intense and are seen only with short echo times, in contrast to SLS. The intensity of signal changes in T2-weighted sequences in SLS does not correlate with age, severity of neurologic deficits, or height of the lipid peak in MRS.[10]

The diagnostic process begins with the identification of the clinical phenotype of early-onset neurocutaneous disorder. It must be kept in mind that the clinical features unfold with age. Preterm delivery and congenital ichthyosis are initial manifestations. Retarded motor function, intellectual disability, and retinal abnormalities develop subsequently.[1,2] The diagnostic suspicion is further strengthened by characteristic brain MRI changes and confirmed by targeted sequencing of the *ALDH3A2* gene. The biochemical defect can be demonstrated by direct estimation of FALDH activity in leucocytes and cultured skin fibroblasts. In patients with SLS, FALDH is reduced to 0% to 25% of the control mean. LTB4 degradation capacity of fresh leucocytes also reflects the FALDH activity.[1] Increased free fatty alcohols, octadecanol, and hexadecanol in plasma and increased urinary excretion of LTB4 or its metabolites are other useful diagnostic tests.[1]

Affected patients are managed by a multidisciplinary team of neurologists, ophthalmologists, dermatologists, and rehabilitation specialists, among others. Dietary modification to reduce total fat intake and to increase the linoleic/linolenic acid ratio has limited benefit. Symptomatic treatment of ichthyosis consists

of applying emollients, keratolytics, and topical calcipotriol. Bezafibrate has potential biochemical benefit in cultured fibroblasts from patients with SLS with certain missense mutations. Carotenoids have been tried but have not been found to have any therapeutic effect.[2] Gene therapy is in the pipeline. Zileuton blocks leukotriene synthesis and has been used off-label in SLS to reduce pruritus. However, no convincing evidence has been found that Zileuton improves pruritus.[5] A subset of patients have a mild phenotype.[1] Whether dietary habits or other genetic factors that modulate endogenous lipogenesis govern the clinical severity remains to be established.

AUTHOR CONTRIBUTIONS

M. Nagappa: wrote the first draft, data analysis and interpretation, and critical revision of the manuscript for important intellectual content. P.S. Bindu: study concept and design, data analysis and interpretation, study supervision, critical revision of the manuscript for important intellectual content, and approved final draft. S. Chiplunkar: data collection and interpretation. N. Gupta: clinical data collection. S. Sinha: study supervision and critical revision of the manuscript for important intellectual content. P.S. Mathuranath: critical revision of the manuscript for important intellectual content. R.D. Bharath: analyzed and interpreted MRI data. A.B. Taly: study supervision and critical revision of the manuscript for important intellectual content.

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DISCLOSURE

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