Sjögren-Larsson syndrome: report of monozygote twins and a case with a novel mutation

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Sjögren-Larsson syndrome is an autosomal recessive neurocutaneous disease caused by mutations in the *ALDH3A2* gene for fatty aldehyde dehydrogenase, a microsomal enzyme that catalyzes the oxidation of medium- and long-chain aliphatic aldehydes fatty acids. We studied three Turkish Sjögren-Larsson syndrome patients with ichthyosis, developmental delay, spastic diplegia, and brain white matter disease. One patient was homozygous for a novel ALDH3A2 mutation in exon 5. The mutation involves the codon 228 (CGC) with the transversion G->A modifying the codon in CAC, leading to the substitution of the original arginine with a histidine (R228H), modifying the stereospecific properties of this region. These results add to the understanding of the genetic basis of Sjögren-Larsson syndrome and will be useful for DNA diagnosis of this disease.

Key words: Sjögren-Larsson syndrome, ichthyosis, ALDH3A2 gene.

Sjögren-Larsson syndrome is an autosomal recessive neurocutaneous disorder characterized by congenital ichthyosis, spastic diplegia or tetraplegia and mental retardation[1]. Worldwide incidence is estimated to be 0.4 per 100,000[2]. The disease is caused by mutations in the *ALDH3A2* gene that encodes fatty aldehyde dehydrogenase[3]. The enzyme catalyzes the oxidation of fatty aldehyde to fatty acid. Accumulation of fatty alcohols, aldehyde-modified macromolecules and elevated concentrations of active lipids are considered to be the reasons for the cutaneous and neurologic symptoms of the disease[4].

Case Reports

Cases 1-2

Monozygotic twins aged four years from a Turkish family presented with generalized dryness of skin since birth and tip-toe walking. They were born at 34 weeks of gestation. They were first evaluated for delayed walking at two years of age, and brain magnetic resonance imaging revealed symmetrical white matter lesions (Fig. 1). The diagnosis was spastic diplegia, which resulted from premature birth and periventricular leukomalacia. The parents were first-degree relatives. The examination at four years of age revealed generalized ichthyosis on the entire body. Neurologic examination revealed brisk deep tendon reflexes in all extremities and spasticity, which was more prominent in the lower extremities. Social contact, language and fine motor skills were also abnormal according to the Denver scale. Metabolic investigations including serum lactate, pyruvate, tandem mass spectrometry, urine organic acids, activity of sulfatase enzymes, and isoelectric transferrin focusing revealed no abnormality. Developmental delay together with ichthyosis and white matter lesions suggested Sjögren-Larsson syndrome, and fatty aldehyde dehydrogenase gene mutation analysis was performed on the affected twins. Genetic analysis of the patients, performed by amplifying and direct sequencing of exon 8 of the fatty aldehyde dehydrogenase gene (*FALDH*), demonstrated the presence of a homozygous G->C transition in codon 380 (AGT->AAT), leading to the substitution of the serine with an asparagine (S380N). Since the serine contains as residue a -OH group, the substitution with an amidic group can be

considered not conservative, and it can modify the activity of the enzyme.

Case 3

A six-year-old girl was consulted for epilepsy and tetraplegic cerebral palsy. She was the first child of consanguineous parents. Birth history was unremarkable, and she had had severe ichthyosis since birth (Fig. 2). She had global developmental delay and had had generalized seizures since three years of age, which were controlled with multiple antiepileptic medications. Neurological examination revealed increased deep tendon reflexes, spastic tetraplegia and ankle clonus. Magnetic resonance imaging of the brain showed periventricular white matter abnormalities. Metabolic investigations including serum lactate, pyruvate, tandem mass spectrometry, urine organic acids, activity of sulfatase enzymes, and isoelectric transferrin focusing revealed no abnormality. Clinical findings suggested Sjögren-Larsson syndrome, and the mutation analysis of the *FALDH* gene revealed a novel mutation in exon 5. The mutation involved the codon 228 (CGC) with the transversion G->A modifying the codon in CAC, leading to the substitution of the original arginine with a histidine (R228H), modifying the stereospecific properties of this region.

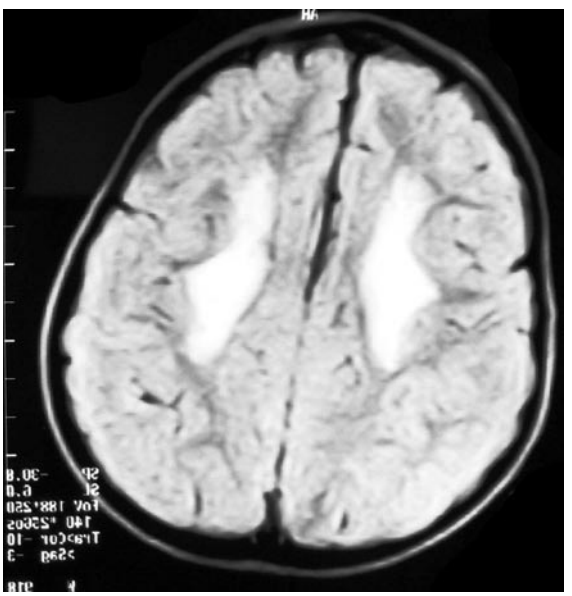

Figure 1. T2-weighted images reveal increased signal intensity in the cerebral white matter.

