PRINT: ISSN 0972-3757 ONLINE: 2456-6360
Int J Hum Genet, 2(4): 223-232 (2002)
DOI: 10.31901/24566330.2002/02.04.02

Genetics of Sjögren Larsson Syndrome and a Case Report from India

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KEY WORDS Sjögren Larsson Syndrome; ALDH3A2; FALDH1; SLS

ABSTRACT Sjögren Larsson syndrome (SLS) is a rare autosomal disorder that is characterised by congenital ichthyosis, spastic diplegia or qudriplegia and mental retardation. It is caused by the deficiency of the enzyme, fatty aldehyde dehydrogenase (FALDH) that is required for the oxidation of fatty alcohol to fatty acid. The metabolism of leukotrine B4 (LTB4) has also been reported to be defective in SLS patients. The gene, ADLH3A2, encoding for FALDH has been localised at 17p11.2 and mutations in it cause SLS. The worldwide frequency of SLS is reported to be less than 1: 100,000 births but rarely a case has been reported from India. This article reviews the genetic factors in SLS and reports a case of SLS from India, with two similarly affected sibs. The management of SLS including genetic counselling and prenatal diagnostic possibilities are also discussed.

INTRODUCTION

Sjögren-Larsson Syndrome (SLS), sometimes called T. Sjögren syndrome to differentiate it from Sicca syndrome, is a rare neurocutaneous disorder that exhibits autosomal recessive inheritance. It is characterised by mental retardation, congenital ichthyosis, spastic diplegia or quadriplegia (Sjögren 1956; Sjögren and Larsson 1957). Mutations in the ADLH3A2 gene situated at 17p11.2 and encoding for fatty alcohol dehydrogenase (FALDH) are responsible for the causation of SLS.

Worldwide the incidence of SLS is reported to be less than 1:100,000 births. However, its frequency amongst mentally retarded patients is observed as 1 in 1000 patients and 1 in 2500 amongst paediatric dermatology patients. Very high prevalence of SLS has been observed in north east of Sweden where an incident of 8.3:100,000 births has been reported (Jagell et al. 1981). However, there are no epidemiological reports on its frequency in the Indian population, and only rarely a case has been reported from here (Sood et al. 2002).

The typical phenotype and clinical features of the SLS include congenital ichthysosis, lamellar-type hyperkeratosis, mental retardation, development delay, proportionate short stature, pigmentary abnormality of macula (Gilbert et al. 1968; Jagell et al. 1981), hypohidrotic or dry skin. However, symptoms like Dandy-Walker malformation (Fivenson et al. 1989), microcephaly, hypertelorism, juvenile macular dystrophy of retina (Willemsen et al. 2000a), enamel abnormalities, retinitis pigmentosa, chorioretinitis (Gilbert et al. 1968), widely spaced teeth, cataract, seizures, abnormal EEG, spasticity, and increased tendon reflex, have also been reported to be frequently associated with this syndrome (Winter and Baraitser 2000). Clinically ichthyosis is usually present at birth in patients with SLS, but in some it may be seen only after patients are one year old. There may be hyperkeratosis around the umbilicus, neck and the flexures. Mental retardation and spastic quadriplegia/diplegia are usually evident by the third year of life (Lacour 1996). Arms are usually less severely affected than the legs. About 20% of the cases show glistening spots on the macula (Theile 1974).

The main biochemical defect underlying the SLS is the deficiency of the enzyme, fatty aldehyde dehydrogenase (FALDH), which is a component of the fatty alcohol:NAD oxidoreductase enzyme complex (FAO). The FALDH is a microsomal enzyme that is required

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to oxidize fatty alcohol to fatty acid. It catalyzes the oxidation of medium- and long-chain fatty aldehydes (aliphatic) that are derived from fatty alcohols to their corresponding carboxylic acids (Rizzo et al. 1988). It is accumulation of the long chain fatty alcohols and the modifications of macromolecules caused by the presence of excess of fatty aldehydes that are believed to cause the manifestations of SLS symptoms. These accumulations distort the epithelial water balance and are responsible for increased transepidermal water loss, which results in the development of ichthyosis (Avigan et al. 1985). The deficiency of fatty aldehyde dehydrogenase has also been demonstrated in the cultured skin fibroblasts of SLS patients (Rizzo et al. 1991). The metabolism of leukotrine B4 (LTB 4) has been reported to be defective in SLS patients and its defective inactivation may be responsible for the presence of pruritis seen in the patients with SLS (Willemsen et al. 2000b).

