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CASE REPORT

A Saudi child with Sphingosine Phosphate Lyase insufficiency syndrome

Lamya Ahmad Faisal Alrayes[1], Mohammed Alotaibi[2], Afaf Alsagheir[2*]

ABSTRACT

Background: Sphingosine Phosphate Lyase Insufficiency Syndrome SPLIS is a recently described condition, which is associated with loss of function mutations in SGPL1, encoding sphingosine-1-phosphate lyase.

In 2017, several groups reported this novel childhood syndrome that featured a wide range of presentations including fetal hydrops, steroid-resistant nephrotic syndrome (SRNS), primary adrenal insufficiency (PAI), rapid or insidious neurological deterioration, immunodeficiency, acanthosis and endocrine abnormalities.

Case Presentation: A 7-year-old boy was presented to us with primary adrenal insufficiency on hydrocortisone following pediatrics endocrinology at our hospital. Genetic testing identified a homozygous variant of sphingosine-1-phosphate lyase 1 (NM 003901: exon8: c.665G>A: p.R222Q). At the same time, he was found to have nephrotic syndrome, and renal function rapidly deteriorated. Biopsy of the right kidney showed focal segmental glomerulosclerosis with collapsing features and acute interstitial nephritis. Later, he received a living-related renal transplant. He is doing well after the transplant.

Conclusion: Patients with primary adrenal insufficiency should be carefully followed to develop nephrotic syndrome features, and molecular testing is the key to the diagnosis of the underlying etiology. This is the first reported case with sphingosine-1-phosphate lyase 1 that underwent renal transplantation in our region.

Keywords: Primary adrenal insufficiency, focal segmental glomerulosclerosis, SGPL-1.

Introduction

Primary adrenal insufficiency occurs due to decreased production of glucocorticoids with or without mineralocorticoids from the adrenal cortex (1). The diagnosis of adrenal insufficiency is confirmed when the morning serum cortisol level is low in the presence of a markedly elevated serum Adrenocorticotropic hormone (ACTH) concentration with or without an increase in plasma renin activity (2). Patients with adrenal insufficiency usually present with variable symptoms of chronic fatigue, anorexia, orthostatic hypotension, nausea, vomiting, loss of appetite, weight loss, abdominal pain, weakness, and a lack of energy. Moreover, increase skin pigmentation because of excess melanocyte-stimulating hormone and salt craving (1,4). Sphingosine Phosphate Lyase Insufficiency syndrome (SPLIS) is a recently described condition, which in the main, incorporates steroid-resistant nephrotic syndrome and primary adrenal insufficiency (PAI). The disease is associated with the loss of function mutations in sphingosine-1-phosphate lyase (*SGPL1*), encoding sphingosine-1-phosphate lyase that irreversibly binds sphingosine 1-phosphate (S1P) and commits it to the final degradative step in sphingolipid metabolism. *SGPL-1* mutations cause nephrotic syndrome, ichthyosis, facultative adrenal insufficiency, immunodeficiency, and neurologic defects in humans (5). Other studies reported patients presented a variable phenotype, including PAI, nephrotic syndrome, and a combination of skin abnormalities, central nervous system manifestations, immunodeficiency, hypothyroidism, skeletal abnormalities, muscular hypotonia, and genital abnormalities (3). We present a Saudi patient with primary adrenal insufficiency associated with nephrotic syndrome secondary to SGPL-1 gene mutation post-renal transplant.

Case presentation

A 7 years old boy was referred to our hospital at the age of 4 years as a case of isolated glucocorticoid deficiency, diagnosed in the UK at the age of 1 year. The initial

Correspondence to: Afaf Alsagheir
*King Faisal Specialist Hospital and Research Center, Pediatric Endocrinology, Riyadh, Saudi Arabia.
Email: asagheir@kfshrc.edu.sa
Full list of author information is available at the end of the article.
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patient presentation was a decrease in activity, skin hyperpigmentation on his flexors, and frequent respiratory tract infections, which required hospital admissions. He was developmentally normal. There is no evidence of neurologic defects, such as developmental delay, muscular hypotonia, abnormal gait, ataxia, sensorineural deafness, seizures, and microcephaly. Besides, no manifestations of immunodeficiency, hypothyroidism, skeletal deformities, nor genital abnormalities. He was started on hydrocortisone replacement and to get a stress dose of hydrocortisone during illnesses. The patient's elder sister is normal. The patient's family does not recall any history of a similar condition in their predecessors; however, parents are first degree cousins. on the first visit to our hospital when he was 4 years old, he was doing well with mild hyperpigmentation on the mucus membranes, moon face, buffalo hump, and normal blood pressure. The patient did not have periorbital edema nor peripheral edema. Laboratory investigations revealed ACTH level was 1,131 pg/ml (10-60 pg/ml) (most probably due to noncompliance to medication), normal electrolytes, and plasma rennin activity. Therefore, he was diagnosed with isolated glucocorticoid deficiency.

