



A rare cause of nephrotic syndrome—sphingosine-1-phosphate lyase (SGPL1) deficiency: 6 cases and a review of the literature

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Abstract

Background Recently, recessive mutations in *SGPL1* (sphingosine-1-phosphate lyase), which encodes the final enzyme of sphingolipid metabolism, have been reported to cause steroid-resistant nephrotic syndrome, adrenal insufficiency, and many other organ/system involvements. We aimed to determine the clinical and genetic characteristics, and outcomes in patients with *SGPL1* mutations.

Methods The study included 6 patients with bi-allelic *SGPL1* mutation. Clinical, genetic, and laboratory characteristics, and outcomes of the patients were evaluated retrospectively. We also reviewed previously reported patients with *SGPL1* mutations and compared them to the presented patients.

Results The median age at kidney presentation was 5 months. Four patients (67%) were diagnosed before age 1 year. Kidney biopsy showed focal segmental glomerulosclerosis in 2 patients and diffuse mesangial sclerosis in one patient. Steroids were given to 3 patients, but they did not respond. All 6 patients progressed to chronic kidney disease; 5 required kidney replacement therapy (KRT) at a median age of 6 months. Deceased kidney transplantation was performed in one patient. All 6 patients had adrenal insufficiency, of which 5 were diagnosed at age < 6 months. Three patients had hypothyroidism, 2 had ichthyosis, 4 had immunodeficiency, 5 had neurological findings, and 2 had genitourinary system anomalies. Four patients died at a median age of 30.5 months. Two patients are being followed up with KRT. One patient had a novel mutation.

Conclusions Patients with *SGPL1* mutations have a poor prognosis, and many types of extrarenal organ/system involvement beyond adrenal insufficiency can be seen. Genetic diagnosis of such patients is important for treatment, genetic counseling, and screening for comorbid conditions.

Keywords Sphingosine-1-phosphate lyase · *SGPL1* · Nephrotic syndrome · Sphingolipidosis · Adrenal insufficiency

Introduction

Nephrotic syndrome is one of the most common glomerular diseases in children, and 10–15% of cases of idiopathic nephrotic syndrome are steroid-resistant. Steroid-resistant nephrotic syndrome (SRNS) has a poor prognosis; approximately half of patients progress to stage 5 chronic kidney disease (CKD) in 10–15 years [1–3]. Monogenic forms of SRNS are increasingly being recognized [4]. In 2017, two different research groups simultaneously identified the *SGPL1* gene, which encodes sphingosine-1-phosphate lyase (SGPL1) and leads to SRNS and adrenal insufficiency when mutated. Both studies reported that patients with *SGPL1* mutations have early-onset adrenal insufficiency and poor kidney prognosis. Moreover, ichthyosis, immunodeficiency, and neurological findings were observed in some of the

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patients in both studies [5, 6]. The mutations described in the patients were loss-of-function, resulting in reduced or absent SGPL1 protein and enzymatic activity [5].

The multisystemic features of *SGPL1*-related disease highlight the critical role of sphingosine-1-phosphate (S1P) metabolism not only in the kidneys but also in other organs. Whereas some sphingolipids serve as a structural component of cell membranes, others, such as S1P, also serve as signal molecules that regulate cell migration, differentiation, survival, and other complex physiological processes [6, 7]. *SGPL1* is an important endoplasmic reticulum enzyme involved in sphingolipid catabolism; it converts S1P into ethanolamine phosphate and hexadecenal (Fig. 1), and is expressed in all human tissues [6]. An elevated circulating S1P level, changes in the blood level of intermediates of sphingolipid metabolism, and the absence of *SGPL1* staining in kidney tissue have been previously reported in patients with *SGPL1* mutations [6, 8, 9]. These findings indicate that intracellular S1P accumulation and imbalance of other sphingoid species can result in dysfunction in various organs [5, 8]. Therefore, this relatively new entity has been recognized as a novel sphingolipidosis [10]. In cases of this type of sphingolipidosis, also known as sphingosine phosphate lyase deficiency syndrome (SPLIS), the prominent phenotype is congenital nephrotic syndrome/SRNS and primary adrenal insufficiency; however, the disease is characterized by phenotypic heterogeneity varying from severe multi-organ involvement to isolated single-organ disease [5, 6]. The disease is extremely rare and, therefore, little is known about its phenotypic spectrum. The present study aimed to present the clinical features of 6 patients with bi-allelic

SGPL1 mutation, in order to expand the clinical and genetic spectrum of the disease, as well as to review previously reported cases and compare them to the presented patients.