GENETIC FACTORS IN SJÖGREN LARSSON SYNDROME

SLS has always been reported as an autosomal recessive condition that is usually evident either from the presence of consanguinity or by the prevalence of the condition amongst the sibs only. Not many large families have been reported in the literature. Although no detailed epidemiological studies are available, its incidence is reported to be higher in those populations were consanguinity is more prevalent, e.g. Haliwas of Halifax, Warren counties in North Carolina, Vasterbotten and Norrbotten counties in Sweden (Zalewska et al. 2002).

Sjörgen (1956), Sjörgen and Larsson (1957) who first reported this syndrome suggested that all of their 28 cases may be derived from the same mutation. They speculated that the mutation probably occurred about 600 years ago, and that approximately 1.3% of the population of northern Sweden is heterozygous for this gene.

Rayner et al. (1978) reported two brothers and one sister suspected to be SLS. Gedde-Dahl et al. (1984) reported a family having 3 sibs affected with ichthyosis similar to that of SLS. Mohrenschlager et al. (2000) reported a case from Germany of 3.5 year old girl with SLS. In India, the SLS has rarely been reported, but recently, Sood et al. (2002) reported one case of SLS in a 6 year old girl.

Jagell et al. (1981) traced 58 patients in 41 Swedish families. 45 from these patients were born in a small area of the northeastern Sweden known as county of Vasterbotten. The prevalence of the disorder, frequency of the heterozygotes, and the gene frequency in that area were estimated to be 8.3 per 100,000 persons, 2.0%, and 0.01, respectively.

The SLS gene was mapped to chromosome 17 by linkage analysis and allelic associations (Pigg et al. 1994). Meiotic recombinations suggested that the gene is flanked by the microsatellite marker D17S805 on the centromeric side and D17S783, D17S959, D17S842, and D17S925 markers on the telomeric side. The strong allelic association to D17S805 suggested that the mutation is located close to this marker.

Rogers et al. (1995) undertook the analysis of 7 pedigrees of diverse ethnic origins (Arabic, mixed European, Native American and Swedish descent) and confirming the observations of Pigg et al. (1994) also linked the SLS gene to the pericentric region of the 17th chromosome (17p11). Amongst their patients from 2 consanguineous Egyptian families, they found homozygosity at all 9 marker loci in this region which suggested that the region carrying the SLS gene is identical by descent.

The human FALDH cDNA was cloned by DeLaurenzi et al. (1996) who also demonstrated that it maps to chromosome 17 and it is estimated to be within 600 kb of the SLS gene (Pigg et al. 1994; Rogers et al. 1995). The first mutation in the FALDH gene, that causes SLS, was reported by DeLaurenzi et al. (1996). They also reported that the sequence analysis of FALDH gene from 3 unrelated patients with SLS showed distinct mutations in them. Sillen et al. (1998a) undertook the detailed genetic and physical mapping of the region surrounding the SLS/FALDH locus, using microsatellite markers, radiation hybrid panel, and yeast artificial chromosomes (YACs) and localised the gene to the 17p11.2. Rizzo et al. (2001) reported that the FALDH gene consists of 11 exons and is closely linked to the gene for ALDH3.