The patient continued on hydrocortisone 12 mg/m ^{2}/ day without any concerns, and he was having normal ACTH, electrolyte, and renal function during his regular visits every 6 months. At that time, we did not have any identified cause for his isolated glucocorticoid deficiency. At the age of 6 years, the whole-exome analysis was done, and a homozygous variant of *SGPL1* (exon8: c.665G>A: p.R222Q) (this mutation was reported previously as pathogenic in Clinvar database) was identified in this patient and parents were heterozygous for this gene mutation. At that time, the patient was called for further testing. He was found to have periorbital edema and lower limb edema, and renal function test showed: serum urea 13.9 mmol/l (2.3-6.7 mmol/l), serum creatinine 235 µmol/l (26-58 µmol/l), and albumin 23.5 g/l (40-50 g/l), random urine protein /creatinine ratio 1,800 mg/ mmol (very high) (less than 20 mg/mmol). Right renal biopsy was done, and it showed a glomerulus with the segmental collapse of glomerular tuft associated with podocyte hyperplasia and protein resorption droplets (Periodic Acid Schiff stain; 400×) (Figure 1). Electron microscopic image of a glomerulus showed diffuse podocyte foot process effacement (Figure 2). Besides, an immunofluorescence study showed no significant staining for immunoglobulins and complements. After diagnosing nephrotic syndrome, he was given IV pulse steroids and discharged on prednisolone 60 mg. Few days after discharge, he presented to the emergency department because of lower limb edema and weight gain. His creatinine did not improve, so a second-line agent (Tacrolimus) was added. Within 2 weeks, he was readmitted with generalized edema, and his renal function rapidly deteriorated with very high serum urea 38.2 mmol/l (2.3-6.7 mmol/l) and serum creatinine 965 µmol/l (26-58 µmol/l). He progressed to end-stage renal disease (end-stage renal disease), and he was started on hemodialysis sessions 4 days every week for 5 months then he received a living-related renal transplant from his father. Currently, he is doing well 1 year after the

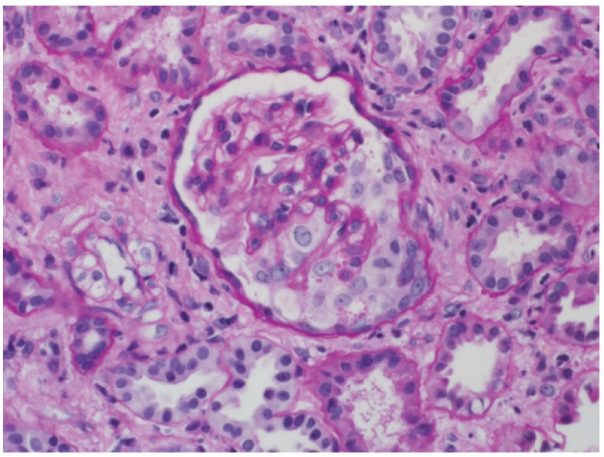

Figure 1. *A glomerulus with segmental collapse of glomerular tuft associated with podocyte hyperplasia and protein resorption droplets (Periodic Acid Schiff stain; 400×).*

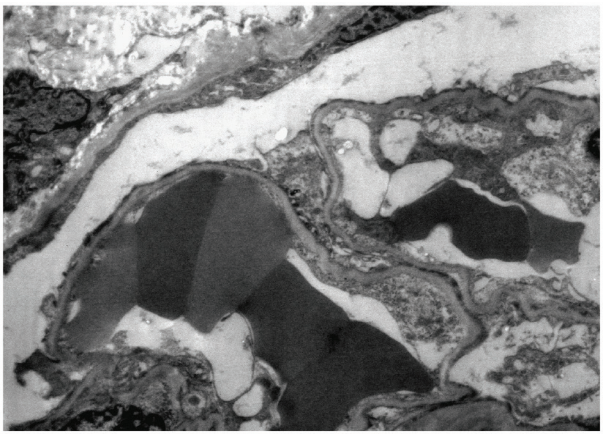

Figure 2. *Electron microscopic image of a glomerulus showing diffuse podocyte foot process effacement.*

renal transplant, and his latest renal functions were with normal limits: serum urea 3.5 mmol/l (2.3-6.7 mmol/l), and serum creatinine 50 mol/l (26-58 µmol/l).

