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CLINICAL REPORT

Sjögren-Larsson Syndrome: A Study of Clinical Symptoms and Dermatological Treatment in 34 Swedish Patients*

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Sjögren-Larsson syndrome (SLS) is a recessively inherited disease with congenital ichthyosis, spastic diplegia or tetraplegia and mental retardation, caused by a deficiency of fatty aldehyde dehydrogenase. The aim of this study was to examine all 34 Swedish patients with SLS, emphasizing skin symptoms, dermatological treatment, and neurological symptoms (evaluated in some cases for more than 25 years by one and the same investigator). Structured interviews were conducted with the patients and their close relatives. All patients had generalized ichthyosis. The degree of scaling varied markedly interindividually from moderate to severe, but there was no obvious change with age. Most patients had pruritus, suffered from hypohidrosis, and had palmo-plantar keratoderma. Nineteen patients (56%) were on oral acitretin and all patients were using some type of topical therapy. Motor disability with spasticity and muscular paresis was most pronounced in the legs and fairly slight in the arms. Twenty patients (59%) were dependent on a wheelchair for mobility. Poor blood circulation in the lower legs and oedematous feet were frequently found in adults. All patients had learning disability, which varied from slight to pronounced and was expressed in their speech disorders. Thirteen patients (38%) were being treated medically for epilepsy and all had photophobia. In conclusion, SLS is a chronic, severely disabling neurocutaneous disease in which optimal dermatological therapy is essential to relieve at least the patient's ichthyosis problem. ***Key words: ichthyosis; Sjögren-Larsson syndrome; skin disease; topical treatment.***

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Sjögren-Larsson syndrome (SLS) was first defined as a clinical entity by Sjögren in 1956 and by Sjögren & Larsson in 1957 (1, 2). It is a rare genetic disorder with autosomal recessive inheritance, characterized by the three cardinal symptoms: congenital ichthyosis, spastic di/tetraplegia and learning disability/mental retardation. Preterm birth is a common finding in SLS (3, 4). SLS has been shown to be due to mutations in the fatty aldehyde dehydrogenase (*FALDH*) gene on 17p11.2 (5, 6) causing lipid abnormalities with clinical symptoms from the skin, eyes and nervous tissue (7).

The syndrome has been reported in small numbers of patients from many countries, but in Sweden more than 60 patients have been found since the syndrome was originally described (7). Thirty-three were alive in the year 2003 and one more patient was born in 2005 (7, 8).

There is no permanent cure for SLS and no specific therapy. Ideally, a multidisciplinary approach should be used to find the best help and treatment for this group of patients. Symptomatic treatment of ichthyosis in SLS can be quite effective and today encompasses oral retinoids (9, 10) and a wide variety of emollients containing hydrating and keratolytic agents such as urea, propylene glycol, salicylic acid and alpha-hydroxy acids, e.g. lactic acid (10, 11). Topical treatment with calcipotriol has also been used in this group of patients (12) and zileuton has been tried for pruritus (13). Learning disability and spastic di/tetraplegia are treated according to the general principles for these conditions (14).

We present here the results of a clinical survey conducted in the years 2003 to 2006 of all known patients with SLS in Sweden.

MATERIALS AND METHODS

The study was approved by the research ethics committees of the Faculties of Medicine in Uppsala and Umeå Universities. The study comprised 34 patients with SLS, 16 females and 18 males, age range 1–76 years, with a median age of 39 years, from 31 families. Most patients were already known at the Uppsala Genodermatosis Centre and from earlier studies of SLS (7, 9, 15, 16) and a few more patients were recruited through the Swedish patient organization for ichthyosis. The study probably encompasses all patients with SLS in Sweden in the years 2003 to 2006.

Twenty-seven patients were descendents from families originating from the northern half of Sweden and another four patients came from the southern half of Sweden. Three more patients with SLS were of foreign extraction; one girl from Colombia and two sisters from Lebanon.

A questionnaire was posted to the patients and their close relatives, together with a letter explaining the purpose and design of the study and requesting their consent to participate. The questionnaire included questions about skin symptoms, sweating ability, itching, and skin symptoms at birth. There were also ques-

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tions about the patients' ongoing systemic and external therapies and the procedures used for skin lubrication and bathing.

