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A Neurodegenerative Phenotype Associated with Sjögren-Larsson Syndrome

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Abstract

Sjögren-Larsson syndrome (SLS) is a rare neurologic disorder caused by pathogenic sequence variants in *ALDH3A2* and characterized by ichthyosis, spasticity, intellectual disability and a crystalline retinopathy. Neurologic symptoms develop in the first two years of life. Except for worsening ambulation due to spastic diplegia and contractures, the neurologic disease has been considered static and a neurodegenerative course is distinctly unusual. We describe a young SLS child who exhibited an early and severely progressive neurologic phenotype that may have been triggered by a febrile rotavirus infection. Together with 7 additional published cases of these atypical patients, we emphasize that a neurodegenerative course can be an extreme outcome for a minority of SLS patients.

Keywords

ichthyosis; spasticity; intellectual disability; myelin; leukodystrophy

INTRODUCTION

Sjögren-Larsson syndrome (SLS) is a rare genetic disease characterized by ichthyosis, spasticity, intellectual disability and a crystalline retinopathy ¹. The disease is caused by mutations in *ALDH3A2*, which codes for fatty aldehyde dehydrogenase (FALDH) and results in accumulation of fatty aldehydes and alcohols ². SLS has an estimated incidence of approximately 1 in 250,000. Although originally recognized in Sweden ³, the disease has subsequently been seen worldwide and in many ethnic populations ⁴⁵.

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AUTHOR CONTRIBUTIONS

SW and WBR contributed to design and drafting of the manuscript; TL contributed to data analysis and interpretation; all authors critically reviewed the manuscript.

DECLARATION OF CONFLICTING INTERESTS

All authors declare no conflicts of interest.

ETHICAL APPROVAL

This human research was approved by the Institutional Review Board at the University of Nebraska Medical Center (protocol 560-12-FB). The parents of our patient provided informed consent for their child's participation.

SLS has a distinctive phenotype that develops over time. Patients typically exhibit ichthyosis at birth and develop spastic diplegia and motor delay in the first 2 years of life. Intellectual disability, delayed speech with dysarthria, and a dysmyelinating white matter disease with a periventricular distribution on MRI appear in the first few years of life. The neurologic changes may be preceded by abnormal accumulation of lipids in cerebral white matter as detected on MR spectroscopy ⁶. Spastic diplegia with impaired walking typically occurs and slowly progressive contractures can result in complete loss of ambulation. A very small proportion of SLS patients have exhibited spastic quadriplegia rather than the usual diplegia. Conversely, a milder neurologic phenotype has been recognized in patients ⁷ The *ALDH3A2* genotype does not correlate with clinical severity of SLS ⁵, suggesting the presence of modifying genes or environmental influences.

SLS is usually considered a static leukoencephalopathy and most patients live into adulthood. A neurodegenerative course is very unusual. However, progression of neurologic disease in childhood has recently been identified, usually attributed to uncontrolled seizures ^{8–12}. We now report a young SLS patient who developed a striking neurodegenerative course that was apparently triggered by an infectious illness. We further review additional published cases of SLS associated with loss of neurological function beyond that expected from slowly progressive spastic contractures. Together, these reports highlight a previously unappreciated severe neurodegenerative course in SLS, which has major implications for prognosis and family counseling.

CASE REPORT

A female patient (P1) was born in China and raised in an orphanage until she was adopted and brought to the United States at 10 m of age. Her earlier medical history is not known but there was reference to ichthyosis and developmental delay. While her adoptive parents were meeting her in China, they noticed an episode during which she stared upward and toward the left for about 1 minute and was minimally responsive. There were no associated abnormal movements. Six days later, upon arriving in the United States, she developed a focal seizure characterized by upward deviation of her eyes with jerky eyebrow movements, body stiffening and clenched jaw. She became cyanotic and her father administered CPR. By the time the ambulance arrived, the seizure had stopped. At the hospital, physical examination showed dry skin and positional plagiocephaly with right parietal flattening and a mild torticollis. A neurology consultation noted axial hypotonia with brisk lower extremity reflexes. An EEG showed focal epileptiform abnormalities and she was started on levetiracetam. Brain MRI demonstrated mild bilateral periventricular white matter disease. A dilated funduscopy examination was unremarkable for lens or retinal abnormalities. Developmental assessment placed her at a 6-9-month level. Plasma amino acids, acylcarnitine profile, lactate/pyruvate, glycosylated transferrin, very long chain fatty acids, urine organic acids, urine oligosaccharides and serum cortisol were all normal. With suspicion for SLS, sequencing of the *ALDH3A2* gene revealed homozygous pathogenic variants (c.1157A>G; p.N386S).