Methods

Patients

The study included 6 patients with homozygous *SGPL1* mutation who were examined between 2017 and 2020 at 4 pediatric nephrology centers in Turkey. Their genetic analyses were performed at the Hacettepe University Nephro genetics Laboratory using a gene panel containing 47 genes, including *SGPL1*, via next-generation sequencing in patients #1, 4, and 5 or Sanger sequencing of all exons of *SGPL1* based on typical phenotypic features highly suggesting *SGPL1*-related disease in patients #2, 3, and 6 (Table 1). Gene panel results were confirmed via Sanger sequencing. All mutations, except p.Gln239fs*8, were previously reported and associated with the phenotype. We also considered p.Gln239fs*8 variation as disease-causing, as it is predicted to cause a truncated protein.

We retrospectively obtained data from medical records and requested from the other centers to complete a questionnaire, which included data on demographic, clinical, and laboratory characteristics at the kidney presentation, other organ involvements, treatments, and outcomes.

Definitions

Nephrotic syndrome was defined as proteinuria (i.e., a spot urine protein/creatinine ratio [UPCR] > 2 mg/mg or 24-h urine protein > 40 mg/m²/h), hypoalbuminemia (serum albumin < 2.5 g/dl), edema, and hyperlipidemia. The estimated glomerular filtration rate (eGFR) was calculated using the modified Schwartz formula [11]. Chronic kidney disease was defined and staged according to the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines [12]. Hypertension was defined as systolic and/or diastolic blood pressure ≥ 95th percentile for gender, age, and height.

Standard deviation scores (SDS) of height and weight for height were assessed at kidney presentation and the last follow-up visit, based on growth curves for Turkish children [13].

Statistics

All data were analyzed using IBM SPSS Statistics for Windows v.21 (IBM Corp., Armonk, NY). Descriptive analyses were performed to obtain information on characteristics of the patients. Variables without normal distribution were presented as median (min–max).

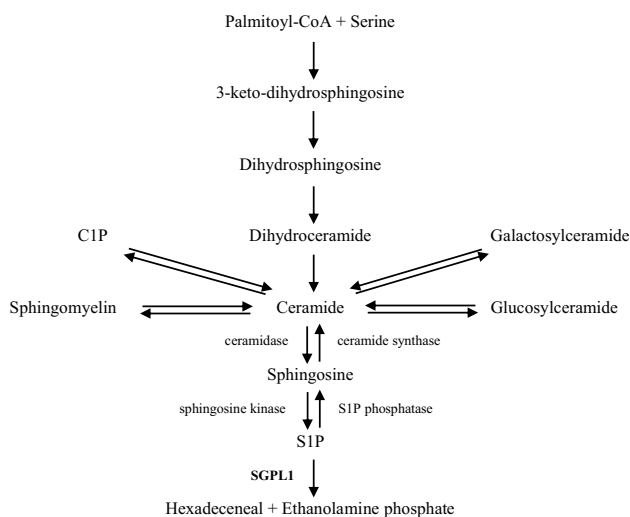


Fig. 1 Sphingolipid metabolic pathway. Sphingosine-1-phosphate lyase enzyme catalyzes the cleavage of S1P irreversibly in the last step of the sphingolipid pathway. CIP, ceramide-1-phosphate; S1P, sphingosine-1-phosphate; *SGPL1*, sphingosine-1-phosphate lyase