Several gene symbols have been used for Sjögren Larsson syndrome. These include SLS, FALDH, ALDH10, and ALDH3A2. The primary gene symbol for this syndrome is now ALDH3A2 and FALDH is its alias; and the symbols SLS and ALDH10 are now considered

Table 1: The basic genetic information about Sjögren Larsson syndrome

Disease phenotype	Sjögren Larsson syndrome
Cytogenetic location	17p11.2
Inheritance pattern	Autosomal recessive
MIM number	270200
HUGO/GDB nomenclature (Approved gene symbol)	ALDH3A2
Alias gene symbol	FALDH1
Earlier gene nomenclature	ALDH 10; SLS
Approved gene name	Aldehyde dehydrogenase 3 family, member A2
Total number of bases	3673 bp
HGNC ID	403
Sequence accession ID	L47162
Nucleotide accession ID	NM_000382
PMIDs	7894487
GDB ID	1316855
Locus ID	224
Protein ID	NP_000373.1
Coriell Cell Respository number	NA 10641
Mouse homologue	Aldh 3a2

obsolete. Similarly, the name aldehyde dehydrogenase 10 (fatty aldehyde dehydrogenase) is considered to be obsolete (GDB 2002; Table 1).

Sillen et al. (1998) investigated 16 SLS families from Europe & Middle East and identified 11 different mutations. These included, 5 nucleotide substitutions resulting in amino acid changes, 5 frame shift mutations introducing a stop codon, and one in-frame deletion with insertion at the same position. They also reported presence of polymorphism. Pigg et al. (1998) analysed 12 microsatellite markers in 10 additional non-Swedish families with SLS originating from Germany, Lebanon, Spain and Canada and gave the evidence that SLS is a homogenous disorder. However, their haplotype analysis of 7 German families did not give any evidence that they carry the same mutation or the major "Swedish SLS gene".

Rizzo et al. (1999) did mutation analysis of the FALDH gene in 63 SLS cases and reported presence of mutations in all of them. These included 49 different mutations viz. 10 deletions, 2 insertions, 22 amino acid substitutions, 3 nonsense mutations, 9 splice-site defects, and 3 complex mutations. They also reported 4 single nucleotide polymorphisms (SNPs) in the FALDH gene. Four of the common mutations (551C→T, 682C→T, 733G→A and 798+1delG) were found to be associated with multiple SNP haplotypes. Kraus et al. (2000) through a method based on RT-PCR and protein truncation test identified mutations in eight of the nine German SLS families. These included seven different mutations: an exon 2 splice donor mutation; two exon 3 splice donor mutations; a 906delT deletion in exon 6; a genomic deletion of about 6 kb including exon 9; a 1277T>G transversion; and a 1297delGa deletion.

Willemsen et al. (2001b) who studied 19 patients with SLS reported 8 different mutations in these, including 3 new ones: a large 26-base pair deletion (21-46 del), a missence mutation (80C→T), and an insertion mutation (487-488 insA). Missence mutations involving 24 amino acid positions in the FALDH gene have also been reported (Rizzo et al. 2001).

Till now 62 mutations that have been reported for the ALDH3A2 gene include; 37 nucleotide substitutions, 16 small deletions, 3 small insertions, 3 small indels, 1 gross deletion and 2 complex rearrangements (HGMD, 2002; Table-2a, Table-2b). 10 SNPs for the ALDH3A2 gene have also been documented of which 8 are of intron type (GeneCards 2002).

GENETIC COUNSELLING ASPECTS IN SLS CASES

The recurrent risk for SLS, as for any other autosomal recessive disorder, is 25% for each subsequent pregnancy. The determination of heterozygous status of the individuals in the families having a SLS case is important for genetic counselling. Its significance increases substantially if consanguinity is prevalent in that population. Apart from it, the determination of frequency of different types of mutations of SLS in a particular population is of significance for DNA based diagnostics as well as genetic counselling.

Rizzo et al. (1997) identified a frequent FALDH mutation (a 2-bp deletion) in exon 9 among 10 of their 21 European SLS probands. This deletion of nucleotides GA1297-1298 resulted in the premature termination of translation at codon 435 along with substitution of Arg and Cys for Glu 433 and Gly, respectively. They observed that this mutation along with another mutation, 9C943Y accounts for 48% of the SLS alleles in the European SLS patients. Similarly, Sillen et al.

