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CASE REPORT

Sjogren- Larsson Syndrome with Type-1 Distal Renal Tubular Acidosis in Siblings

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Abstract

Sjogren-Larsson syndrome (SLS) is a rare autosomal recessive lipid metabolic disorder caused because of the defect in fatty alcohol oxidation resulting from fatty aldehyde dehydrogenase (FALDH3A2) deficiency. Sjogren-Larsson syndrome is constituted by the trio of generalised spastic paralysis, intellectual impairment, & ichthyosis. The inability of hydrogen ions secretion from the distal tubule characterises dRTA (distal (Type 1) renal tubular acidosis). The dRTA aetiology is diverse, but it can be acquired or inherited. We report siblings who presented with congenital ichthyotic hyperkeratosis, spastic diplegia and severe learning disabilities, which were suggestive of SLS. Distal renal tubular acidosis diagnosis was done on the basis of severe serum hypokalaemia, urine electrolytes showing high potassium levels, metabolic acidosis with a positive anion gap, high pH of urine, Urinary & Blood PCO_2 difference (UB PCO_2) on the lower side, ($FeHCO_3$%) showing mild bicarbonaturia (<5%), medullary nephrocalcinosis, Hypercalciuria as well as the omission of other differential diagnosis. Management in SLS was supportive. The child demonstrated symptomatic improvement after starting standard therapy for SLS & distal renal tubular acidosis. To conclude, distal renal tubular acidosis ailment in children can be controlled with a good long-term prognosis, but precise diagnosis as well as management are critical. Early detection can assist the physician in implementing appropriate supportive care as well as possible curative gene therapy.

Keywords: Ichthyosis; spastic diplegia; Intellectual disability; Distal Renal Tubular Acidosis; Hypokalaemia

Introduction

Sjogren-Larsson syndrome (SLS) is a rare neurocutaneous disease featuring tetraplegia or spastic diplegia, congenital ichthyosis & mild to moderate intellectual impairment.[1] SLS occurs due to an

abnormality of fatty alcohol oxidation that results from microsomal fatty aldehyde dehydrogenase (FALDH3A2) deficiency, a fatty alcohol component: Nicotinamide Adenine Dinucleotide (NAD) -oxidoreductase enzyme complex, deficiency of FALDH may result in long-chain fatty alcohols' build-up, compromising structural consequences for cell membrane integrity and disrupting the barrier functioning of skin as well as the brain's white matter.[2] The FALDH gene was discovered on chromosome 17p11.2 in the year 1994, and its location was determined. In patients with SLS, mutation assessment has shown a variety of mutations in the FALDH gene.[3] It affects people of all races, with an estimated incidence of 0.4 per 100,000 or less. Over two hundred cases have been recorded around the world.[3]

The inability of hydrogen ions secretion from the distal tubule characterises dRTA (distal (Type 1) renal tubular acidosis). In the year 1946, it was first identified & marked by hypokalaemia, severe metabolic acidosis with a positive anion gap, high pH of urine (>5.5), nephrolithiasis, and nephrocalcinosis as a clinical syndrome. During infancy, chief features include failure to thrive, weakness, polyuria and polydipsia. Later rachitic manifestations become prominent. Some patients have sensorineural deafness.[4] Here, we describe siblings who were diagnosed with SLS (Sjogren-Larsson syndrome) having Intellectual impairment, bilateral lower spasticity as well as ichthyosis.

Clinical Description

Siblings, aged 9 years and 15 years old males, born to a 2nd degree consanguineous married couple, born through Full Term Normal Delivery, cried immediately after birth, exclusively breastfed up to 6 months, completely immunized till date, presented with complaints of generalized dryness of skin, difficulty in walking since the age of 2yrs with delayed attainment of speech. There was a developmental delay in both siblings. They both had a poor scholastic performance—no history of similar complaints in other siblings.