Table 1 Clinical and laboratory characteristics of patients

	Patient 1 PN1850	Patient 2 PN1658	Patient 3 PN1381	Patient 4 PN2309	Patient 5 PN1861	Patient 6 PN2112
Sex	Female	Female	Female	Male	Male	Male
Birth characteristics	Term, AGA (BW 3000 g)	Term, AGA (BW 2540 g)	Term, AGA (BW 3100 g)	Term, AGA (BW 3400 g)	Term, AGA (BW 3250 g)	Term, AGA (BW 3045 g)
Consanguinity	+	+	+	+	+	+
Characteristics at the renal presentation						
Age (year)	2.7	5.3	0.2 (2 months)	0.5	0.3	0.03 (10 days)
Height (cm)/SDS	NA	98/ -2.74	NA	62/ -2.28	NA	49/ -0.98
Weight (kg)/SDS for height age	12.5/NA	13/ -1.02	NA	7.1/0.56	NA	3.6/ -0.25
Presentation signs	Nephrotic syndrome	Nephrotic syndrome	Nephrotic syndrome, oliguria	Nephrotic syndrome, oligoanuria	Nephrotic syndrome	Nephrotic syndrome
Hypertension	-	-	+	+	-	-
Serum creatinine (mg/dl)	NA	0.42	NA	1.17	0.2	0.91
Serum albumin (g/dl)	NA	2.7	NA	2.2	1.68	1.26
Kidney ultrasonography findings	Increased echogenicity	Increased echogenicity, disappearance of cortex-medulla separation	Increased echogenicity, disappearance of cortex-medulla separation	Increased echogenicity	N	NA
Kidney biopsy findings	FSGS	FSGS	Mild mesangial cell increase, arteriolar hyaline degeneration, tubular dilatation	-	DMS	-
Treatment for kidney disease						
Steroid	Resistant	Resistant	-	-	Resistant	-
Calcineurin inhibitor	-	Partial remission	-	-	No response	-
ACE/ARB	-	+	-	-	+	+
Other	-	-	-	Pyridoxine	Pyridoxine	-
Renal outcome						
CKD stage 5	+	-(eGFR 21.7)	+	+	+	+
Age at development of CKD stage 5 (year)	3.4	-	0.3	0.5	2.3	0.07 (25 days)
Kidney replacement therapy	PD, HD	-	PD, HD	PD	PD, Ktx	PD
Extrarenal involvements						
Adrenal insufficiency (age at onset, months)	+(5)	+(6)	+(5)	+(6)	+(29)	+(<1)

Table 1 (continued)

	Patient 1 PN1850	Patient 2 PN1658	Patient 3 PN1381	Patient 4 PN2309	Patient 5 PN1861	Patient 6 PN2112
Hypothyroidism (age at onset, months)	+(NA)	+(6)	+(3.5)	-	-	-
Ichthyosis	-	+	-	-	+	-
Lymphopenia	+(ALC 600/ μ l, ANC 4400/ μ l)	+(ALC 967/ μ l, ANC 7161/ μ l)	-	-(Humoral immunodeficiency)	-(IgA deficiency)	-
Cardiac features	LVH	Aberrant band in the left ventricle	N	N	LVH	VSD
Neurological features	Developmental delay	Seizure, ataxia, intellectual disability, speech delay	Seizure	Microcephaly, developmental delay	Hydrocephalus	-
Eye	N	Night blindness	N	N	N	NA
Sensorineural hearing loss	NA	+	NA	-	-	NA
Genitourinary system anomaly	-	-	-	Bilateral cryptorchidism	-	Ambiguous genitalia
Radiological findings						
Adrenal calcification	+	-	-	-	-	-
Cranial MRI (age at performed)	Symmetrical T2 hyperintensity in the vicinity of the bilateral lateral ventricle frontal horns	Pathological contrast enhancements in the thalamus, mesencephalon, pons, bulbous, and cerebellar peduncle.	N	Thin corpus callosum, increase in depth and width of the cerebral sulcus	Tetравentricular hydrocephalus (3 years)	-
	Cerebral and mild cerebellar volume loss (39 months)	Cerebral and cerebellar atrophy (8 years)				
Anthropometric measurements at the last visit						
Height (cm)/SDS	91/-3.22	114/-2.51	61/-3.00	77/-2.05	102/-2.36	NA
Weight (kg)/SDS for height age	11.5/-1.05	20/-0.02	5/-1.49	9.7/-0.39	16.3/0.05	NA
Outcome	Exitus (4.4 years)	Exitus (8.6 years)	Exitus (0.7 years)	Alive (PD, 1.8 years)	Alive (Ktx, 5.7 years)	Exitus (35 days)
Mutation/protein	c.665G>A/p.Arg222Gln (H)	c.1635_1637delCTT/p.Phe545del (H)	c.1079G>T/p.Gly360Val (H)	c.1018C>T/p.Arg340Trp (H)	c.1018C>T/p.Arg340Trp (H)	c.715dupC/p.Gln239fs*8 (H)

