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Case Report

Novel sphingosine-1-phosphate lyase mutation causes multisystemic diseases: case report

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ABSTRACT

Background. Sphingosine phosphate lyase insufficiency syndrome (SPLIS) caused by inactivating mutations in the human *SGPL1* gene results in congenital nephrotic syndrome, adrenal insufficiency, ichthyosis, immunodeficiency, and a wide range of pathological neurological features. We present a novel mutation in the *SGPL1* gene causing hypocalcemia, primary adrenal insufficiency (PAI), nephrotic syndrome, subclinical hypothyroidism, lymphopenia, ptosis, and pathologic neuroimaging findings.

Case. A Turkish male infant presented with bruising at 2 months of age and was diagnosed with hypocalcemia, PAI, and subclinical hypothyroidism. At the age of 15 months, he was admitted to the hospital with ptosis. Other systemic manifestations included persistent lymphopenia and nephrotic syndrome. Magnetic resonance imaging (MRI) of the brain and orbit demonstrated asymmetric contrast enhancement in the left cavernosal sinus, orbital apex, and thinning at the bilateral optic nerve. Whole exome sequencing (WES) revealed a homozygous c.1432C>G (p.Gln478Glu) variant in the *SGPL1* gene (NM_003901.4), which has not previously been reported in the literature.

Conclusions. Novel mutations in *SGPL1* are still being identified. This case reminded us that SPLIS should not be considered for patients with nephrotic syndrome alone. Still, PAI may also include patients with neurological disorders, hypocalcemia, and pathological neuroimaging findings such as thinning at the bilateral optic nerve.

Key words: sphingolipids, Sphingosine phosphate lyase insufficiency syndrome, adrenal insufficiency, Nephrotic syndrome, Ptosis.

Sphingolipids (SLs) were discovered by Thudichum in 1884 and are considered normal components of the plasma membrane, myelin sheath, and plasma.[1,2] SLs are degraded into bioactive intermediates that can join in signal transduction pathways that play a role in the regulation of cell survival, migration, programmed cell death, and intracellular functions.[3] In the degradation and recycling of SLs, a highly preserved group of enzymes are involved. Sphingolipidoses, a storage disorder, is caused by the accumulation of different classes of SLs due to the deficiency of these enzymes.[4]

Ceramide and sphingosine 1 phosphate (S1P) are two important bioactive SLs.[5] S1P can be degraded into two non-SL products, hexadecanal and ethanolamine phosphate, by sphingosine 1 phosphate lyase (SGPL1).[6] The only known exit pathway of SL metabolism is the production of these two compounds. SGPL1, the last enzyme in the sphingolipid degradation pathway, catalyzes the irreversible division of long-chain base phosphates.[7]

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In reports between 2017 and 2018, a new childhood syndrome called sphingosine phosphate lyase insufficiency syndrome (SPLIS) was defined. SPLIS is caused by inactivating mutations in the human *SGPL1* gene that encodes SGPL1.[8-10] SPLIS includes a combination of ichthyosis/acanthosis, steroid-resistant nephrotic syndrome, hypothyroidism, primary adrenal insufficiency (PAI), gonadal dysgenesis, lymphopenia and/or neurological disorders including microcephaly, cranial nerve defects, and peripheral neuropathy. The pathogenesis of findings other than lymphopenia has yet to be fully elucidated. In the literature, it has been reported that clinical findings may be caused by excess intracellular S1P, accumulation of other SLs, abnormal S1P receptor signaling, or loss of SGPL1 products.[11] Accumulation of the species S1P, sphingosine, and ceramide, have been associated with the induction of cytotoxicity and apoptosis.[12,13] S1P functions as a ligand for a family of 5 specific G-protein coupled receptors (S1PR1-5).[14] S1PR1, the prototype of S1PR, regulates the outflow of T lymphocytes from the thymus and peripheral lymphoid organs.[15] While S1P levels are extremely low in most tissues other than blood and lymph, they are kept at low concentration levels in tissues by SGPL1.[10] When SGPL1 activity is disrupted, this gradient cannot occur, and increased S1P level reduces the S1P chemotactic gradient or the ability of the lymphocyte to detect it, which leads to lymphopenia.[16]

Herein, we present a novel mutation in *SGPL1* causing multi-systemic disease.