Cutaneous examination in siblings revealed generalized skin dryness with fine scales predominantly in flexural folds & around the umbilicus suggestive of ichthyosis. Neurological investigation showed increased tone in both lower limbs, moderate intellectual disability, exaggerated deep tendon reflexes (4+) with patellar & ankle clonus and extensor plantar response suggestive of spastic diplegia. Examination of upper limbs was normal. Gait was a diplegic type in my younger brother. Examination of the cranial nerve was normal. No sensory, cerebellar, or extrapyramidal signs were seen in siblings.

A complete ophthalmic evaluation showed dry eyes in both of them, and no other abnormalities were noted. No skeletal abnormalities were noted. Dental examination in elder brother showed lower molar teeth abscess, for which dental opinion has been taken and treated, otherwise normal in younger brother. Cardiovascular, respiratory system and abdominal systemic examinations were normal in both of them.

Management and Outcome

Blood investigations like Complete blood picture, HbA1c, renal and liver function tests of both were within normal ranges. ABG displayed severe metabolic acidosis with blood pH less than 7.2, and bicarbonate was less than 10mEq/l in both brothers. Serum electrolytes showed persistent Hypokalaemia (<2.5mEq/L) in both brothers, for which correction was given and treated accordingly. Serum calcium, serum phosphorous, and Blood Urea Nitrogen (BUN) were decreased in siblings. Serum magnesium levels were within normal limits. Anti-Nuclear Antibody, Rheumatoid factor, Anti-RO and Anti-LA antibodies are negative in both of them. Mutation analysis of the ALDH3A2 gene couldn't be done because of financial constraints.

Urine analysis showed pH of 6.5 and 7 in the elder and younger brothers, respectively. Fractional bicarbonate excretion ($FeHCO_3$%) showed mild bicarbonaturia (<5%), and others were within normal limits in both brothers. Urine electrolytes showed high potassium levels, with others being within normal limits, and the Urine Anion gap was in the Positive range in both brothers. Urinary and Blood PCO_2 difference (UB PCO_2) was <10mmHg, and Urine osmolality was decreased (<200mOsm/kgH_2O) in brothers. Urine calcium 24hrs was in hypercalciuric levels(>350mg/day) in siblings. 24-hour Urinary Protein and Urine phosphorous were within normal limits. All these features were suggestive of Distal RTA (Type -1 RTA).

USG abdomen in younger brother showed B/L enlarged echogenic mild hydronephrosis kidneys and in elder showed features suggestive of early medullary nephrocalcinosis. Electroencephalogram (EEG) was normal in siblings. BERA showed moderate sensorineural hearing loss in siblings. MRI Brain in elder brother revealed non-specific white matter hyperintensities in bilateral peritrigonal region and centrum semiovale. Asymmetrical lateral ventricles with right lateral ventricle being more prominent-anatomic variant. MRI brain in younger brother revealed T2/FLAIR confluent white matter hyperintensities involving bilateral centrum semiovale with posterior and occipital predominance-s/o white matter demyelination. SLS with Distal RTA (Type-1) was diagnosed based on all these radiological as well as clinical outcomes.

Management in SLS was supportive. It involved a multidisciplinary squad of Paediatricians, Dermatologists, Ophthalmologists, rehabilitation specialists & ENT and others. Dietary changes to lower intake of total fat & raise the ratio of linoleic/linolenic acid have only minor health advantages. Topical moisturizing lotion, keratolytic agents and oral retinoids were used in the management of ichthyosis. Home-based physiotherapy was taught to prevent contrac-

tures.[5] Distal RTA was treated with correction of acidosis with alkali 2-3mEq/kg/day, potassium, vitamin D and multivitamin supplementation. Hearing aids were advised. Siblings showed significant improvement, and no further progression was noted.