AGA, appropriate for gestational age; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; BW, birth weight; CKD, chronic kidney disease; DMS, diffuse mesangial sclerosis; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; H, homozygous; HD, hemodialysis; Ktx, kidney transplantation; LVH, left ventricular hypertrophy; N, normal; NA, not available; PD, peritoneal dialysis; VSD, ventricular septal defect. Transcript number: NM_003901

Review of the literature

PubMed and MEDLINE were searched using the following keywords: *SGPL1*, *SGPL1* deficiency, *SPLIS*, sphingosine phosphate lyase (*SPL*), sphingosine-1-phosphate, and *SPL* insufficiency syndrome. Articles published in English since 2017 (the year *SGPL1* mutation and clinical presentation were identified), including case reports, case series, and original articles, were reviewed.

Results

A total of 6 patients (3 female and 3 male) with homozygous *SGPL1* mutations were retrospectively analyzed. The median age at kidney presentation was 5 months (10 days–5.3 years) (Table 1). Parental consanguinity was noted in all patients. Four patients (67%) were diagnosed with nephrotic syndrome under 1 year of age; of them, one patient was diagnosed as early as the tenth postnatal day. The other 2 patients were diagnosed at the age of 2.7 and 5.3 years, respectively. At the time of diagnosis, 2 patients had hypertension and 2 had stage 4 CKD. Kidney ultrasonography (USG) showed increased kidney echogenicity in 4 patients and loss of corticomedullary differentiation in 2 patients. Kidney biopsy was performed in 4 patients, of which 2 had focal segmental glomerulosclerosis, one had diffuse mesangial sclerosis (DMS), and one had an increase in mesangial cells and hyaline degeneration in arterioles. Three patients received steroids without any benefit prior to genetic diagnosis. All patients progressed to CKD; one patient stage 4 CKD and the remaining patients stage 5 CKD. Kidney replacement therapy (KRT) was initiated in all but one at a median age of 6 months. Kidney transplantation from a deceased donor was performed in patient #5 at age 3.3 years. His last (2.5 years after kidney transplantation) eGFR was 79 ml/min/1.73 m² without proteinuria. At the last follow-up visit, all patients were requiring antihypertensive treatment.

Extrarenal manifestations

All patients had adrenal insufficiency (Table 1). Five of the patients were diagnosed before 6 months of age; one was diagnosed at the age of 29 months. While glucocorticoid deficiency was observed in all patients, mineralocorticoid deficiency was also present in 2 patients (patients #2 and #4). Adrenal calcification was noted in only one patient. In addition, 3 of the patients had hypothyroidism, 2 patients had ichthyosis, and 4 had immunodeficiency, namely lymphopenia in two patients, humoral immunodeficiency in one, and Ig A deficiency in one. Although 2 patients with lymphopenia died due to sepsis, they did not have a history of severe recurrent infections other than mild upper respiratory

tract infection and acute gastroenteritis. The patient with humoral immunodeficiency and the patient with selective IgA deficiency also did not have a history of recurrent infections requiring hospitalization. Two patients had genitourinary system anomalies; bilateral cryptorchidism was present in one patient and ambiguous genitalia in another patient.