Case Report

A male Turkish patient was the fourth child of first-degree consanguineous healthy parents without a family history of chronic diseases. After an uneventful pregnancy, he was born at 39th weeks of gestation, with a birth weight of 2800 g. His elder siblings were healthy. He was referred to an external center with a complaint of bruising at two months of age. Biochemical tests revealed calcium: 5.3 mg/dL (9–11), phosphorus: 7.3 mg/dL (3.7–6.5), magnesium: 1.7 mg/dL (1.3-2.7), alkaline phosphatase: 658 IU/mL (122–469), parathyroid hormone: 157 pg/mL (15–65), and 25OH vitamin D: 6.72 ng/mL (20-30) levels. Complete blood count, electrolyte, glucose, liver, and kidney tests were normal. Treatment with calcium and vitamin D was started. High doses of intravenous and oral calcium were required to treat his hypocalcemia. Thyroid hormone replacement was started due to the results of the thyroid stimulating hormone (TSH): 10.2 IU/mL (0.27–4.2) and fT4: 14.25 pmol/L (12-22). No problems were detected on the thyroid ultrasound. When cholestasis developed during his hospitalization, an evaluation was conducted and resulted in an adrenocorticotropic hormone (ACTH) level of 722 pg/mL and cortisol level of 2.2 ug/dL; thus, he was diagnosed with PAI, and hydrocortisone treatment was started. Cholestasis was improved after hydrocortisone treatment.

At the age of 15 months, he was admitted to our hospital with a preliminary diagnosis of periorbital cellulitis and complaints of ptosis and eyelid swelling. Body weight was measured as 8 kg (–2.73 standard deviation score [SDS]), height as 72 cm (–2.79 SDS), and head circumference as 44 cm (–2.76 SDS). The cranial nerve and ophthalmological examination revealed nearly complete ophthalmoplegia of the left eye, without direct light reflex. Ophthalmological examination of the right eye was normal, and there was no other motor or sensory neurological deficit. The patient was transferred to the ophthalmology department for further assessment and management. Upon ophthalmological and neurological examination there was severe ptosis on the left, and when the right eye was fixed, the left eye was in an abducted position, indicating oculomotor and trochlear nerve palsies on the left side (Fig. 1). This exotropia was at a large angle in the primary gaze position. When the right eye was manually closed, the patient was unable to bring his exotropic left eye to the midline. Direct pupillary light reflex was not obtained

Fig. 1. The patient at 15 months of age presenting with ptosis.

from the left eye but it was normal for the right eye. Biomicroscopic and fundus examinations were normal for both eyes. Other system examinations including the genitourinary system were normal. The laboratory results of the patient are given in Table I.

The echocardiography was normal. He had nephrotic range proteinuria (2.5 g/day, 200 mg/m²/h) and hypoalbuminemia (26 g/L). He was administered captopril first. A hearing test was normal. Malignancy was excluded. Investigations for infectious diseases were normal. No thrombus was detected on orbital venography. Abdominal computed tomography imaging was normal. No adrenal calcification was detected. Immunological evaluation was performed due to the detection of lymphopenia (650–1500/mm³), and the number of B cells and CD4+ T cells were found to be low. Trimethoprim-sulfamethoxazole, fluconazole and monthly IVIG treatments were started prophylactically. Metabolic investigations including very long chain fatty acids, acyl carnitines, urinary organic acids, urine and plasma amino acids, lactic and pyruvic acids were all normal.

T1 weighted (T1W) magnetic resonance imaging (MRI) of the brain and orbit demonstrated asymmetric contrast enhancement in the left cavernosal sinus and orbital apex (Fig. 2-3). MRI also showed thinning at the bilateral optic nerve (Fig. 2, 4). His imaging findings were discussed with neuroradiology and assumed to likely represent an underlying inflammatory process. Methylprednisolone treatment was started. After 10 weeks of steroid treatment, no

Table I. The results of the initial laboratory investigations (at 15 months)