Discussion

SLS (Sjogren-Larsson syndrome) is a rare autosomal recessive lipid metabolism inborn defect and was originally described in Sweden. Sjogren & Larsson identified a patient group suffering from a severe illness with 3 fundamental characteristics in the year 1957; congenital ichthyosis, intellectual disability & spastic diplegia or tetraplegia.[6] Rizzo et al. related Sjogren-Larsson syndrome to FAO (Fatty Alcohol NAD (Nicotinamide Adenine Dinucleotide)- Oxidoreductase) deficiency. Fatty Alcohol NAD (Nicotinamide Adenine Dinucleotide)- Oxidoreductase is a 2 separate protein enzyme with a complex structure. These proteins are known to catalyse the process of oxidation from fatty alcohol to fatty acids through the fatty aldehyde pathway.[7]

FALDH (Fatty Aldehyde Dehydrogenase) activity was discovered in cultured fibroblasts from Sjogren-Larsson syndrome patients when the further investigation was done. Hence, the FAO component Fatty Aldehyde Dehydrogenase was affected in these SLS subjects' groups. Biochemically, Fatty Aldehyde Dehydrogenase is a microsomal enzyme which catalyzes the oxidation of long-chain & medium aliphatic aldehydes produced from several bodily metabolisms. These aldehydes could be by-products of glycerolipid, fatty alcohol, phytanic acid, ether, & leukotriene B4 metabolism.[7] In Sjogren-Larsson syndrome subjects, more than seventy ALDH3A2 mutations have been discovered. Amino acid substitutions, insertions, splicing errors & deletions are among the various mutations identified. Mutations in the ALDH3A2 gene on the 17p11.2 chromosome, which encodes FALDH (fatty aldehyde dehydrogenase), an enzyme which catalyses the process of oxidation of long-chain aldehydes produced from the metabolism of lipid, cause this condition. Although each affected family has its own unique mutation set, there are clinical variances attributable to unknown genetic & or environmental aspects.[8]

ALDH10, also known as ALDH3A2, mutations (in the Fatty Aldehyde Dehydrogenase gene) have verified the enzyme's etiological role. This pathway's significance in normal desquamation was also highlighted. These mutations are postulated to produce abnormal lipid build-up in the skin & brain membranes.[3] As a result, a diagnosis requires a combination of neurologic & cutaneous symptoms. Clinical findings are the main basis of diagnosis, which was seen in our siblings.

There is usually occasionally tetraplegia, spastic diplegia, epilepsy, intellectual disability, speech defects, dermatological, retinal, skeletal, & dental changes.[9] The changes in the skin are in the form of ichthyosis, which is a generalized hyperkeratosis of joints, trunk, & the dorsal aspects of the feet & hands.[3] The most common ophthalmologic defects include photophobia, reduced visual activity, and glistening white spots in the macula.[3] These characteristics are present in one-third of cases but not in ours.

Neuropathologically, SLS is characterised by demyelination of the cerebral white matter, as well as the vestibulospinal & corticospinal tracts inducing spasticity.[6] On the T2W sequence, cerebral magnetic resonance imaging reveals diffuse symmetrical white matter hyperintensities, particularly in parietal, periventricular frontal, corpus callosum, & corona radiate. U fibres in the subcortical white matter are typically spared.[2,10] In our research study, white matter demyelination was seen in siblings. Few papers have recently described proton Magnetic Resonance Imaging spectroscopy outcomes in SLS, demonstrating an abnormal peak of lipid at 1.3 ppm in the region of T2 white matter abnormalities at both TE-30 & 135 ms.[2,3] Due to a lack of equipment, we were unable to perform spectroscopy. Although genetic (ALDH3A2 gene) & biochemical investigations (urinary leukotriene B4 & 20-OH-LT B4 concentration) are desirable in such circumstances, we were unable to carry them out owing to a lack of resources.