By 2 y-3 m of age, the child was rolling over, sitting independently and standing in a walker. She was crawling with minimal use of her legs by using her arms (Army crawl), but was

not speaking words. She was able to feed herself and grasp cereal with a pincer grip. On physical examination, her tone was increased in the hip flexors and knees. Her torticollis and plagiocephaly had improved. She was below the 5th percentile for weight and height but head circumference was at the 15th percentile. Ophthalmologic examination revealed nystagmus, myopia and photophobia.

Shortly afterward, she developed a febrile rotavirus infection that persisted for 3 weeks. During this time and over the subsequent months, she began to regress in gross and fine motor activities associated with markedly decreased upper body strength and head control. She stopped standing, sitting without support or bearing weight on her arms, and could no longer crawl. She exhibited no recurrence of seizures. A repeat MRI within one month showed no significant changes in white matter disease compared to her initial scan. Spine MRI and hip X-rays were normal except for a thoracic kyphosis.

At age 2 y-8 m, physical examination showed generalized ichthyosis with evidence of pruritus (Figure 1). She exhibited spasticity and hyperreflexia in the upper and lower extremities. A brain MRI revealed subtle hyperintense T2 signal in the subcortical periventricular white matter bilaterally and on FLAIR images (Figure 2A). MRS demonstrated a large lipid peak at 1.3 ppm with depressed NAA in the centrum semiovale white matter and smaller peak along the midline superior cerebellar vermis. She had no clinically overt seizures and an EEG was normal while on levetiracetam. Neuropsychological evaluation with Stanford-Binet testing showed a full-scale IQ of 88 (21st percentile) (Figure 3). A Vineland-2 Adaptive Behavior composite score was low with significant reductions in motor skills, communication and daily living scores (Figure 3). Mullens scales were at or below the 1st percentile for age. Dilated ophthalmologic examination revealed nystagmus and photophobia, but no maculopathy.

Over the subsequent months she exhibited continued neurologic deterioration. By 4 y-7 m, she could no longer roll over and had lost much of her fine motor skills, including the ability to feed herself, pick up toys and place them in a basket, hold objects or even clap her hands. She was no longer able to use a pincer grasp and wore arm braces for spasticity and persistent fisting. She required a vest brace for maintaining her trunk position when sitting and standing with support. She was unable to chew solid foods and received a G-tube for nutrition.

Consistent with her neurologic deterioration, serial brain MRIs showed progressively worse FLAIR signal abnormalities within the bilateral periventricular white matter and occipital trigone areas (Figure 2B–D). Seizures did not recur and annual EEGs showed diffuse slowing with no epileptiform activity. Cognitive testing demonstrated a progressive drop to IQ 40 and Vineland-2 Adaptive Behavior testing showed further reductions in all subscores (Figure 3).

Ophthalmologic examination at age 5 y-7 m revealed new appearance of mild pigmentary changes in the macula and perimacular crystalline deposits in both eyes. At 7 y of age, the child developed dystonic movements involving her arms, legs and mouth, which did

not respond to medical management. Excessive drooling and apneic episodes became concerning and she underwent tracheostomy for airway control.

DISCUSSION

We draw attention to a neurodegenerative phenotype in SLS that has not been generally appreciated. Although isolated SLS patients have been reported to exhibit loss of neurologic function, it has usually been ascribed to uncontrolled seizures¹⁰. In contrast, our patient's decline was seemingly triggered by a febrile rotavirus infection, after which she began to develop a striking loss of motor and cognitive abilities over the subsequent 3 years. Prior to her infection, she displayed the typical clinical course of most SLS patients with spastic diplegia and intellectual disability. Nothing in her prior history would predict a neurodegenerative sequela. Although it is possible that our patient's particularly severe neurologic phenotype would have manifested in the absence of a rotavirus infection or at an older age, her clinical course prior to the infectious illness was typical for SLS and her neurologic trajectory after the infection was distinctly changed.

We⁸⁻¹⁰ and others^{11,12} have described seven additional SLS patients with a neurodegenerative clinical course (see Table 1). All were genetically confirmed with pathologic variants in *ALDH3A2*, or in one case (P7)¹² was genetically related to the original Swedish SLS cohort which carry a common c.943C>T pathologic variant^{14,15}. Regressive changes ranged from the temporary loss of motor and verbal skills (P5)¹⁰ to a permanent loss of verbal, cognitive and motor abilities^{8,9} and/or progressive tremor, dystonia and decreased upper limb function¹¹. All of the patients with a neurodegenerative phenotype were children. The age of onset of regression ranged from 6-7 m to 12 y. At the time of publication, all of the cases were alive despite their severe neurologic condition.