Table 2a: The mutations (nucleotide substitutions) reported in the ALDH3A2 gene resulting in Sjögren Larsson Syndrome phenotype (after HGMD, 2002)

a. Missense/nonsense (n=28)

Codon	*Nucleotide*	*Amino acid*	*Reference*
10	aCAG-TAG	Gln-Term	Rizzo et al. (1999)
45	cATC-TTC	I1e-Phe	Rizzo et al. (1999)
64	GTC-GAC	Val-Asp	Rizzo et al. (1999)
78	TGG-TAG	Trp-Term	Rizzo et al. (1999)
106	CTG-CGG	Leu-Arg	Sillen et al. (1999)
114	CCC-CTC	Pro-Leu	Rizzo et al. (1999)
121	CCA-CTA	Pro-Leu	Rizzo et al. (1999)
184	ACG-AGG	Thr-Arg	Rizzo et al. (1999)
184	ACG-ATG	Thr-Met	Rizzo et al. (1999)
185	GGA-GCA	Gly-Ala	Rizzo et al. (1999)
214	TGT-TAT	Cys-Tyr	DeLaurenzi et al. (1996)
226	TGCa-TGG	Cys-Trp	Sillen et al. (1998)
228	aCGC-TGC	Arg-Cys	Rizzo et al. (1999)
237	TGT-TAT	Cys-Tyr	Rizzo et al. (1999)
245	cGAC-AAC	Asp-Asn	Rizzo et al. (1999)
279	tTAT-AAT	Tyr-Asn	Rizzo et al. (1999)
315	cCCA-TCA	Pro-Ser	DeLaurenzi et al. (1997)
328	ATGc-ATC	Met-I1e	Rizzo et al. (1999)
365	TCG-TTG	Ser-Leu	Sillen et al. (1998)
386	AAT-AGT	Asn-Ser	Aoki et al. (2000)
406	tGGG-AGG	Gly-Arg	Rizzo et al. (1999)
411	tCAC-TAC	His-Tyr	Rizzo et al. (1999)
412	cGGA-AGA	Gly-Arg	Sillen et al. (1998)
415	AGT-AAT	Ser-Asn	Rizzo et al. (1999)
419	TTT-TCT	Phe-Ser	Rizzo et al. (1999)
423	CGT-CAT	Arg-His	Rizzo et al. (1999)
426	TTA-TGA	Leu-Term	Kraus et al. (2000)
447	aAAG-GAG	Lys-Glu	Rizzo et al. (1999)

b. Splicing (n=9)

IVS	*Relative location*	*Substitution*	*Reference*
2	+2	T-C	Kraus et al. (2000)
3	-2	A-G	Rizzo et al. (1999)
3	+1	G-C	Kraus et al. (2000)
3	+2	T-G	Rizzo et al. (1999)
4	-2	A-G	Rizzo et al. (1999)
4	-14	T-A	Rizzo et al. (1999)
5	+5	G-A	Rizzo et al. (1999)
5	-1	G-C	Rizzo et al. (1999)
7	-1	G-C	Rizzo et al. (1999)

(1997a) reported the presence of a common point mutation in exon 7, resulting in C→T exchange at nucleotide position 943, in SLS patients of northern Swedish origin. This mutation causes the replacement of a highly conserved proline with a serine. The presence of this mutation observed by them in 49 out of the 58 affected chromosomes is of significance for genetic counselling.

Kraus et al. (2000) have also reported that just 2 mutations: the genomic exon 9 deletion and the 906delT in exon 6 affected five out of their seven SLS patients, from a small region of Northern Bavaria in Germany, and thus accounted for 71% (10/14 chromosomes) of Bavarian SLS alleles and these had not been described in SLS families from other countries.

Table 2b: The mutations, other than nucleotide substitutions, reported in the ALDH3A2 gene resulting in Sjögren Larsson Syndrome phenotype (after HGMD, 2002)

a. Small insertions (n=3)			
Condon	*Nucleotide*	*Insertion*	*Reference*
207	620	G	Rizzo et al. (1999)
288	865	T	Sillen et al. (1998)
437	1311	ACAAA	Tsukamoto et al. (1997)
b. Small deletions (n=16)			
Location/Codon involved in deletion			***Reference***
34			Sillen et al. (1998)
95, 112, 124, 156, 157, 266 (2), 273, 322, 366, 430			Rizzo et al. (1999)
173, 269			DeLaurenzi et al. (1996)
432			Tsukamoto et al. (1997)
461			Willemsen et al. (1999)
c. Small indels (n=3)			
Location/Codon involved in deletion			***Reference***
7,373			Rizzo et al. (1999)
316			DeLaurenzi (1996)
d. Gross deletions and complex rearrangements (n=3)			
Deletion/Rearrangement	***Numbers reported***		***Reference***
Deletion	1		Sillen et al. (1998)
Complex rearrangements	2		Sillen et al. (1998); Rizzo et al. (1999)