In children, dRTA (distal renal tubular acidosis) is often inherited. However, its occurrence is secondary to autoimmune diseases, toxin & drug exposure & obstructive uropathies. We found no other plausible cause of secondary distal renal tubular acidosis in our study, implying that distal renal tubular acidosis was caused by a sporadic or main (hereditary) aetiology in this subject. Depletion of potassium in distal renal tubular acidosis can be secondary to several cellular metabolism-related genetic defects that present as an autosomal dominant or recessive ailment. Phosphate as well calcium levels in distal renal tubular acidosis are typically normal. Moreover, due to bone resorption to buffer chronic metabolic acidosis, rickets is frequent in untreated distal renal tubular acidosis. Cardiac arrhythmias & respiratory failure are the leading causes of death following hypokalaemic paralysis in patients. dRTA management comprises the replacement of potassium as well as alkali together with underlying ailments' treatment.[5]

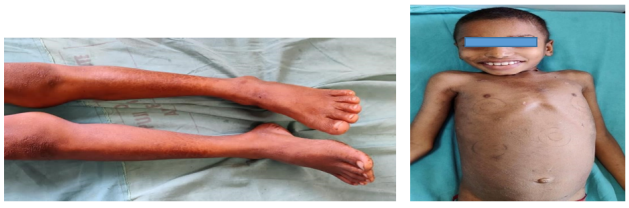

Fig 1. Shows ichthyotic lesions over the chest, abdomen and both upper and lower limbs in younger brother

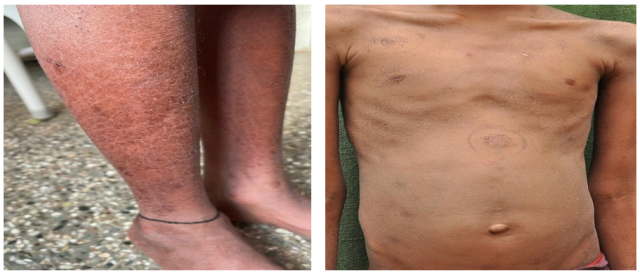

Fig 2. Shows ichthyotic lesions over the forehead, chest, abdomen, back and both upper and lower limbs in elder brother.

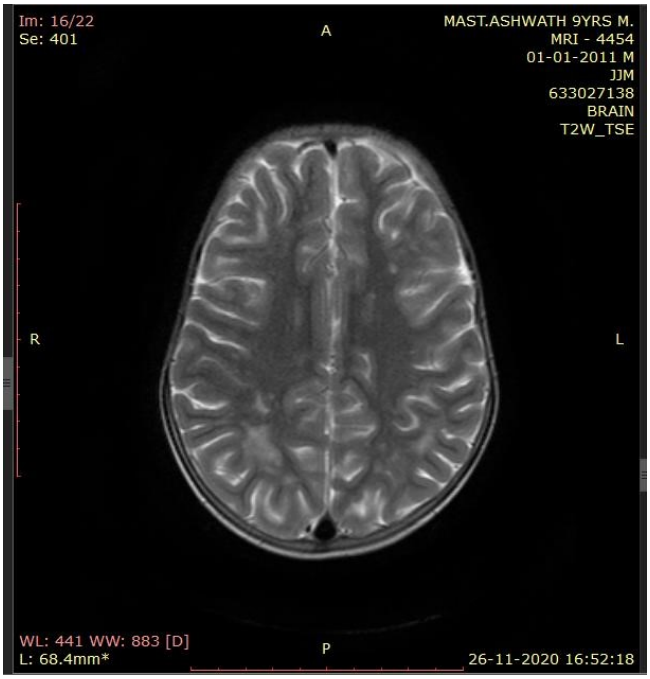

Fig 3. MRI in Younger brother - T2W images showing confluent white matter hyperintensities involving bilateral centrum semiovale with posterior and occipital predominance- s/o white matter demyelination

Conclusion

Patients must be educated on how to treat dry skin as well as receive proper counselling on the disease's genetic origin. Children who are suffering from distal renal tubular acidosis can be treated with a good long-term prognosis, but precise diagnosis as well as management are critical. Though this is a single case study report of distal renal tubular acidosis in association with Sjogren – Larsson syndrome, the cause for an association is not known.