Approximately 40% of SLS patients experience one or more seizures¹³, but most are easily managed with anticonvulsant therapy. Five of 8 patients listed in Table 1 (P3, P4, P6, P7, P8) had poorly controlled seizures, either overt or subclinical, which may be a harbinger of a more aggressive neurologic disease. However, it is not possible to know whether seizures contribute to a neurodegenerative course in SLS or are simply a marker or risk factor of more severe disease. Our patient did not have clinical or EEG evidence for recurrent seizure activity when she started to regress or afterward. One SLS patient (P5)¹⁰ showed a temporary loss of neurologic function after a single seizure at 9 months of age. He later regained most of his lost abilities and exhibited the more typical SLS phenotype with spastic diplegia and intellectual disability at 11 y of age. Thus, a neuro-regressive course in infancy may be reversible and is not always an ominous prognostic sign.

What distinguishes SLS patients with a neurodegenerative course from the much larger population of patients with a more typical neurologic phenotype? Clues do not come from the gestational age, sex, geographic origin, or ethnic background (Table 1).

The *ALDH3A2* genotype is also not a distinguishing factor in the neurodegenerative patients. SLS is caused by at least 90 unique and diverse *ALDH3A2* variants including missense (33.3%), frameshift (32.2%), splice site (15.6%), nonsense (10.0%), insertion/

deletions (5.6%) and large rearrangements (3.3%)⁵. Three of the SLS patients in Table 1 have complex deletion or frameshift variants that are expected to completely destroy FALDH protein function, whereas the remainder have missense or splicing defects that could theoretically encode a FALDH enzyme with a small amount of residual enzyme activity. P2 carries a homozygous continuous gene deletion with complete loss of the *ALDH3A2* gene and 4 additional flanking genes; her clinical course, however, is not ostensibly worse than the others. Seven of the 8 SLS patients in Table 1 are consanguineous and have homozygous *ALDH3A2* genotypes; they could possess regions of homozygosity encompassing modifier genes that contribute to the severe phenotype. However, homozygosity for *ALDH3A2* variants is common in the SLS population at large, being present in 74.7% of 178 published cases⁵. Significantly, there is no convincing evidence for a strong genotype-phenotype correlation in SLS⁵.

The neurologic disease in SLS is related to FALDH deficiency, which leads to accumulation of fatty aldehydes and alcohols². In brain white matter, MR spectroscopy reveals a characteristic major lipid peak at 1.3 ppm⁶. Recent lipidomic analysis of autopsied brain from an adult SLS patient demonstrated accumulation of fatty alcohols of unusually long chain length (C18-C24) together with their corresponding ether lipid synthesis products¹⁶. These lipids were highest in white matter but also accumulated in gray matter. It is likely that the fatty alcohols and ether lipids disrupt myelin membranes and account for the lipid peak seen on MR spectroscopy. Whether our patient's lipid accumulation in brain is unusually high compared to SLS patients with a more typical phenotype is not known.

In addition to biochemical changes, the potential influence of environmental factors such as perinatal complications, preterm birth, diet, stressful life events, or head trauma are unknown. Our patient did have poor growth as manifested by weight and length gain, but her head growth was normal.

Together with the mildly affected SLS patients⁷, the severe neurodegenerative cases represent the extremes of the phenotypic spectrum in this disease. The prevalence of a neurodegenerative phenotype in SLS is not known, but it must represent a small proportion of the population. More than 200 SLS patients have been reported to date, but our literature review and personal experience only identified a small fraction (8 cases) with this severe phenotype. Since few published reports of SLS patients provide longitudinal data, however, it is possible, if not likely, that additional cases will be recognized.

Our findings are important for counseling physicians and parents of newly diagnosed SLS patients regarding prognosis, and to alert them that it is possible that loss of cognitive and physical abilities can occur during childhood. Although the etiologic contribution of our patient's rotavirus illness cannot be proven without additional experience, we caution physicians who care for SLS patients to aggressively treat febrile infections and seizures. Furthermore, neurologists and families should be aware of the possibility that their SLS patients may exhibit an unexpected loss of neurologic function associated with physical stresses, such as infection or uncontrolled seizures.