Parameter	Value	Unit	Reference range	Parameter	Value	Unit	Reference range
Corrected Ca	7.1	mg/dL	9.1-10.3	Hgb	8.2	g/dL	10.2-13.4
Phosphorus	3.8	mg/dL	4.1-6.5	PLT	198	x10⁹/L	220-490
ALP	192	U/L	142-336	WBC	3.34	x10⁹/L	5.4-13.8
PTH	108	ng/L	18.4-80.1	Lymphocytes	0.76	x10⁹/L	3-10
25OH-D	19	nmol/L	75-375	ALT	8	U/L	0-32
Creatinine	0.1	mg/dL	0.1-0.4	AST	46	U/L	0-46
Urea	9	mg/dL	11-39	Na	138	mEq/L	132-146
ACTH	903	pg/mL	<46	K	3.0	mEq/L	3.5-5.5
Cortisol	8.2	μg/dL	5.2-22	Cl	109	mEq/L	99-109
TSH	15.3	mU/L	0.5-4.9	Glucose	86	mg/dL	<100
fT4	0.97	ng/dL	0.83-1.43	Albumin	26	g/L	32-48
FSH	1.9	U/L	0.3-10.1	Prot. (urinalysis)	++++	-	negative
LH	0.1	U/L	<0.6	Prot./cre (urine)	21.4	mg/mg	<0.5
Renin	0.47	ng/mL/h	1.7-11.2	24h urine prot.	200	mg/m²/h	<4
Aldosterone	12	pg/mL	10-160				

25OH-D: 25-hydroxyvitamin D, ACTH: adrenocorticotropic hormone, ALP: alkaline phosphatase, ALT: alanine transaminase, AST: aspartate transaminase, cre: creatinine, FSH: follicle-stimulating hormone, fT4: free thyroxine, Hgb: hemoglobin, LH: luteinizing hormone, PLT: platelet, Prot.: protein, PTH: parathyroid hormone, TSH: thyroid-stimulating hormone, WBC: white blood cell.

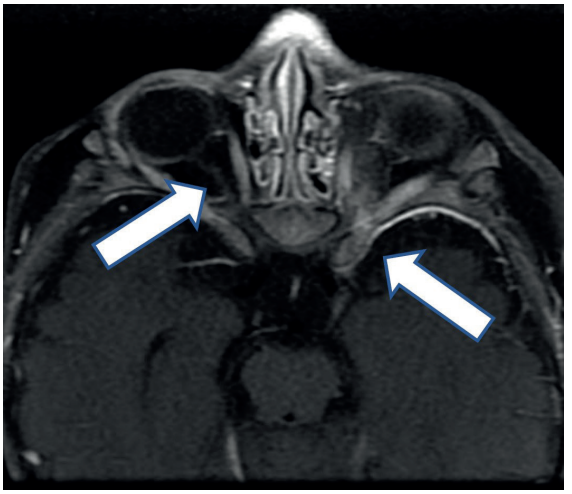

Fig. 2. Axial contrast enhancing T1W MRI shows asymetric contrast enhancement at the left orbital apex, thinning of the optic nerve.

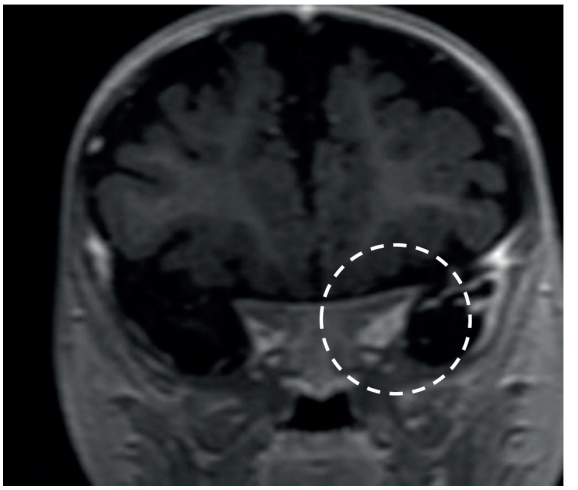

Fig. 3. Coronal contrast enhancing T1W MRI shows asymetric contrast enhancement at the left orbital apex.

