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A Rare Case Report of Neonate with RENI Syndrome

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Abstract: ***RENI syndrome (RENAL, ENDOCRINE, NEUROLOGIC, AND IMMUNE SYNDROME) is an autosomal recessive form of steroid-resistant nephrotic syndrome with multisystemic manifestations such as ichthyosis, acanthosis, adrenal insufficiency, immunodeficiency, and neurologic defects. It is caused by homozygous or compound heterozygous mutation in the SGPL1 gene causing Sphingosine Phosphate Lyase Insufficiency. We describe a case of full-term neonate who presented with generalized oedema, ichthyosis and multiple orofacial abnormalities since birth which was followed by respiratory distress, feed intolerance, congenital nephrotic syndrome, congenital hypothyroidism and refractory convulsions and eventually refractory shock, all leading to death of the patient. He was diagnosed to be suffering from RENI syndrome through clinical exome sequencing.***

Keywords: Renal, Endocrine, Neurologic and Immune (RENI), Sphingosine Phosphate Lyase (SPL), Steroid resistant nephrotic syndrome (SRNS), Primary adrenal insufficiency (PAI), Ichthyosis

1. Introduction

RENI syndrome is caused by mutation in SGPL1 gene which is located on chromosome 10 and encodes for SPL (Sphingosine Phosphate Lyase), an endoplasmic reticulum enzyme involved in sphingolipid catabolism. Inactivation of SPL leads to accumulation of sphingolipid intermediates. SGPL1 is expressed in various human tissues particularly kidneys, adrenal cortex, testis, central nervous system and thyroid gland. Therefore, loss of SGPL1 function results in multisystemic involvement and glomerulopathy characterized by steroid-resistant nephrotic syndrome. Age of presentation is usually infancy or early childhood and most of the patients develop end-stage renal disease within a few years. Herein, we describe a case of RENI syndrome with presentation in the neonatal period.

2. Case Report

A third born male child to 22 years old mother through third degree consanguineous marriage with first expired male child on 10th day of life due to meconium aspiration syndrome and a second healthy female child. Baby delivered by lower segment caesarean section (LSCS) indication being previous two LSCS with birth weight 2.7 Kg. Antenatal Ultrasonography showed no abnormality. Maternal history revealed no medical or pregnancy induced illness. There was no history of any drug exposure.

Baby cried immediately after birth. Baby was admitted in NICU on day 1 in view of respiratory distress with poor sucking and was kept on oxygen support with baseline antibiotics.

Thorough physical examination revealed generalized oedema and ichthyosis. Head and facial examination was suggestive of sparse hair, flattened nose, microphthalmia with absent eyebrows, bilateral upper eyelid sparse eyelashes with ectropion and absent lower eyelid eyelashes. Anisocoria with absent pupillary reaction was also noted in left eye. Oral cavity examination showed a high arched palate with submucosal cleft palate and an absent uvula. Genital examination also revealed bilateral cryptorchidism.

Oxygen requirement reduced gradually and minimal nasogastric feeds were started. This baby had repeated episodes of feed intolerance. X- ray erect abdomen and ultrasonography of abdomen was done to rule out any gastrointestinal abnormality with no significant findings. CBC showed Hemoglobin- 18.2gm%, WBC count- 6500/mm^3 with Lymphopenia (1250/mm^3) and Platelet count- 1.84 Lakhs. Septic screen was also negative. In view of lethargy and persistent oedema, thyriod function tests were done that showed baby had primary congenital hypothyroidism and was started on Levothyroxine tablets. But the oedema was progressive and later baby developed oliguria. Local ultrasonography with doppler of bilateral lower limbs revealed lymphatic obstruction with no venous thrombosis. On further investigations, baby had hypoalbuminemia, hypertriglyceridemia, deranged renal function tests with raised creatinine and urinary protein creatinine ratio and 4+ proteinuria, hence diagnosis of congenital nephrotic syndrome was established. Bedside renal biopsy was done that showed features of Focal Segmental Glomerulosclerosis (FSGS). Baby was started on intravenous Methylprednisolone therapy for the same. On Day 21, baby had tonic clonic seizures initially focal followed by secondary generalization. Antiepileptic drugs were given. Baby also had resistant hypoglycemia. He was put on mechanical ventilation due to weak respiratory efforts. With steroid resistant nephrotic syndrome causing generalized oedema, anuria and refractory shock baby ultimately succumbed to death.

Proper diagnostic workup was done to rule out other associated anomalies. 2 D-echo was suggestive of small PDA 2.5 mm with left to right shunt. Ultrasonography of kidney,

ureter and pelvis detected no abnormality. Transcranial USG also showed normal findings. For molecular diagnostics, Clinical-exome sequencing was done that revealed homozygous missense variation in exon 8 of the SGPL1 gene on chromosome 10 causing deficiency of Sphingosine Phosphate Lyase enzyme resulting in RENI syndrome.