Except for one patient (patient #6) who died at age 35 days, all the patients had various neurological findings, including seizure, developmental delay, intellectual disability, microcephaly, ataxia, speech delay, and hydrocephalus. Pathological cranial magnetic resonance imaging (MRI) findings were detected in all neurologically affected patients, except for one patient (patient #3), who had seizure and died at age 8 months. The cranial MRI findings of the patients are presented in Table 1. Although there was no obvious pathology in the cranial MRI of patient #2, which was performed at age 8 months, pathological contrast enhancements in the thalamus, mesencephalon, pons, bulbus, and cerebellar peduncle, and cerebral and cerebellar atrophy were observed at age 8 years. In addition to seizure, ataxia, intellectual disability, and speech delay, this patient also had sensorineural hearing loss and night blindness.

None of the patients had antenatal hydrops. All patients were born at term, with birth weight appropriate for gestational age.

Outcome

While 2 patients are still being followed up with KRT (i.e., peritoneal dialysis and kidney transplantation), 4 patients died due to sepsis at a median age of 30.5 months. The causes of sepsis were catheter-related infection (patient #1), pneumonia (patient #2), and intraabdominal infection after gastrostomy tube insertion (patient #3); the cause of sepsis could not be determined in patient #6. Height standard deviation scores (SDS) were below –2 SDS at the last follow-up visit in 5 patients. Both of the 2 surviving patients were also receiving pyridoxine therapy. Pyridoxine treatment was started in patient #4 four months after initiation of peritoneal dialysis and in patient #5 1.5 years after kidney transplantation. No change was observed in the extrarenal findings of the 2 patients who were receiving pyridoxine during 10 months follow-up period.

Discussion

In this study, we present clinical aspects of 6 patients with *SGPL1*-related disease. One of our patients (patient #3) was previously reported [14, 15]. To date, 43 patients (+4 fetal demise) from 28 families have been reported [5, 6, 8–10, 14–23]. Following the identification of *SGPL1*, the number of cases has been increasing gradually. However,

this condition remains rare and more patients need to be described to increase our understanding of its spectrum. In this context, we wanted to present one of the largest case series ever with one novel mutation, in order to expand the known phenotypic and genotypic features of the disease.

The mechanism of organ dysfunction in patients with *SGPL1* deficiency is complex and still needs to be investigated. Dysfunction of *SGPL1* causes accumulation of S1P, which is a bioactive molecule involved in the control of cell migration and survival, and organization of the cytoskeleton. S1P signaling regulates diverse immunological processes, and plays an important role in the angiogenesis and fibrosis in multiple organ systems and other physiological processes [24]. It is thought that organ dysfunction resulting from *SGPL1* deficiency is caused by impaired S1P signaling and its intracellular effects, cytotoxic sphingolipid accumulation such as ceramide and sphingosine, deficiency of *SGPL1* products, disturbed lipid homeostasis, or various combinations of these factors [25, 26].

As previously reported, the main presentation of *SGPL1*-related disease in the presented patients was congenital or steroid-resistant nephrotic syndrome. Although nephrotic syndrome is generally diagnosed early in life, 2 patients diagnosed at age 18 and 19 years have also been reported (Online Resource 1) [5]. In the present study, kidney biopsy was performed in 4 patients. FSGS or DMS were the histopathological diagnoses consistent with the other reports in the literature. Kidney prognosis in such patients is poor as it was in our patients as well (Online Resource 1). Two of our patients were in the process of CKD at the time of diagnosis. During follow-up, 5 patients progressed to stage 5 CKD, and one of them successfully underwent kidney transplant without disease recurrence. In the literature, kidney transplantation was reported in 6 patients with *SGPL1* mutation. Proteinuria recurred in 2 of the transplant recipients at 3 and 12 years post-transplantation. Graft loss developed in a patient who developed proteinuria in the 12th year of transplantation, and her graft biopsy was consistent with chronic rejection [5, 6]. In our patient, the graft is functioning 2.5 years after transplantation, indicating that kidney transplantation can be successfully performed in these patients and should be considered for patient survival.