HETEROZYGOTE IDENTIFICATION AND PRENATAL DIAGNOSIS

Kaminaga et al. (2001) reported that a moderate decrease in FAO (fatty alcohol: NAD+oxidoreductase complex) activity can be detected by proton magnetic resonance spectroscopy (1H-MRS) in the heterozygous SLS cases and observed that 1H-MRS can be used as a powerful tool for screening of SLS hetrozygotes.

Prenatal diagnosis of SLS was first attempted by Kausseff et al. (1982). Tabsh et al. (1993) reported a pregnancy where foetal skin biopsy at 19 weeks was normal but abnormal at 23.5 weeks. However, Rizzo et al. (1994) observed that prenatal diagnosis by foetal skin biopsy was unreliable as ichthyosis was not always present at birth. They reported prenatal diagnosis in two cases by measuring FAO and FALDH levels in cultured amniocytes, chorionic villus cells and fibroblasts. All showed significant deficiency of FAO and FALDH.

Sillen et al. (1997) demonstrated that the prenatal diagnosis of SLS is possible. They undertook PCR-based mutation analysis during pregnancy where the parents were heterozygous carries for the C943T mutation in the FALDH gene. The foetus was found to be homozygous for the mutation and thus affected by SLS.

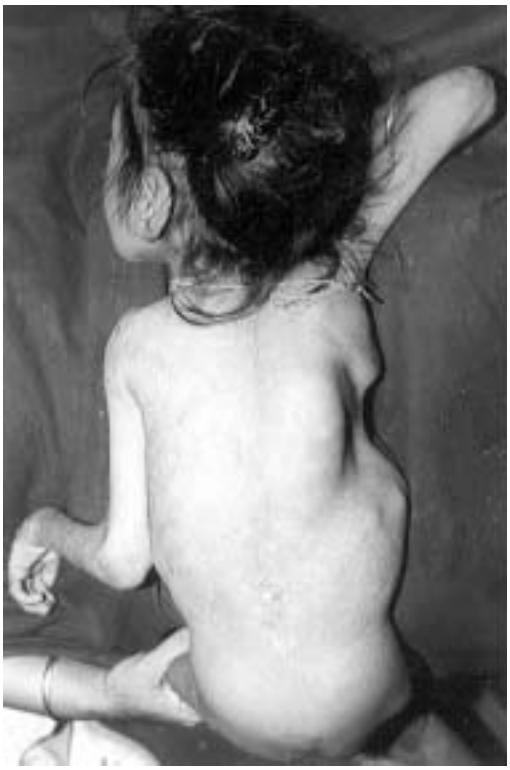

Fig. 1. The presence of kyphoscoliosis is clearly seen in the patient

THE CASE REPORT OF SLS FROM INDIA

A nine and half year old boy was referred to the Centre for Genetic Disorders with a history of dry ichthyotic and hyperpigmented skin patches since birth, birth asphyxia and peripheral cyanosis. He was born to a third para mother by normal vaginal delivery at 34 weeks gestation. There was a history of frequent attacks of high grade fever and chest infections. At the age of two years the child had developed generalized tonic clonic seizures as well as jerky movements of the lower limbs during sleep. All physical and neurological milestones were severely delayed. In addition there was a marked regression of milestones at the age of three years when the child stopped talking and crawling. There was hypertonia in the upper and lower limbs. Flexion contractures at the elbows and knees developed by five years of age.