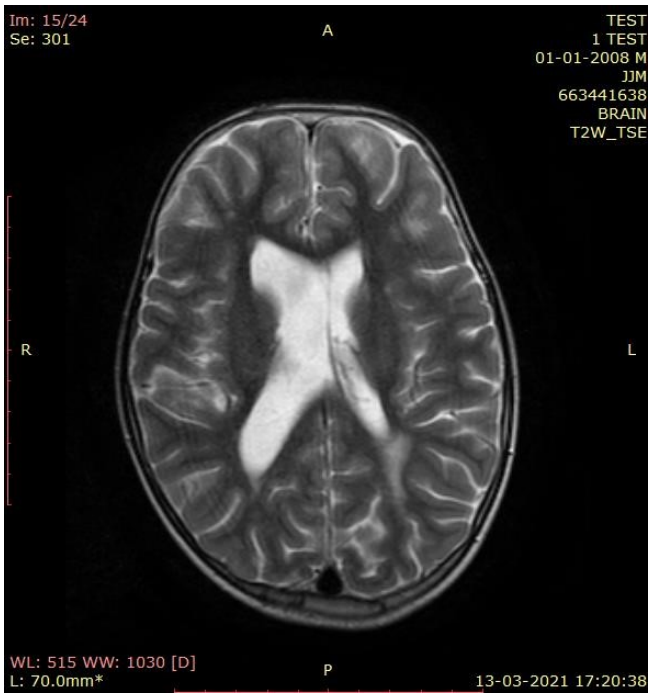

Fig 4. MRI in Elder brother - T2W images showing non-specific white matter hyperintensities in bilateral peritrigonal region and centrum semiovale and Asymmetrical lateral ventricles with right lateral ventricle being more prominent

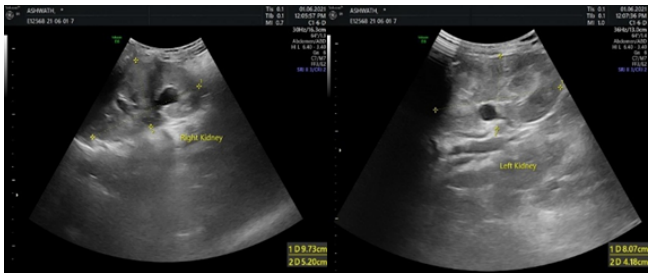

Fig 5. USG Abdomen of Younger brother showed B/L Enlargedechogenic mild hydronephrosis kidneys

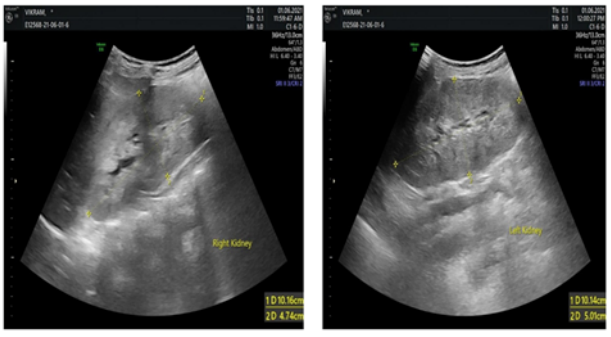

Fig 6. USG Abdomen of Younger brother showed B/L Enlarged echogenic mild hydronephrosis kidneys.

Key Points

1. For any child with congenital ichthyosis and emerging neurological symptoms, it is vital to consider Sjogren-Larsson syndrome as a differential diagnosis, although it is a rare ailment.
2. The significance of renal tubular acidosis & hypokalaemia in association with the neurological syndrome is highlighted in this research study.
3. Early diagnosis and management with alkali therapy, potassium and vitamin D supplementation enable rapid clinical recovery.

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