Adrenal insufficiency is another major presentation seen in cases of *SGPL1* deficiency. Such patients are commonly diagnosed before age 1 year; however, there is report of a patient who was diagnosed at age 11 years [5]. While adrenal insufficiency can present as isolated glucocorticoid deficiency, some cases with concomitant mineralocorticoid deficiency have been reported. In addition, adrenal androgen deficiency was reported in a post-pubertal patient [6]. We identified glucocorticoid deficiency in all patients, but only 2 also had mineralocorticoid deficiency. It is possible that androgen deficiency will also develop in these patients

if they reach adolescence. Therefore, all patients should be monitored for all adrenal functions. We observed adrenal calcification in one patient. In the literature, while adrenal calcification was reported in 13 of 43 patients, no data were available in the other reported patients (Online Resource 1). It remains unknown if these other patients had adrenal calcification. Nevertheless, it seems that this finding, which can also be observed even in the prenatal period, is common and should suggest *SGPL1*-related disease in the differential diagnosis when detected [9, 20].

Neurological abnormalities are common and important features of *SGPL1* deficiency and can be seen in a range from isolated peripheral nerve paralysis and sensorineural hearing loss to developmental delay and chronic progressive encephalopathy (Online Resource 1). We identified various brain abnormalities in 4 patients via MRI. Contrast enhancement of the midbrain, pons, cerebellum, and cortical atrophy were the main abnormalities. As in patient #2, the progression of MRI findings over the years has also been clearly demonstrated in some cases [9, 20]. Our observations with existing literature data suggest that patients can be neurologically normal during early course of the disease, but that they should be meticulously followed up for neurological findings that can develop later and may be progressive in nature. In the present study, we identified night blindness in patient #2 for the first time, which expands the neurologic spectrum of the disease.

Hypothyroidism, ichthyosis, immunodeficiency, and genitourinary anomalies are other frequently reported phenotypic features (Online Resource 1), and were also noted in some of our patients. On the other hand, cardiac pathology is not a common finding in cases of *SGPL1* deficiency, as it has been reported in only 2 patients (Online Resource 1); one of them had dilated cardiomyopathy and the other patient had patent ductus arteriosus, patent foramen ovale, and pulmonary hypertension [5, 19]. One of our patients had a ventricular septal defect, and two patients had left ventricular hypertrophy (LVH), the latter of which can also be associated with CKD. Although the prevalence of LVH is 20–30% in patients with stages 2–4 CKD, it can be as high as 85% in those receiving maintenance dialysis, and systolic hypertension, stage of CKD, and an elevated serum fibroblast growth factor 23 levels are the most strongly associated factors [27].

Twenty-six different variants have been described in 43 patients from 28 families to date (Online Resource 1). Although Bamborschke et al. suggested that individuals with severe neurological features harbored mutations in the active pyridoxal-dependent decarboxylase domain, a clear genotype–phenotype relationship has not yet been established. Even siblings with the same *SGPL1* mutation can exhibit different courses, indicating the presence of phenotypic heterogeneity [17, 21]. In the present study, we detected

previously identified mutations in 5 patients and a new mutation in one patient. Moreover, the clinical features of patients #4 and #5 differ from patients with the same mutation in the literature, which expands the phenotypic spectrum of the disease (Table 2).

Our patients were of normal weight at birth and subsequently developed growth retardation in agreement with previous reports [10, 18, 21]. However, fetal hydrops had also been reported in a few patients who died in the intrauterine period or a few months after birth (Online Resource 1).

In general, patient survival is poor in those with SGPL1-related disease given the fact that more than 40% of reported cases died. Our 4 patients died due to sepsis secondary to various infections, whereas immunodeficiency was present in two patients; the others were not immunocompromised. As such, mortality in these cases cannot be explained by immunodeficiency alone, but adrenal insufficiency might have been a precipitating factor during infections, indicating that physicians should immediately increase the steroid dose in case of stress conditions, including infections [28].