The physical examination revealed proportionate short stature with kyphoscoliosis (Fig.1). There were flexion contactures at the wrist, elbow, metacarpophalangeal, interphalangeal, knee and ankle joints. Anaemia and grade III clubbing of the fingers was also present. Central nervous system examination revealed severe mental retardation and spastic quadriplegia since birth. Lower limbs were more severely involved than the upper limbs. Deep tendon reflexes were exaggerated and ankle clonus was present. The plantars were bilaterally upgoing and the chest was prominent with pectus carinatum. The respiration was laboured and there was a pronounced inspiratory effort and respiratory distress.

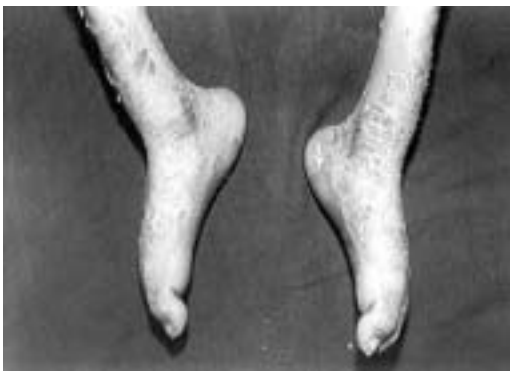

Fig. 2. Photograph showing the presence of hyperkeratosis on the lower limbs and feet of the patient

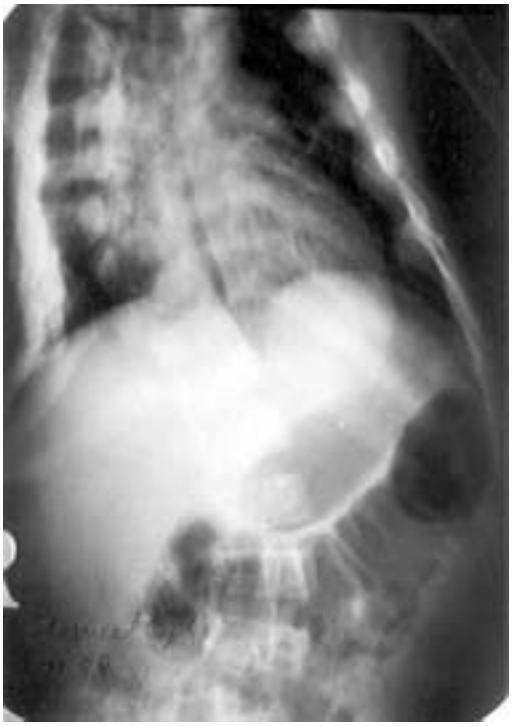

Fig. 3. The X-ray showing the presence of kyphoscoliosis of the spine in the patient

Fundoscopy revealed presence of bilateral diffuse white spots on the retina. The skin examination showed generalized ichthyosis. The hyperkeratosis was present over the face, trunk and extensor surface of the limbs and there was axillary and antecubital hyperpigmentation. The palms and soles were also hyperkeratotic (Fig. 2). There was decreased sweating, and dental enamel discolouration. The hair were fine but sparse.

The laboratory investigations were negative except for severe anaemia. The EEG and CT scan were also both normal. The skin biopsy showed parakeratosis, irregular acanthosis, follicular plugging and decreased number of sweat glands.

The X-ray of spine showed kyphoscoliosis, irregular end plates of vertebrae and platyspondyly (Fig. 3). X-ray hands showed cone shaped epiphysis of phalanges while the X-ray of long bones showed irregular epiphysis, wide metaphysis and osteosclerosis. However, the bone age was less than the chronological age. The chromosomal constitution of the

proband was 46,XY.

The family history revealed that the proband was born to a 27 year old woman from a non-consanguineous marriage. The eldest sib was a female who died at birth with massive ichthyosis. The second child was a term female child who was normal at birth. At the time of presentation she was 13 years old and had only leucoderma. The youngest child was also born with massive ichthyosis and she had died on the 13th day of life. No other positive findings was seen upon detailed pedigree analysis except that the maternal and paternal great-grand parents of the proband belonged to nearby villages from a particular area of Rawalpindi, now in Pakistan.

