CASE REPORT

Sjögren-Larsson syndrome: a rare disease of the skin and central nervous system

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SUMMARY

Sjögren-Larsson syndrome is a recessively inherited disease caused by a deficiency of fatty aldehyde dehydrogenase with presenting features of congenital ichthyosis, spastic diplegia or tetraplegia, and mental retardation. The basic pathogenic mechanism is deficiency of fatty aldehyde dehydrogenase, which may lead to an accumulation of long-chain fatty alcohols hampering cell membrane integrity, which further disrupts the barrier function of skin and white matter of the brain. MRI of the brain shows diffuse symmetrical white matter hyperintensities on T2-weighted sequences. Although there is no definitive cure for Sjögren-Larsson syndrome, most patients survive until adulthood and management involves therapies directed towards controlling specific problems. We present a case of Sjögren-Larsson syndrome with classical clinical and MRI features, including a few distinctly atypical characteristics in various attributes.

BACKGROUND

Sjögren-Larsson syndrome (SLS) is an inborn error of lipid metabolism characterised by dry, scaly skin (ichthyosis) along with neurological and eye problems. This disease was first observed in Sweden, where the prevalence of the condition was reported to be 1/250 000 individuals, however, it apparently seems to occur much more rarely worldwide.¹ It is inherited as an autosomal recessive trait and is caused by a deficiency of the microsomal enzyme fatty aldehyde dehydrogenase (FALDH) due to mutations in the ALDH3A2 gene (chromosome 17p11.2). However, phenotypic heterogeneity is noted within single families affected and more than 70 mutations in ALDH3A2 have been discovered in patients with SLS, including amino acid substitutions, deletions, insertions and splicing errors.² FALDH catalyses the oxidation of fatty aldehydes to fatty acids, hence, with its deficiency there is lipid accumulation in various tissues, accounting for the cutaneous and neurologic manifestation in SLS.^{3–4} The reason for ichthyosis with pruritus is accumulation of fatty alcohols in the skin, disrupting the epidermal water barrier and resulting in transepidermal water loss.⁵ At the same time, deficiency of fatty alcohol oxidation may impair the structural and/or functional integrity of myelin membranes, thereby leading to the neurological features, especially in the central nervous system.² The neurological manifestations of SLS include spastic diplegia or quadriplegia along with mental retardation and leukoencephalopathy. Apart from these, ocular abnormalities may include

photophobia, macular degeneration with retinal crystals and decreased visual acuity.²

CASE PRESENTATION

A 1½ old boy born of a non-consanguineous marriage, delivered prematurely (at 34 weeks) without history of antenatal or perinatal complications, presented to our department, because of global developmental delay along with dry and lustreless skin since birth. He attained neck holding at the age of 9 months, was not able to sit without support and could only speak in monosyllables. His parents had noticed insidious onset stiffness of both lower limbs, which had started in the latter part of the first year of life, with progressive increase up to the time of presentation. However, there was no significant family history. On general examination, there was facial dysmorphism with depression over the parietal bone of the skull (figure 1A) and kyphoscoliosis along with pes planus (figure 1B, C) and skin changes suggestive of lamellar ichthyosis (figure 1B–D) sparing the face (figure 1A). On neurological examination, the child could not follow commands properly; however, there was spasticity of both lower limbs with normal tone of upper limbs. Additionally, there were brisk deep tendon reflexes and there was bilateral extensor plantar response suggestive of spastic diplegia. Also, the parents had noticed intermittent abnormal posturing of both upper limbs, which would disappear during sleep.

INVESTIGATIONS

Laboratory investigations including routine haematological and biochemical investigations were normal. EEG was normal and so were the other relevant investigations. However, on visual evoked potential testing, P100 latency was prolonged in both eyes. MRI of the brain showed diffuse T2 hyperintensity in periventricular and subcortical white matter of both cerebral hemispheres, relatively sparing the subcortical U fibres, suggestive of dysmyelination (figure 2). MR spectroscopy (MRS) revealed prominent lipid peak at 1.3 ppm and 0.8–0.9 ppm with normal levels of NAA and mildly elevated choline.

DIFFERENTIAL DIAGNOSIS

X linked ichthyosis, lamellar ichthyosis, congenital ichthyosiform erythroderma, Refsum disease, Rud syndrome, Chanarin-Dorfman syndrome, Gaucher disease type 2 and multiple sulfatase deficiency were included in the differential diagnosis.

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Figure 1 (A) Shows depression in the parietal bone of the skull (triple arrow) and absence of ichthyosis on the face. (B) and (C) show ichthyosis on the dorsal surface of the foot and leg (single arrow), and pes planus (double arrow). (D) Shows ichthyosis of the abdomen (arrow with a tail).