Patients with SGPL1 deficiency are often diagnosed after kidney and/or extrarenal complications develop, and treatments are often directed toward complications. However, some targeted treatment approaches are also tried. Zhao

et al. studied the effectiveness of vitamin B6 supplementation in patients with *SGPL1* mutation, as pyridoxal phosphate is also a cofactor of sphingosine phosphate lyase. They reported that disease biomarkers responded to vitamin B6 supplementation and lymphopenia improved in 2 patients with kidney failure [19]. In our study, 2 patients were receiving vitamin B6 supplementation; however, no beneficial effect was observed during the follow-up period. Until we have evidence-based results regarding the beneficial effect of pyridoxine, recommendation of routine use cannot be suggested.

Further studies on this treatment are definitely warranted to reach a correct conclusion. In a recent preclinical study, Zhao et al. also reported that survival increased dramatically with gene therapy in *Sgpl1*-knock out mice, and nephrosis and neurodevelopmental delay were prevented with early treatment [26]. Enzyme replacement therapy, gene editing with CRISPR, bone marrow transplantation, and S1P receptor targeting are among the possible treatment modalities that have yet to be tested in this disorder [29]. Genetic diagnosis will prevent patients from unnecessary immunosuppressive therapies by yielding early and correct diagnosis.

Our study has some limitations, as are commonly encountered in retrospective and multicenter studies. Clinical

Table 2 Clinical characteristics of our patients and previously reported patients with the same mutation

Patient no	Mutation/protein	Clinical characteristics	Previously reported patients		
			Characteristics	Deaths/patients	Reference
1	c.665G>A/p.Arg222Gln	NS, AI, hypothyroidism, lymphopenia, developmental delay, LVH	NS, AI, lymphopenia, ptosis, median and ulnar nerve paralysis, right arm paralysis progressing to hemiparesis, carpal tunnel syndrome, strabismus, lazy right eye, ichthyosis, calcinosis cutis, hepatic transaminase elevation, hearing loss	1/10	[5, 6, 18–20]
2	c.1635_1637delCTT/p.Phe545del	NS, AI, hypothyroidism, lymphopenia, ichthyosis, seizure, ataxia, intellectual disability, speech delay, SND, night blindness, aberrant band in the left ventricle	NS, AI, hypothyroidism, lymphopenia, ichthyosis, neurodevelopmental delay, ataxia, SND	0/1	[6]
3	c.1079G>T/p.Gly360Val	NS, AI, hypothyroidism, seizure	NS, lymphopenia, left radial neuritis, lower extremity weakness, chronic progressive encephalopathy, strabismus	1/1	[19, 20]
4, 5	c.1018C>T/p.Arg340Trp	NS, AI, humoral immunodeficiency, Ig A deficiency, ichthyosis, microcephaly, developmental delay, hydrocephalus, LVH, bilateral cryptorchidism	NS, AI	2/2	[10]

AI, adrenal insufficiency; LVH, left ventricular hypertrophy; NS, nephrotic syndrome; SND, sensorineural deafness. Transcript number: NM_003901

approaches varied between the participating centers; therefore, we could not adequately assess treatment responses.

In conclusion, SGPL1 deficiency should be considered in patients with nephrotic syndrome accompanied by adrenal insufficiency. Genetic diagnosis of nephrotic syndrome patients with SGPL1 deficiency is important for treatment, genetic counseling, and screening for comorbid conditions. Kidney transplantation can be safely performed and should definitely be considered in such patients. Targeted therapies offer promise; however, additional studies are required to further delineate their efficacy and safety profile.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00467-022-05656-5>.

Author contribution RT and FO: research formulation and study design. RT, FO, TTO, NC, SS, USB, and OS: data acquisition. RT, FO, and TTO: data analysis/interpretation. FO: genetic analysis. RT: supervision/mentorship. The first draft of the manuscript was written by TTO and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval The study protocol was approved by the Hacettepe University Ethics Committee (GO 22/275).

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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