All patients were examined by two of the authors. They examined the patients dermatologically (AG) and neurologically (SJ) at the dermatological clinics in Umeå, Skellefteå and Uppsala, or in the patient's home. The patients and their close relatives were also interviewed and the patients' medical records were scrutinized.

The patients were instructed to discontinue their ordinary topical treatment for 24 h prior to the examination. The severity of ichthyosis and erythema was scored by AG separately on a scale from 0 (none) to 4 (very severe) in nine different skin regions (trunk, arms, legs, face, scalp/neck, hands, feet, knees/elbows, and flexural areas). A weighted sum of the nine scores was obtained after multiplying each value by a factor calculated as the size of the corresponding skin area relative to the whole body surface (calculated from the "rule of nine", i.e., trunk 0.36, legs and feet 0.36, arms and hands 0.18, and so on). In this way a maximum weighted total score of 4.0 was possible for ichthyosis and for erythema (17).

Speech disorder was scored on a scale from 0 to 3, where 3 corresponds to speaking with single word sentences with or without dysarthria, 2 speaking short sentences with almost correct pronunciation, 1 speaking with almost normal pronunciation, and 0 normal pronunciation for their age. Motor disability in arms and legs, foot deformity was scored from 0 to 3 (0 = none, 1 = slight, 2 = moderate, 3 = pronounced disability).

RESULTS

Basic characteristics of the cohort

The ages and sex of the 34 patients and the clinical findings are shown in Table I. According to the clinical records the deliveries were often a few weeks premature, but the weight and length at birth were normal according to pregnancy. The case histories showed that spasticity in the arms/legs and learning disability/mental retardation developed between the ages of 4 and 34 months. Subsequently, the neurological symptoms appeared to be constant into adulthood.

Genetic analysis

Mutations in the *FALDH* gene were found in all except one of the SLS patients in this study (Table I). The exceptional patient was a girl with typical clinical SLS symptoms and with deficient FALDH enzyme activity (18), which confirmed her SLS diagnosis, although her mutation has not yet been found. Twenty-five patients from northern Sweden were homozygous for the same mutation (C943T) (19). This indicates a genetic relationship most certainly through a founder effect in northern Sweden, which can be traced back to the early 14th century (19). The remaining eight patients mostly came from the south of Sweden and had various other mutations (nt103delC, C678G, nt865insT, nt941del3ins21, and nt1297delGA) (19, 20).

Dermatological symptoms

All patients except two were reported to have had generalized ichthyosis at birth, but no patient presented with the collodion-baby phenotype. At our examination all 34 patients showed generalized ichthyosis, but the face was mostly unaffected. The teeth and hair were normal in all patients. Hyperkeratotic skin thickening resembling lichenification was commonly seen, especially on the neck, axillary folds (Fig. 1) and lower abdomen. The ichthyosis score (0–4) was highest for feet and hands (median 1.3) and lowest for the face (median 0.3).

Table I shows the weighted ichthyosis scores, which further emphasize the phenotypic variation between the patients (score range 0.1–2.7, median 0.9). Since many of the patients were on retinoids, the severity of their ichthyosis is not a true measure of natural history. Unsurprisingly the ichthyosis score was lower (median 0.5) in the group of patients treated with oral acitretin than in the group without such therapy (median 1.7). The erythema score was low in all patients, (median 0.0, range 0.0–0.9). Most patients (88%) had pruritus, as exemplified in Fig. 2; 65% suffered from hypohidrosis and 47% had mild to moderate keratoderma palmoplantaris.

Ichthyosis treatment

Nineteen patients (56%) were treated with oral acitretin at the time of examination and this therapy was considered unethical to interrupt. The acitretin dosage varied from 10 mg per week to 25 mg per day (Table I). Reportedly, the patients' skin symptoms improved markedly when oral retinoid treatment was started, in most cases as early as in the 1980s. Two of the female patients (29 and 30 years old), who were taking 25 mg acitretin per day, exhibited retinoid dermatitis with small erosions and excoriations on the arms and back. We found that when the acitretin dose was reduced to 25 mg every second day itching and erosions improved, but the skin became somewhat scalier within weeks. Eight of the patients, four of whom were on retinoid therapy, were seen regularly by a dermatologist for their skin symptoms. All other patients were occasionally seen by their general practitioner. All patients were using some kind of topical therapy, and creams containing urea 2–10% were the most common ones and were used by half of the patients. Topical therapy was usually applied 1–2 times per day, but three patients applied the cream only 1–3 times per week. One patient managed to lubricate herself, but the rest had assistance from parents or nursing staff. The treatment also included showering and bathing, sometimes with soaking, at a frequency ranging from twice a day to once a week. Four of the patients were able to shower or bath themselves and the rest had help from parents or nursing staff.