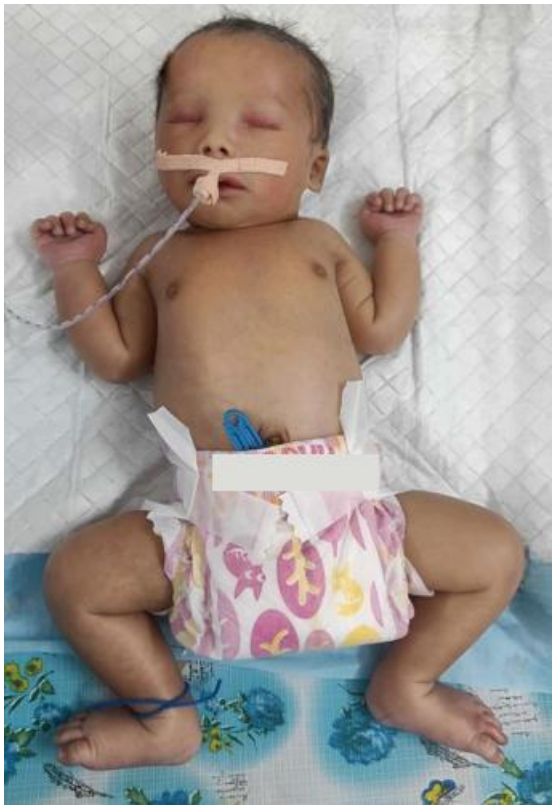

Figure 1: Generalized ichthyosis

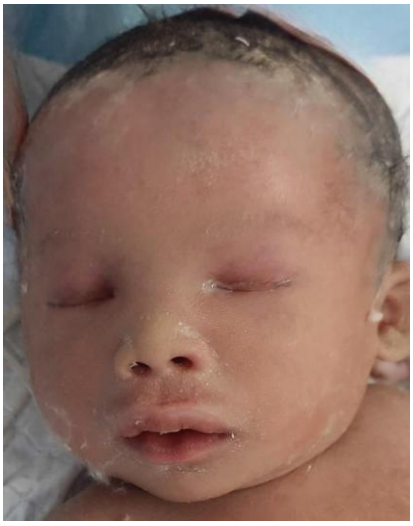

Figure 2: Facial features showing sparse hair with posteriorly receding anterior hairline, microphthalmia with absent eyebrows and flat nasal bridge

Figure 3: Bilateral non pitting lower limb oedema

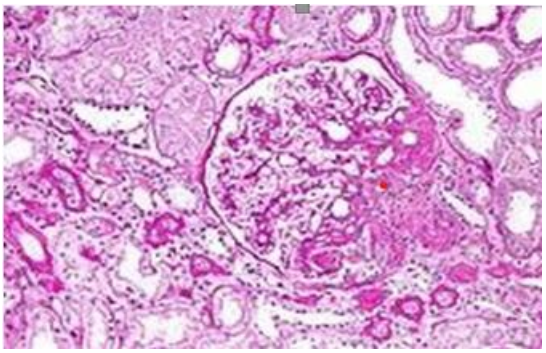

Figure 4: Renal Biopsy showing Focal Segmental Glomerulosclerosis

Gene[#] (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification[$]
SGPL1 **(+)** (ENST00000373202.8)	Exon 8	c.625G>T **(p.Gly209Trp)**	Homozygous	RENI syndrome (OMIM#617575)	Autosomal recessive	Uncertain Significance • **(PM2,PP3)**

3. Discussion

RENI syndrome was first recognized as a monogenic cause of steroid resistant nephrotic syndrome and primary adrenal insufficiency in 2017. In total, 76 genetically confirmed patients are known with survival rate of 50% [1].

The most consistent feature of this Sphingosine Phosphate Lyase Insufficiency syndrome (SPLIS) has been Steroid Resistant Nephrotic Syndrome (SRNS) [2]. Endothelial cells, mesangial cells and podocytes in the kidney are typical cells expressing *SGPL1* [3]. Term NPHS14 has been given for this syndromic SRNS caused by mutations of SGPL1 [4]. Histologically, SRNS manifests mostly as Focal segmental

glomerulosclerosis (FSGS) [5].

In a study conducted by Lovric et al. in 2017, it was found that homozygous missense mutation in gene coding for SGPL1 presented with a more severe phenotype, with neonatal onset and profound immunodeficiency. Our case also presented with features of SGPL1 deficiency within neonatal period. Clinical exome sequencing showed homozygous missense variant of SGPL1 gene, thus establishing the severity of homozygous mutations and significant role of SGPL1 enzyme in vital organs.

Among the endocrine abnormalities, Primary adrenal insufficiency (PAI) is a life-threatening disorder that results from bilateral destruction or dysfunction of the adrenal cortex [6]. PAI manifests with acute symptoms such as vomiting, electrolyte disturbances, hypoglycemia, and hypotension as also seen in our case [7]. Later resistant hypotension seen can be attributed to Addisonian crisis.

Additionally, proteinuria particularly in nephrotic syndrome, often results in the urinary loss of thyroid hormones with associated thyroid binding proteins, resulting in a reduction in serum total thyroid hormone levels [8].

Some cases can also have immunologic abnormality with Low absolute lymphocyte counts and Low-to-normal immunoglobulins [9].

Many cases also present with Testicular insufficiency with micro penis, cryptorchidism or microorchidism. [10].

Features like SRNS need to be diagnosed at an early stage and administration of nephrotoxic drugs needs to be avoided. Primary adrenal insufficiency manifesting shortly after birth can be due to extensive accumulation of sphingolipid metabolites and altering steroid synthesis.

Overall the case had deficiency of SGPL1 enzyme with multisystemic involvement and features of SRNS, adrenal insufficiency and refractory convulsions proved to be life-threatening.

4. Conclusion

RENI Syndrome, being an autosomal recessive disorder disrupting sphingolipid metabolism is fatal either in early infancy or childhood.

Most of the cases present with multisystemic involvement with renal being the primary organ of involvement. Children with Congenital nephrotic syndrome and SRNS who present with extra-renal manifestations should be genetically tested for SGPL1.

Due to autosomal recessive pattern of inheritance, identification of pathological variant in parents, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing holds great importance.

Emphasis should be put on early diagnosis and appropriate management to prevent death due to failure of primarily involved vital organs.

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Conflicts of interest
There are no conflicts of interest.

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