

Sjögren-Larsson Syndrome: A Case Report and Literature Review

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GOAL

To understand Sjögren-Larsson syndrome (SLS) to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the clinical features of SLS.
2. Discuss the genetic component of SLS.
3. Identify potential therapeutic options for patients with SLS.

CME Test on page 36.

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Sjögren-Larsson syndrome (SLS) is an autosomal recessive neurocutaneous disorder most commonly seen in the Scandinavian population and characterized by congenital ichthyosis, mental retardation, and spastic diplegia or quadriplegia. We report a case of SLS in an 11-month-old girl of Lebanese and Mexican-Syrian ancestry who presented with ichthyosis, developmental delay, and spasticity. Results of an enzymatic assay and genomic DNA testing in cultured skin fibroblasts confirmed a homozygous C237Y mutation. These findings support the rich diversity of mutations associated with this syndrome.

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Originally described in 1967, Sjögren-Larsson syndrome (SLS) is an autosomal recessive disorder characterized by congenital ichthyosis, mental retardation, and spastic diplegia or quadriplegia.¹ Skin findings are present at birth and include varying degrees of erythema and ichthyosis. The ichthyosis ranges from a fine white scale to larger plaquelike scales or nonscaling hyperkeratosis with accentuation of skin markings. SLS is generally considered when there is a positive family history or Scandinavian ancestry or when the emerging neurologic signs complete the clinical picture.¹

Physicians should have a heightened awareness of newborns with congenital ichthyosis; early diagnosis of SLS is important to provide accurate prognostic information, genetic counseling, and therapeutic intervention. Defective fatty alcohol oxidation because of deficiency of fatty aldehyde dehydrogenase (FALDH) is the underlying pathophysiologic mechanism that gives rise to the symptoms.^{2,3} There also is evidence of defective leukotriene B₄ (LTB₄) degradation caused by FALDH deficiency in patients with SLS.^{4,5} Thus, SLS is caused by an inborn error of metabolism. The enzymatic marker assay provides a reliable means for its diagnosis and suggests new avenues for investigation of the pathogenesis, diversity of genetic mutations, and treatment of the disorder.⁵⁻⁷ DNA diagnosis is available, and more than 72 mutations have been described.⁸ The purpose of this article is to summarize the clinical features of SLS, review the heterogeneity in genetic-biochemical abnormalities seen in this disease's worldwide distribution, and discuss potential therapeutic options.

Case Report

An 11-month-old girl with Lebanese and Mexican-Syrian ancestry presented to pediatric dermatology for evaluation of scaly skin. Results of an examination found white scale with evidence of pruritus over the extremities and abdomen, and relative sparing of the face and back. Her palms and soles were slightly thickened. A mild amount of scaling on the scalp also was present (Figure). Her nails were unaffected. Developmental motor milestones were delayed; she was unable to crawl, rollover, or sit up.

The patient's medical history revealed that she was delivered at 39 weeks of gestation by placental abruption. The primipara mother had 2 prior first trimester spontaneous abortions. The patient's weight and length at birth were 2.7 kg and 50 cm, respectively. She remained on high-frequency oscillatory ventilation for 15 days, and her course was

complicated by septicemia, pneumonia, respiratory failure, and hypotonia. The patient's skin finely desquamated until 2 weeks of age and then slightly thickened, especially in the flexural areas, palms, and soles.

Newborn screening for thyroid disease, cystic fibrosis, congenital adrenal hyperplasia, biotinidase deficiency, and glucose-6-phosphate dehydrogenase deficiency were negative; amino acid levels, acylcarnitine profile, and TORCH (toxoplasmosis, other infections, rubella, cytomegalovirus infection, and herpes simplex) titers were unremarkable.