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Figure 1.
SLS patient showing the appearance of her ichthyosis at 2 y-8 m.

Figure 2.
Serial FLAIR images of SLS patient showing progression of white matter disease. A. 2 y-6 m. B. 3 y-7 m. C. 4 y-7 m. D. 5 y-7 m.

Figure 3.
Decline in functional testing of SLS patient (P1) over time. Vineland-2 behavior scores and Stanford-Binet full scale IQ are shown.

Table 1.

SLS patients reported to have a neurodegenerative phenotype. Genetically or enzymatically confirmed patients are included.

Case	Age	Sex	Gestational age	<i>ALDH3A2</i> Genotype	Age of Onset of Neurologic Regression	Complicating Medical Factor	Clinical Outcome	Reference (case)
P1	7 y	F	Unknown	Homozygous c.1157A>G (p.N386S)	2.5 y	Febrile rotavirus infection at 2.4 y.	By 7 y: spastic quadriplegia with no sitting, rolling over, crawling, holding objects, speaking or clasp hands. Requires G-tube feedings. Dystonia, apnea prompted tracheostomy.	This report
P2	17 y	F	32 w	Homozygous contiguous gene deletion of <i>ALDH3A2</i>	6-7 m	Febrile illness triggered temporary loss of developmental skills in infancy.	Two febrile illnesses prior to temporary loss of ability to roll over and limbs stiffened. At 3 y: spastic diplegia, developmental delay. At 10-12 y: onset of dysphagia, increased drooling prompted G-tube. By 14 y: spastic quadriplegia and no ambulation.	8 (case 1)
P3	6.5 y	M	40 w	Homozygous c.1309A>T (p.K437X)	3 y	At 3 y: episode of ITP* and NEB** with interruption of anticonvulsants for 3 m.	Myoclonic seizure disorder began at 18 m. Prior to 3 y: sitting, transferring objects, eating with spoon; then regression to severe spastic quadriplegia by 3.5 y.	9 (case 2)
P4	10 y	F	36 w	Homozygous c.733G>A;c.901G>C;c.906delT;c.909T>G	4.5 y	Myoclonic seizures began at 4 m; treated at 15 m with anticonvulsants.	Sat with support at 18 m, crawled at 3 y, spoke 3-word sentences at 3.5 y; sat independently and walked 100 steps with support by 4.5 y. Then, uncontrolled tonic-clonic seizures began with cognitive and motor decline; lost sitting, crawling, and walking. Speech stopped by 6 y. At 9 y, no purposeful interaction.	10 (case 4)
P5	11 y	M	37 w	Homozygous c.103C>T (p.Gln35Ter)	9 m	Seizure at 9 m	Sat independently (8 m), stood with assistance (9 m). At 9 m: one seizure and lost sitting, standing, holding toys, vocalizing sounds. Regained vocalizing at 18 m, and sat without support and walked with walker (3 y). At 11 y, had typical SLS phenotype with spastic diplegia.	10 (case 7)
P6	3 y	M	Full term	Homozygous c.631A>G (p.Lys211Glu)	2 y	Tonic-clonic seizures began at 4 days and were not controlled despite anticonvulsants.	Motor milestones mildly delayed in first year. Held head up (6 m), sat with support (8 m), clapped and imitated parents (11 m), held toys and started speaking (12 m). At 2 y: lost holding toys, clapping, crawling, standing. At 3 y: spastic diplegia, unable to sit unsupported.	10 (case 1)
P7	19 y	F	Full term	Heterozygous c.1291_1292 delAA (p.Lys431fs) and c.798+1delG splicing variant	12 y	Probable subclinical seizure activity (abnormal EEG at 8 y, 13 y and 19 y).	Before 12 y: spastic diplegia, walking with walker, psychomotor delay, IQ 31. At 12 y: onset of dystonia and tremor, worsening dysarthria and upper limb dysfunction. At 19 y: delayed motor-evoked potentials and SSEP (previously normal at 13 y).	11
P8	22 y	F	Full term?	Genetically related to Swedish cases. Homozygous c.743C>T (p.Pro315Ser)	12-13 y	Epileptic seizures from 7 m onward, worse at 12 y, daily tonic-clonic seizures.	Initially, typical SLS spastic diplegia phenotype. At 12-13 y: developed pronounced hypotonia, lost walking or moving. At 15 y: no patellar or Achilles reflexes.	12 (case 38)

* Idiopathic thrombocytopenic purpura

Necrolytic epidermolysis bullosa
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