DISCUSSION

The term "Sjögren Larsson syndrome" was first introduced by Baar et al. (1960) to describe the series of cases reported by Sjögren (1956) and by Sjögren and Larsson (1957), which were characterised by congenital ichthyosis, spastic disorders and mental retardation. Similar cases had also been documented earlier. A case of female child from Cuba, with spastic paraplagia, ichthyosis and mental deficiency was reported by Pardo-Castello and Faz in 1932. Two years later, three brothers with similar clinical features were reported from Italy (Pisani and Cacchione, 1934). The cases of Sjögren Larsson syndrome have now been reported in patients belonging to diverse ethnic origins (Rayner et al. 1978; Rogers et al. 1995; Pigg et al. 1998; Sillen et al. 1998; Rizzo et al. 1999; Mohrenschlager et al. 2000). Though its frequency has been reported to vary from 1 in 1000 mentally retarded patients to 1 in 2500 pediatric dermatology patients (Zalewska et al. 2002), it has rarely been reported from India. Just three reports of SLS cases were found from India wherein a single case each had been reported (Kirubakaran et al. 1982; Shrivastava et al. 1986; Sood et al. 2002). Two sisters of Indian origin have also been reported from UK (Thakur and Smith 1991).

The SLS cases have always been reported as autosomal recessive (OMIM 2002) and the presence of parental consanguinity is expected. Our case had two more sibs who had similar symptoms and had died due to massive ichthyosis. No consanguinity was observed in this family. However, the detailed pedigree analysis revealed, that the proband's grandparents had migrated from Rawalpindi (now in Pakistan) in 1947 and his maternal and paternal great-grand parents all had lived in the same area in nearby villages. Though direct consanguinity could not be traced, the same having been there, another generation or two earlier, cannot be completely ruled out on account of the religio-socio reasons.

The SLS patients have been reported from both the sexes and the disease does not show any sex preference (Zalewsta et al. 2002). In the sibship of our case also, two female and one male were affected.

In SLS patients, ichthyosis is usually seen at birth or appears within the first few days of life and its severity increases with age. The ichthosis is usually generalised, but at the trunk, flexures and dorsal aspects of the hands and feet it is more accentuated while the face is normally spared. The hair and nails are also usually normal. The ichthyosis in the SLS patients is of non-bullous type and is associated with pruritus that differentiates it from the other types of ichthyosis. The skin gradually becomes thick and scaly during the 1st year of life, and lamellar-type hyperkeratosis with thin scales can also be seen in these cases. Dental enamel hypoplasia also reported in such cases. In our case too generalised ichthyosis was present and hyperkeratosis was also seen over the trunk and external surface of the limbs, palms and soles. However, the face was also involved and the dental enamel had discolouration.

The skin biopsy in SLS patients shows hyperkeratosis, focal parakeratosis, acanthosis, papillomatosis, and sparse dermal lymphocytic inflammatory infiltrate. Similar findings were present in our case also. The ultrastructural examination in such cases shows abnormal lamellar inclusions in the cytoplasm of spinous, granular and horny cells, prominent Golgi apparatus, and increased number of mitochondria. Sometimes lipid droplets in the horny layer are also present (Ito et al. 1991).

The EEG and CT scan were normal in our case. Sood et al. (2002) have also reported normal EEG in their cases. Fivenson et al. (1989) too reported a case of SLS with normal MRI. However, Zalewska et al. (2002) observed that in SLS patients, the EEG may show multifocal epileptic discharges in the presence of

disorganized background activity and the CT scan may show cortical atrophy. The severity of CT findings usually correlates with the severity of neurological symptoms. The brain MRI shows hypomyelination. The protein MR spectometery shows abnormal signals at lipid region in the periventricular white matter suggesting presence of free lipids or lipophilic substances.

The postmortem histopathologic examination of the brain suggests a basic disorder of the central myelination, usually mild loss of gray matter including basal ganglia, with astrocytic accumulation and also accumulation of lipids and lipofuscin like pigments (Yamaguchi et al. 1998).