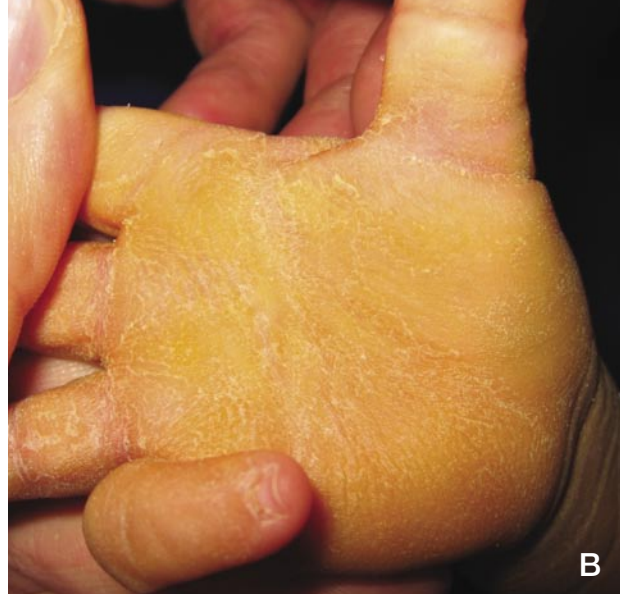
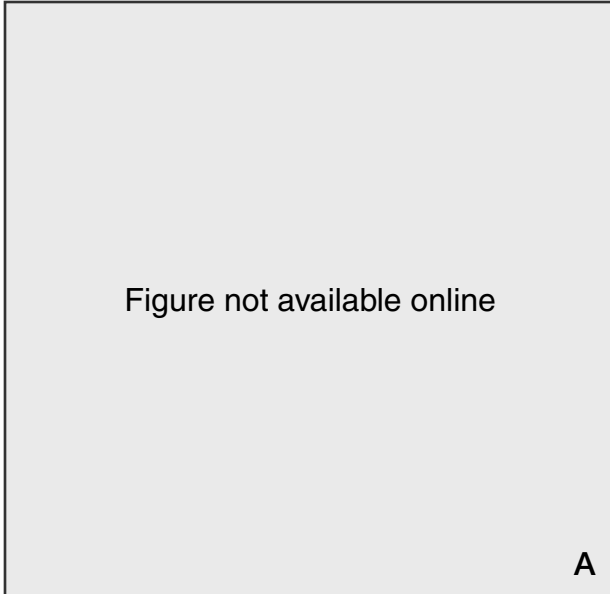
A skin biopsy was obtained for fibroblast culture and histopathology. Results of DNA analysis from cultured skin fibroblasts detected a missense homozygous C237Y mutation in the aldehyde dehydrogenase 10 (ALDH10) gene, confirming the diagnosis of SLS.

Comment

The key triad of symptoms for SLS includes non-bullous congenital ichthyosiform erythroderma, mental retardation developing in the first 3 years of life, and spastic diplegia or quadriplegia. Additional symptoms include other dermatologic manifestations, ophthalmologic signs, speech defects, seizures, dental problems, and skeletal abnormalities (Table).^{1,2} In the neonatal period, skin changes are most obvious on the lower trunk with flexural accentuation. Over time, infants with SLS are profoundly pruritic, out of proportion with the skin findings. The skin gradually becomes thickened and scaly in the first year. A variety of lesions may be observed, including generalized ichthyosis, with the trunk, flexures, and dorsal aspects of the hands and feet most severely affected; furfuraceous (dandrufflike) scaling; lamellar-type hyperkeratosis with thin scales; or nonscaly thickening of the stratum corneum.^{1,2,6,7,9}

The erythema lessens with age, and extensive thickening of the skin results in dark yellow-brown discoloration, most prominent around the umbilicus and at the main flexures. Desquamation, especially of the palms and soles, occurs in some cases. The face, hair, and nails usually are spared.