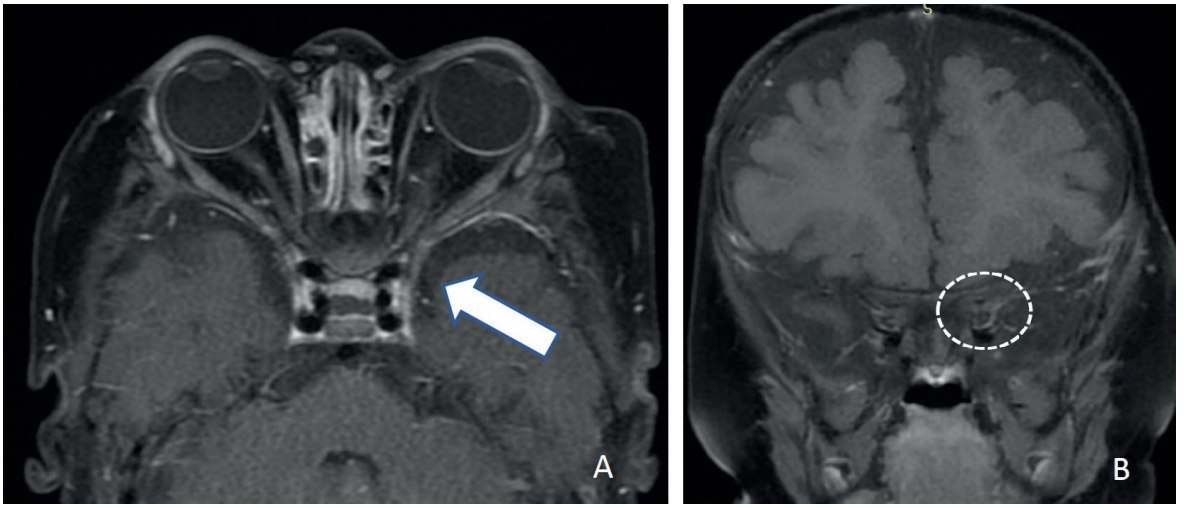

Fig. 4. There is no asymmetric contrast enhancement at left orbital apex.

asymmetric contrast enhancement in the left cavernosal sinus and orbital apex was detected on the MRI (Fig. 4). Despite the enhancement in MRI findings, there was no improvement in ptosis.

With the findings of hypocalcemia, PAI, nephrotic syndrome, subclinic hypothyroidism, lymphopenia, and ptosis, a homozygous mutation was found in the *SGPL1* gene, confirming SPLIS.

Whole exome sequencing (WES) was performed using the TWIST Comprehensive Exome Kit and MGI DNB SEQ G400. WES revealed a homozygous c.1432C>G (p.Gln478Glu) variant in the *SGPL1* gene (NM_003901.4), which was not previously reported in the literature. The variant was not found in the gnomAD genomes, 1000G and ExAC databases. This variant is classified as VUS according to the American College of Medical Genetics and Genomics (ACMG) guidelines and estimated to be deleterious by in silico pathogenicity prediction tools such as MutationTaster, SIFT, and Polyphen-2 (score 0.999). The detected variant resides in a highly conserved protein region according to the

Fig. 5. Schematic representation of the evolutionary conservation of the SGPL1 protein region involved in c.1432C>G (p.Gln478Glu) variant among various species.

GERP++ in-silico prediction (GERP score= 5.78) (Fig. 5). Sanger sequencing was carried out for validation and segregation analysis showed that his parents were heterozygous carriers for the same variant. Informed consent was obtained from the patient's family for the publication of this case report, including photographs.

Discussion

We described the phenotypic features and molecular diagnosis of SPLIS in a Turkish male patient who had a novel homozygous variant discovered in the *SGPL1* gene using WES. In the current case, hypocalcemia, PAI, and subclinic hypothyroidism were found in the first year of life. Lymphopenia, ptosis, and nephrotic syndrome were detected between one and two years of age. Also, an MRI showed thinning of the bilateral optic nerves. To date, less than 70 confirmed cases of SPLIS have been reported, and 13 patients stated in the literature were of Turkish origin. All cases reported from Turkey had homozygous variants, and all of the patients had consanguineous parents, just like our patient. Although the most common initial clinical manifestations of reported patients were kidney disorders; our patient presented with endocrine disorders at the age of two months. In our patient, who is currently 2.7 years old, there were no new findings other than the clinical manifestations we reported above.

In a recent review, 55 patients with SPLIS from 19 articles were identified. Endocrine disorders, especially PAI, were found to be the most prevalent clinical features.[17] While most patients affected by adrenal insufficiency present with signs of glucocorticoid deficiency, cases of mineralocorticoid deficiency and adrenal androgen deficiency have also been reported.[18,19] It was reported that disrupted adrenocortical zonation and defective expression of steroidogenic enzymes may cause adrenal insufficiency in Sgpl1 null mice.[20] Ceramide, sphingosine, and sphingosine 1-phosphate are modulators of the steroidogenic pathway.[18]

While S1P plays a role at multiple levels in the steroidogenic pathway to upregulate cortisol biosynthesis, ceramide and sphingosine play a role in reducing steroidogenesis.[21,22] The study by Maharaj et al.[23] reported that sphingolipid accumulation may impair steroidogenesis by impairing mitochondrial morphology and function. Elevated ceramide levels in the mitochondria may lead to inner mitochondrial membrane dysfunction.[24] In addition, adrenal calcification detected in many of the SPLIS patients suggests that adrenal insufficiency may occur with lipid accumulation in the adrenal gland.[18] Expression of SGPL1 in the testes and thyroid gland explains thyroid dysfunction and/or testosterone deficiency in such cases.[18,20,25] To date, no endocrinopathy other than hypocalcemia, adrenal insufficiency and subclinic hypothyroidism has been detected in our patient.