The presence of severe mental retardation, spastic qudriplegia, and kyphoscoliosis as seen in our case, is characteristically associated with SLS patients. Initially the neurological signs are non-specific but by the age of 1-2 years the severe neuromotor and mental development delay become obvious (Wallis and Klushiner 1960). The speech is either delayed or is impaired. The mental retardation is usually progressive and in 70% of the SLS cases the IQ is < 50. Epilepsy has been reported to be present in about 30-50% of the patients. After the appearance of the neurological symptoms (age 1-2 y), the developmental milestones are progressively delayed. As a result of the progressive spasticity, the initial ability to walk short distances alone is also lost. After the puberty, there is no progression of the neurological findings or mental retardation.

The other changes commonly observed in patients of SLS are tooth enamel dysplasia, epilepsy, hypertelorism and decreased sweating (Selmanowitz and Porter 1967). Moldanado et al. (1975) reported that ichthyosis, hypogonadism and mental retardation were the most common features while epilepsy, short stature and polyneuritis were less commonly seen. Irregularities in the length of the fingers and abnormal dermatoglyphic findings in SLS have also been reported (Richards et al. 1957). The retinal changes, like diffuse white spots on retina in our case, and macular degeneration are reported in about a third of SLS patients (Gilbert et al. 1968).

Similar to our case, the negative findings in routine laboratory investigations have also been reported by others. Willemsen et al. (2001) found no diagnostic abnormality in the plasma, urine, and cerebrospinal fluid in their SLS patients. Sood et al. (2002) reported that the haematological and biochemical parameters were within normal limits in their single SLS patient. However, Willemsen et al. (2001) from their studies on the estimation of the LTB4 and its metabolites in the urine and cerebrospinal fluid as well as the degradation capacity for LTB4 in fresh polymorphonuclear leukocytes of SLS patients reported that defective LTB4 degradation can be used as a non-invasive diagnostic tools for such patients.

MANAGEMENT AND TREATMENT STRATEGIES

As currently no established curative treatment is available, therefore, the management of the SLS patients assumes greater significance. The management of SLS patient requires a multi disciplinary approach and needs the involvement of a dermatologist, a paediatrician, a neurologist, an ophthalmologist, an orthopeditian, and a physiotherapist. The management is primarily of rehabilitative nature for the physical and neurological defects. The early physiotherapy, and subsequent soft tissue surgery e.g. hamstring release surgery and braces help in controlling the spasticity of limbs and facilitate the patient to move around (Haddad et al. 1999). The sauna baths and frequent showers help in reducing the pruritic condition of the SLS patients.

The symptomatic treatment for ichthyosis is usually the local application of soft paraffin, lanolin, 5% citric acid ointment or mineral oil (Kondremul, Zymenol). The skin retinoids (Soriatane, etc.), emollients (Vitamin D-3 analogues) and keratolytic (urea) agents are also recommended for SLS patients as they reduce the increased epidermal turn over and soften the epidermis (Ito et al. 1991; Lucker et al. 1995; Lacour 1996). Leukotriene synthesis inhibitors were predicted as curative treatment of the future for the ichthyosis and prutitus of the SLS patients (Willemsen et al. 2000c).

Willemsen et al. (2001a) observed that patients with SLS might benefit from treatment with zileuton, especially for pruritus. Zileutron is effective as it inhibits the synthesis of leukotriene (LT)B4, whose degradation is one of the defective metabolic routes in SLS. Willemsen et al. (2000c) also made similar observation that

inhibtion of 5-lipoxygenase reduces the severity of pruritus in the SLS patients. Audada et al. (2002) reported clinical improvement in 3 cases upon treatment with topical keratolytic agents and a dietary program that included reduced total fatty intake at 30% of the total calories, n-3 and n-6 acids (canola oil) as well as unsaturated fatty acids (Milupan milk). Earlier, similar findings were reported by Taube et al. (1998).

Molecular analysis of the SLS patients is essential for prenatal diagnostics and proper genetic counselling. Till now 62 mutations in the ALDH3A2 gene resulting in the Sjögren Larsson syndrome have been reported from various parts of the world. However, till now we have no information about the molecular status of the Indian SLS cases. The mutation analysis of our case is in process.

ACKNOWLEDGEMENT

This work was, in part, supported by DBT grant (BT/TF/09/21/90) awarded to JRS.

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