Discussion

Studies showed that one cause of primary adrenal insufficiency in the pediatric age group is primary adrenal insufficiency syndrome and steroid-resistant nephrotic syndrome, which is happening as a result of loss-of-function mutations in SGPL-1 (3). *SGPL1* encodes SGPL1, which provides the single exit point for the sphingolipid metabolic pathway, irreversibly converting S1P hexadecanal and phosphoethanolamine. Sphingolipids play an integral role as structural components of cell membranes, and sphingolipid intermediates such as S1P, sphingosine, and ceramide are signaling molecules involved in cell migration, differentiation, and cell survival. SPLIS describes the recently reported multi-systemic disease-associated SGPL1 deficiency (6). Different recessive mutations were identified, and it represents a distinct disorder with a variety of manifestations, including ichthyosis, adrenal insufficiency, primary hypothyroidism,

immunodeficiency, neurological symptoms, and cryptorchidism (3,4).

Our patient has homozygous c.665G>A (p.R222Q) mutation which was reported before in four patients (three patients were siblings from Pakistan, and one patient was from Saudi Arabia). PAI Presented in these patients mainly with hyperpigmentation (at the age of 0.6-1.5 years). Two of the Pakistani siblings had steroid-resistant nephrotic syndrome at 2.5-4 years of age, and their biopsy findings were consistent with focal segmental glomerulosclerosis (FSGS). They did not respond to steroids and other immunosuppressive medications. Also, one of them was transplanted at the age of 5 years, but the other one died before he could undergo renal transplantation (3,4). On the other hand, the other two patients did not a manifest nephrotic syndrome (till the time of the report) (3,4). Our patient and the previously reported patients with the same gene mutation did not have other manifestations of SPLIS such as ichthyosis, hypothyroidism, nor neurological features so far, which may suggest that this mutation is not associated with other comorbidities apart from PAI and steroid-resistant nephrotic syndrome. Our patient presented in the first year of life with PAI, and 5 years later, he was diagnosed with nephrotic syndrome due to FSGS. His nephrotic syndrome did not improve on either steroids or tacrolimus. His renal function rapidly deteriorated, requiring hemodialysis and later renal transplantation (similar to the two cases with the same mutation reported by Ram et al. (3). This suggests that patients with similar *SGPL1* mutation do not respond to medical therapy and could deteriorate rapidly. Therefore, we recommend that transplant workup should be done early once the diagnosis of nephrotic syndrome is made. Studies reported six cases of SPLIS affected individuals who underwent renal transplantation, and this is another patient we are adding to the literature (7). A year after transplantation, he is still doing well, but he needs long-term follow-up.

Conclusion

Patients with primary adrenal insufficiency should be carefully followed for the development of features of nephrotic syndrome and tested for *SGPL1* gene mutations. Patients with SPLIS once they develop the nephrotic syndrome, they deteriorate rapidly to ESRD requiring renal transplantation. So, genetic counseling is essential to prevent such devastating disease.

List of Abbreviations

ACTH	Adrenocorticotropic hormone
ESRD	End-stage renal disease
FSGS	Focal segmental glomerulosclerosis
PAI	Primary adrenal insufficiency
S1P	Sphingosine 1-phosphate
SGPL1	Sphingosine-1-phosphate lyase 1
SPLIS	Sphingosine-1-phosphate lyase insufficiency syndrome

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Declaration of conflicting interests

The authors of this report have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

Consent for Publication

Written informed consent was obtained from the parents. ed.

Author details

Lamya Ahmad Faisal Alrayes[1], Mohammed Alotaibi[2], Afaf Alsagheir[2]

1. Alfaisal University, Riyadh, Saudi Arabia.
2. Pediatric Endocrinology Department, King Faisal Specialist Hospital and Research Center,, Riyadh, Saudi Arabia.

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