Neurological and orthopaedic symptoms

Motor disability with spasticity and muscular paresis was most pronounced in the legs and was fairly slight

Table I. *Clinical and genetic characteristics of 34 patients with Sjögren-Larsson syndrome from 31 families in Sweden (in reverse chronological order)*

Patient number	1	2	3	4	5	6	7	8	9[a]	10	11	12	13	14	15	16	17
Sex (male/female)	F	M	M	M	F	F	M	F	M	F	M	M	M	M	M	M	F
Age (years)	76	70	66	63	56	53	51	47	46	45	45	43	43	43	42	40	40
Mutation analysis[1]	A	A	A	A	A	A	A	A	A	A	A	A	A	A	B	B	A
Ichthyosis score (mean)[2]	0.1	1.1	0.4	1.8	0.1	0.3	0.6	0.3	1.5	1.0	1.4	0.5	0.5	0.9	0.9	1.0	0.5
Keratoderma palmoplantaris[3]	−	+	+	−	−	+	−	−	−	+	+	+	−	−	+	−	+
Pruritus[3]	+	−	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Hypohidrosis[3]	−	+	+	+	−	−	+	+	−	+	+	−	+	+	+	+	+
Oral acitretin (mg/day)	25	1.5[#]	20	10	10	20	10	25	10	−	−	−	10	10	10	−	25
Creams containing[4]:	U	O	O	U	P	U	U	P	U	U/O	U	L/P	U	L/P	U	L/P	L/P
Motor disability in arms[5]	1	2	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1
Motor disability in legs[5]	3*	3*	3*	3*	3*	2	3	3*	3	3*	3*	3*	3*	3*	3*	3*	3*
Foot deformity[5]	2	3	3	3	3	2	2	3	2	3	2	3	3	3	3	2	3
Speech disorders[5]	3	3	2	3	1	1	1	3	1	3	1	3	3	2	3	2	2
Epileptic seizures[3]	−	−	−	−	−	−	−	+	−	−	−	−	+	+	+	+	−
Retinal crystals[3]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Photophobia[3]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Patient number, continued	18[a]	19	20	21[b]	22[b]	23	24[c]	25	26	27	28[c]	29	30	31[d]	32	33	34
Sex (male/female)	F	M	M	F	M	M	F	F	F	M	F	M	F	F	F	F	M
Age (years)	38	38	34	33	31	30	30	29	28	26	23	23	17	9	8	4	1
Mutation analysis[1]	A	A/B	A	B	B	A	B	A	A	A	B	A	A	B	A	NA	B
Ichthyosis score (mean)[2]	1.0	2.6	0.5	0.2	0.9	1.7	2.3	0.5	0.5	1.9	2.5	2.7	0.3	1.9	1.2	1.7	1.9
Keratoderma palmoplantaris[3]	−	−	−	−	+	−	+	+	−	+	+	+	−	−	+	+	−
Pruritus[3]	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Hypohidrosis[3]	−	−	−	−	+	+	+	+	+	+	+	−	+	+	+	−	−
Oral acitretin (mg/day)	10	−	−	15	25	10	−	25	25	−	−	−	−	−	−	−	−
Creams containing[4]:	U	O	O	U	U	U	U	O	O	U	U	U	L/P	P	L/P	L/P	L/P
Motor disability in arms[5]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
Motor disability in legs[5]	3*	2	2	3	3*	3	3	3	3*	3*	3*	2	3*	2	3	2	2
Foot deformity[5]	3	1	1	2	3	0	3	2	3	2	3	1	3	0	2	1	0
Speech disorders[5]	3	1	2	0	3	1	3	1	1	3	3	0	2	2	1	2	0
Epileptic seizures[3]	+	+	+	−	+	−	+	−	−	+	+	+	−	−	−	−	−
Retinal crystals[3]	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−
Photophobia[3]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

[a]Siblings, [b]siblings, [c]siblings from Lebanon, [d]adopted from Colombia, *wheelchair bound.