S1P signaling is also known to regulate bone metabolism. The effect of S1P on bone homeostasis is associated with bone remodeling by regulating the circulation of osteoclast progenitors.[26] In the study of Weske et al., it was revealed that raising S1P levels in adult mice through SGPL1 inhibition markedly increased bone formation, mass, and strength, and significantly reduced white adipose tissue. It was reported that S1P signaling via S1PR2 strongly stimulates osteoblastogenesis and inhibits osteoclastogenesis by simultaneously inducing osteoprotegerin.[27] In the literature, hypocalcemia in SPLIS was reported in one case.[12] The patient herein was admitted for the first time with hypocalcemia at the age of 2 months old, and his hypocalcemia continued despite the treatment of vitamin D and calcium. The calcium level was in the normal range, with intravenous calcium, calcitriol and vitamin D treatment. This case may be important in terms of raising awareness about hypocalcemia in patients with SPLIS.

It was reported that kidney disorders were the most common initial manifestations of SPLIS.[17] Damage to glomerular podocytes is reported as one of the causes of kidney pathology in SPLIS. Immunofluorescence experiments in mice detected that SGPL1 is localized in the podocyte, mesangial and endothelial cell endoplasmic reticulum of renal glomerular cells.[12,28] Renal involvement varies from non-immune fetal hydrops to the absence of renal involvement in long-term follow-up. Patients usually present with steroid-resistant nephrotic syndrome that progresses to end-stage renal disease, whose histological findings on renal biopsy are focal segmental glomerulosclerosis (FSGS) and diffuse mesangial sclerosis.[29] This form of congenital nephrotic syndrome is called nephrotic syndrome type 14.[12] Tastemel Ozturk et al.[30] from Turkey reported six patients with homozygous *SGPL1* mutations. The median age at which kidney symptoms manifested in this study was five months, and all of the patients developed chronic kidney disease. The patient herein had nephrotic range proteinuria, hypoalbuminemia and edema accompanied by slightly increased serum cholesterol levels.

The complex biological effects of S1P affect the nervous system as well as many other systems. In patients with SGPL1 deficiency, pathological neurological disorders, such as Charcot-Marie-Tooth neuropathy, neurodevelopmental delay, sensorineural hearing loss, microcephaly, seizures, cranial nerve deficits, strabismus, ptosis, and encephalopathic neurodegenerative disease, have been reported.[8,9,31] Vertebrate and invertebrate models of SGPL1 insufficiency have been shown to cause neurotoxicity.[32] Nevertheless, the underlying mechanisms responsible for the molecular pathogenesis of neurotoxicity remain unresolved. The neuroimaging results encompass a spectrum of observations, including loss of the corpus callosum, progressive cortical atrophy, cerebellar hypoplasia, as well as notable involvement of the globus pallidus, thalamus, and dentate nucleus.[29,33] In the literature, MRI findings are not specific and may show similarities with other toxic, metabolic, mitochondrial, infectious, and post infectious

disorders. Our patient showed asymmetric contrast enhancement in the left orbital apex and cortical atrophy with thinning at the optic nerve. After steroid treatment, no asymmetric contrast enhancement was detected. The cause of this finding is not known. To the best of our knowledge, thinning of the optic nerve has not been reported in SPLIS in the literature. It is not known whether this condition is associated with SPLIS.

In conclusion, SPLIS patients may present with a wide spectrum of findings. Hypocalcemia, adrenal insufficiency and subclinic hypothyroidism were the earliest findings in our case. Early diagnosis can allow early identification of other comorbidities of the disease. As such cases are reported, it will also assist in determining the appropriate genotype-phenotype correlations in patients suffering from SGPL-related pathogenesis.

Ethical approval

Informed consent was obtained from the patient's family.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: GB, KTA, FG; data collection: GB, KTA, GÜD, ED, ŞBE, ÖYA; analysis and interpretation of results: GB, KTA, ÇSK; draft manuscript preparation: GB, KTA, ÇSK, MB, FG. All authors have reviewed and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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