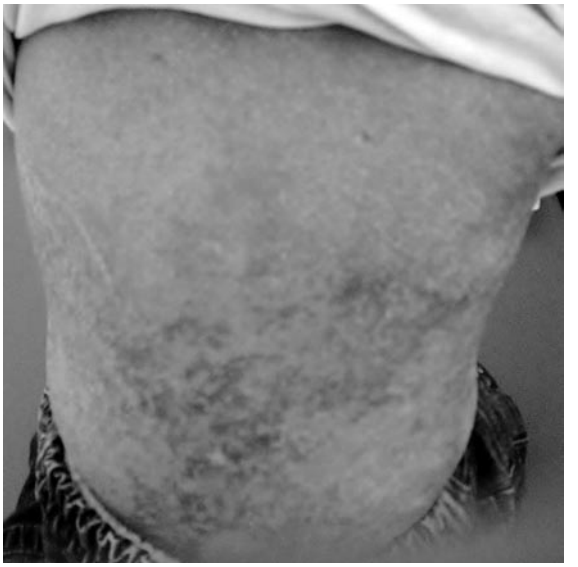

Figure 2. Ichthyosis of Case 2.

Discussion

Sjögren-Larsson syndrome was firstly reported by Sjögren and Larsson, two Swedish doctors, in 1957[1]. The classical triad of the disease is ichthyosis, developmental delay and spastic diplegia or tetraplegia. Dermatologic findings are slight hyperkeratosis at birth, which then progresses to generalized ichthyosis. Pruritus is also an accompanying disabling symptom in these cases. The nails and hair are interestingly normal[5]. Neurologic features of the disease are variable, and global developmental delay is usually obvious at 1 to 2 years of age. Spasticity is more prominent in the lower extremities, and these children are usually followed with the diagnosis of diplegic or tetraplegic cerebral palsy. The disease has a slowly progressive course, and progression of the neurologic findings stops after puberty. Seizures are also present in 40% of patients. Other clinical findings of the disease include short stature, kyphoscoliosis, nystagmus, and retinal changes[2]. Clinical findings may be variable among siblings. The differential diagnosis of the disease includes Refsum's disease, congenital disorders of glycosylation, multiple sulfatase deficiency, neural lipid storage disorder, and mitochondrial disorders[2]. Our patients had the classical triad of the disease, and metabolic investigations were normal.

Magnetic resonance imaging of the brain shows delayed myelination in the periventricular white matter and corticospinal tracts. Brain atrophy is also described. H-MR spectra show a typical lipid peak that is present in all severely affected cases. The lipid peak differs from other white matter storage disorders and is considered to result from the accumulation of long-chain fatty alcohols or fatty aldehydes. The degree of magnetic resonance imaging abnormalities and height of the lipid peak do not correlate with the severity of the neurological features. Some patients may have normal magnetic resonance imaging findings[6-8]. Although some patients may have normal brain magnetic resonance imaging findings, proton magnetic resonance spectroscopy may reveal abnormal spectral peaks in the region expected for lipids[9]. The magnetic resonance imaging of our patients revealed symmetrical white matter lesions, which were confused with the lesions of periventricular leukomalacia.

The deficiency of aldehyde dehydrogenase impairs the oxidation of medium- and long-chain fatty aldehydes. On the other hand, the metabolism of leukotriene B_4, which is a potent pro-inflammatory mediator, is also impaired because it is inactivated by the dehydrogenase enzyme. As a result of defective enzyme activity, aldehyde-modified lipids or fatty alcohol accumulates in the skin and myelin, and impaired leukotriene B_4 metabolism is responsible for pruritus and premature birth. The gene responsible for the disease is located at 17p11.2. More than 70 mutations are described, which include amino acid substitutions, deletions, insertions, and splicing errors[3,4]. The mutations generally decrease the enzymatic activity of *FALDH* in a range of 90-99%. The S380N substitution leads to a residual activity of the enzyme of approximately 1%, as well the mutation involving the R228. These two residues are located in domains important in the biology of pristanic acid and leukotriene metabolism, and their modification can impair these specific pathways[4].

In conclusion, Sjögren-Larsson syndrome should be kept in mind in patients followed with cerebral palsy who have generalized ichthyosis. Treatment is supportive, including skin hydration and a rehabilitation program for developmental delay and spasticity. Mutation analysis of the *ALDH3A2* gene should be performed for prenatal diagnostic purposes in subsequent pregnancies.

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