[1]Mutation analysis; A: the North-Swedish SLS mutation C943T; B: other SLS mutations. No. 19 has both the North-Swedish mutation and another SLS mutation (compound heterozygocity)

[2]Ichthyosis score (0–4): see Methods.

[3]Present (+) or absent (–).

[4]Abbreviations used: U: urea;L: lactic acid; P: propylene glycol; O: other contents.

[5]Motor disability in arms/legs, foot deformity and speech disorders: 0 = none, 1 = slight, 2 = moderate, 3 = pronounced.

[#]Oral acitretin: 10 mg/week.

NA: data not available

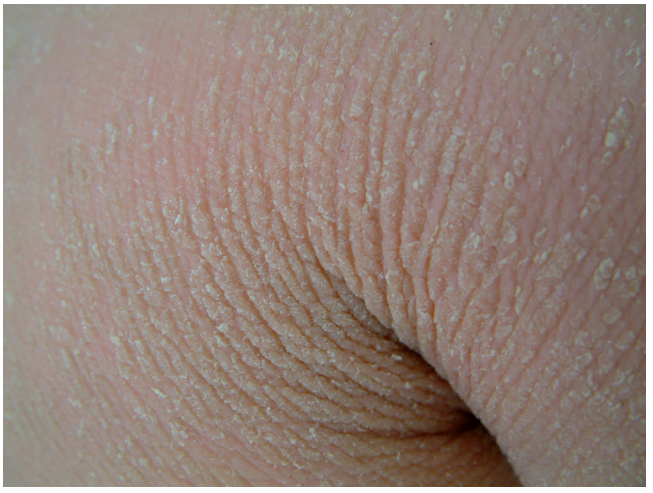

Fig. 1. Skin thickening resembling lichenification in the frontal axillary fold of a 38-year-old man with Sjögren-Larsson syndrome (no retinoid therapy).

in the arms (Table I). Twenty patients (age range 17–76 years) were completely dependent on a wheelchair for mobility, seven patients (aged 29–46 years) sometimes used a wheelchair, and seven patients (aged 1–53 years), who did not use a wheelchair, walked with some support. This latter group included the four youngest patients (1–9 years).

Only one patient had severe scoliosis, but contractures in the legs due to the spasticity were common. Poor blood circulation in the lower legs and oedematous, deformed feet were frequently found in adults (Fig. 3 and Table I).

Learning disability and speech disorders

All patients had learning disability, which varied from slight to pronounced and was expressed in their speech disorders. Thirteen patients spoke with single word sentences and a few also had dysarthria, eight patients spoke short sentences with almost correct pronunciation, and 13 had normal or almost normal pronunciation for their age. Motor dysfunction slightly impaired their pronunciation. Their talking was mostly influenced by their reduced intellectual capacity and not by ageing. There was no obvious correlation between speech disorders and motor disability.

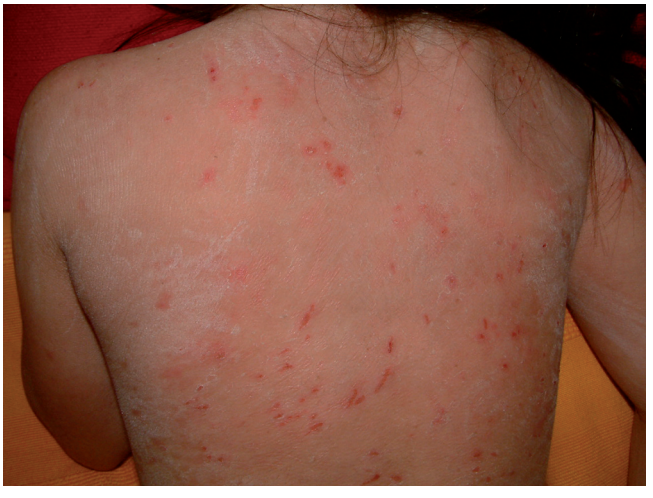

Fig. 2. A 9-year-old girl with Sjögren-Larsson syndrome who had severe pruritus. She was insufficiently treated with bland emollients and had no retinoid therapy.