TREATMENT

Treatment was provided in the form of physical therapy and rehabilitation including speech therapy, language therapy, and mobility and postural support along with family counselling. Cutaneous symptoms were managed with keratolytic agents and measures to maintain skin hydration, including daily water baths and topical moisturising creams.

OUTCOME AND FOLLOW-UP

There was overall clinical improvement with respect to skin symptoms after about 6 weeks of initiation of therapy. Currently, the child is in close follow-up, and further management will be planned according to the clinical progression and evolution of the disease.

DISCUSSION

The clinical symptoms of SLS are apparent mostly in the first years of life, with a relatively static course thereafter.⁶ Although dermatologic features in the form of skin erythema may be the

earliest finding and may be evident at birth, the cardinal skin manifestation in the form of ichthyosis appears mainly in the latter half of the first year of life and mainly involves flexor surfaces of the extremities, neck, axilla and umbilicus, sparing the face. The morphology of the scaling may be fine and dandruff-like, similar to ichthyosis vulgaris. Severe pruritus accompanies ichthyosis in nearly all cases, which differentiates it from other illnesses with ichthyosis.⁷ Our case had similar findings, with ichthyosis sparing the face, however, the child had ichthyosis predominantly on the extensor aspect of the limbs.

Neurological illness may manifest in the form of spasticity, dystonia, cognitive impairment or language impairment. Premature delivery has been commonly reported by researchers,⁶ as was noted in our case. Spasticity develops in the majority of cases in the 2 initial years of life, and lower limbs are more severely affected than upper limbs, so most patients become wheelchair dependent and joint contractures frequently develop in the legs during late childhood or early adolescence, despite attainment of walking in earlier years.⁶ Our case had

Figure 2 (A) and (B) show symmetric hyperintensity in bilateral subcortical white matter and periventricular area sparing U fibres in a T2-weighted axial image (single arrow).

similar findings and spasticity was evident mainly in the lower limbs. Dystonic posturing was present in both upper limbs in the current case, which has rarely been reported.⁸ The child also had gross developmental delay. Although most patients with SLS have mild to moderate mental retardation, a minority have normal intelligence.^{4–6} Speech and language may be affected in SLS owing to both motor and cognitive impairment. Seizures occur commonly and their frequency ranges from 0 to 40%.^{3–4,9} Further, growth delay and contractures may lead to short stature.⁹

Ophthalmological examination in the majority of cases reveals macular dystrophy with intraretinal crystals and foveal pseudocysts beginning in early childhood. Also, there may be reduction of visual acuity due to a defect in the optic pathway due to dysmyelination.^{1–10} In this case, although we could not perform a fundus examination because of non-cooperation of the child, P100 latency was prolonged, suggestive of optic pathway dysmyelination/demyelination.

Brain MRI showed diffuse T2 hyperintensity in periventricular and subcortical white matter of both cerebral hemispheres, relatively sparing the subcortical U fibres. In the literature, frontal or parieto-occipital predominant hyperintensities have been well documented on T2-weighted images mainly in the periventricular white matter, which appear normal or mildly hypointense on T1-weighted sequences suggesting delayed myelination/dysmyelination.¹¹ We performed a MRS, which revealed prominent lipid peak at 1.3 ppm and 0.8–0.9 ppm with normal levels of NAA and mildly elevated choline, which is consistent with the observation of researchers, who have reported high abnormal lipid peak measuring 1.3 ppm in the periventricular white matter, especially around the frontal and posterior trigones with smaller peaks at 0.8–0.9 ppm, which may reflect the methyl (CH₃) and methylene (CH₂) groups on separate lipid molecules. This finding suggests that SLS leads to gliosis without significant axonal loss.¹¹ The lipid peak signifies local accumulation of the unusual free lipids or lipophilic substances, such as long-chain fatty alcohols. Although biochemical investigations including urinary concentration of leukotriene B₄ and 20-OH-LT B₄ and genetic studies for ALDH3A2 gene are

not essentially required for establishment of diagnosis, they should be performed wherever feasible for confirmation and genetic counselling. We ordered these tests for this child but the parents did not consent.

To summarise, the diagnosis of SLS should be considered in an infant presenting with congenital ichthyosis with pruritus and emerging neurological and ocular features. Cerebral MRI reveals arrested myelination or demyelination in subcortical white matter and lipid peak on spectroscopy, which help in diagnosis.

Competing interests None declared.

Patient consent Obtained.

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