Neurologic signs are nonspecific; however, by 1 to 2 years of age, severe motor and mental developmental delay usually is obvious. Spasticity may be apparent before 3 years of age and is more severe in the lower limbs than in other parts of the body.^{2,3,9} Nonprogressive mental retardation, associated with delayed or impaired speech, is an invariable feature of classical SLS and can range from mild to severe. Seventy percent of patients with SLS and mental



An 11-month-old girl with Sjögren-Larsson syndrome. The clinical findings warrant this diagnosis. The patient's nose is flattened and wide at the root, and the eyes are hyperteloritic (A). The patient also had palmar hyperlinearity and severe hyperkeratosis (B), as well as yellowish hyperkeratosis scale with multiple visible scratch marks (C). She also had hyperkeratosis with accentuation of skin markings and diffuse erythema and scaling (D).

Clinical Features of Sjögren-Larsson Syndrome^{1,2}

Major Features

Ichthyosis*
 Glistening white dots on the retina
 Mental retardation*
 Seizures
 Short stature
 Spastic diplegia or quadriplegia*
 Speech defects

Minor Features

Enamel hypoplasia
 Hypertelorism
 Kyphoscoliosis
 Macular degeneration
 Metaphyseal dysplasia
 Wide-spaced teeth

*These features generally are present in all patients with Sjögren-Larsson syndrome.

retardation may have an intelligence quotient of less than 50.¹⁰

The constellation of findings in our patient—accentuated skin markings, history of erythema, progressive ichthyosis in the first year, and neurologic symptoms of spasticity in the left upper extremity—made SLS the leading differential. Other ichthyosislike entities in the differential diagnosis include hereditary and acquired ichthyosis vulgaris, lamellar ichthyosis, X-linked ichthyosis, ichthyosis linearis circumflexa (Netherton syndrome), and phytanic acid storage disease (Refsum disease and Rud syndrome).^{1,11}

Genetics—SLS is an autosomal recessive disorder that is more common in individuals from northern Sweden where the carrier frequency is as high as 1%.⁵ Cultured skin fibroblasts in patients with SLS have impaired fatty alcohol oxidation because of a deficiency of FALDH, a component of the fatty alcohol nicotinamide adenine dinucleotide oxidoreductase complex that catalyzes the oxidation of

long-chain fatty alcohol to fatty acid.^{2,4,6} FALDH deficiency also results in defective LTB₄ degradation, leading to high urinary concentrations of the very active metabolites LTB₄. This finding may be significant in the pathophysiology of preterm birth in SLS and fits in with modern concept of preterm labor as an intrauterine inflammatory response syndrome.^{5,7}

SLS results from mutations in the ALDH3A2 gene (also known as FALDH and ALDH10), which is located on chromosome 17p11.2. The ALDH3A2 gene consists of 10 exons and is widely expressed in tissues.^{12,13} At least 72 mutations have been described.⁸

Our patient was homozygous for a single base change (G→A) in exon 5 of ALDH3A2. This missense mutation is predicted to replace a cysteine with a tyrosine residue at position 237 (C237Y). Rizzo et al¹³ reported this mutation in the homozygous state in 2 subjects with SLS who had Arab-Jewish and Syrian-Jewish ancestry.

Although there is no known consanguinity between our patient's parents, there is maternal Lebanese ancestry and paternal Syrian ancestry. Both parents potentially may have a common Sephardic Jewish ancestor.

Treatment—There is no treatment for SLS other than supportive care. Two approaches have been taken for the treatment of the skin disease in SLS: oral acitretin therapy and dietary intervention (a low-fat diet supplemented with medium-chain fatty acids is currently being evaluated in controlled trials for efficacy in improving neurologic and dermatologic symptoms). Improvement has been reported anecdotally.^{14,15} Topical medications, such as calcipotriene ointment, urea cream, and mineral oils, as well as frequent bathing or showering, have limited efficacy for patients with SLS. Favorable results have been reported with the use of zileuton, which inhibits LTB₄ synthesis.¹⁶ Physical therapy is important to counteract spasticity and preserve mobility for as long as possible.^{14,15}

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