Epilepsy

Thirteen patients were being treated medically and one of them had undergone neurosurgery for epilepsy.

Ophthalmological symptoms

All patients were suffering from photophobia and the great majority (32/34) had retinal crystals in their ocular fundi according to earlier ophthalmological examinations (21) (Table I).

Living conditions

All four children in the study and nine of the adult patients lived with their parents. Nine patients lived alone in specially adapted flats with staff close at hand for help on call. One severely disabled patient had personal assistance 24 h/day and 11 other patients lived in homes for small groups with staff around day and night.

DISCUSSION

Our study, which encompasses one of the largest cohorts of patients with SLS ever published, confirms the great variation in the general condition as well as in the severity of the ichthyosis in this genotypically very homogeneous disorder. Historically, the patients' ichthyosis improved notably after the start of oral retinoid treatment, usually in the 1980s. Very few adverse

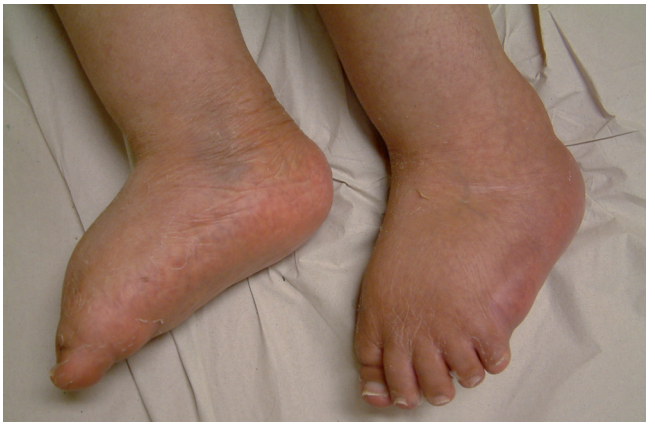

Fig. 3. Oedematous and deformed feet in a 30-year-old woman with Sjögren-Larsson syndrome (patient no. 24).

events occurred. In general, the treatment was well tolerated, especially after dose adjustments. In some cases only low doses of acitretin were needed to control the skin. Only four of the 19 patients on retinoids were regularly seen by a dermatologist, presumably because most of them lived far from a dermatological clinic. The retinoid treatment was usually monitored by a general practitioner who received irregular advice from a dermatologist. In our opinion it is important that these patients have regular medical supervision and follow-up by a dermatologist, as the optimal dose of retinoid varies considerably between patients and cases who were both under- and overtreated with retinoids were encountered in our study.

Sixty-five percent of the patients reported either directly or indirectly via close relatives that sweating capacity was reduced or absent. This is a frequent problem also in patients with other types of congenital ichthyosis (17) and may lead to heat intolerance in hot climate and during exercise.

Eighty-eight percent of the patients reported pruritus, which subsided with improvement of the general skin condition when effective topical treatment and/or systemic therapy with retinoids was given. However, pruritus can occasionally be elicited as a side-effect of too high a dose of retinoids. None of the patients had tested zileuton (13), which is not available in Sweden. Topical therapy is the basis for effective treatment of ichthyosis in SLS, and all but one patient in this study applied this with the help of parents or staff. There is a need for life-long support and help for the skin problems. Clearly there is also a need for improvement in the treatment of ichthyosis in SLS.

Twenty-six participants have been followed up irregularly for more than 25 years by one of the authors (SJ) (7). The ichthyosis generally showed improvement over time, but this was considered to be due to improved internal and external treatment; no obvious change occurred with age *per se*. Similarly no mental deterioration was noted over time. Speech improved in the most talented, probably by stimulation, but some patients remained very poor speakers through life, though without deterioration. Hand function improved a little with training, but gross motor function deteriorated in the most disabled patients, probably as a result of poor training (22).

In conclusion, SLS is a severely disabling disease with variable neurological and skin manifestations. The latter symptoms are amenable to treatment, but a more pronounced improvement in all symptoms will probably have to wait for the introduction of gene therapy in clinical praxis (23).

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