Case Report

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Lathosterolosis: a rare cholesterol metabolism disorder with a wide range of clinical variability

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Abstract

Objectives: Lathosterolosis is a rare autosomal recessive congenital disease that occurs due to homozygous or compound heterozygous mutations in the sterol C5-desaturase (*SC5D*) gene. We report a male patient with biallelic missense variant detected in the *SC5D* gene.

Case presentation: An eight-month-old male patient was referred to the department of paediatric neurology for status epilepticus. He had no remarkable dysmorphic features except micrognathia, ptotic ear and thin-stranded hair. Laboratory tests revealed an alanine aminotransferase level of 502 IU/L and an aspartate aminotransferase level of 279 IU/L; other biochemical test results were normal. The brain MRI revealed atrophic changes in both hemispheres. A decrease in the volume of brain stem and thin corpus callosum were noticeable. Whole exome sequencing was performed because of consanguineous marriage and sibling death in his medical history, and the encountered features were consistent with suspected neurometabolic disease in the cranial imaging and the presence of borderline psychomotor retardation. A biallelic missense variant, c.656T>C p.(Leu219Ser), was identified in the *SC5D* gene.

Conclusions: Lathosterolosis is a rare cholesterol metabolism disorder and can be presented with a wide range of clinical features by newly reported cases. Lathosterolosis should be considered in cases with cataracts, delayed neuromotor developmental milestones and high levels of liver enzymes.

Keywords: cholesterol metabolism; elevated transaminases; lathosterol; microcephaly.

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Introduction

Lathosterolosis (OMIM #607330) is a very rare cholesterol metabolism disorder that is inherited autosomal recessively. In cholesterol biosynthesis, sterol C5-desaturase (SC5D), also called lathosterol dehydrogenase, catalyses the synthesis of 7-dehydrocholesterol from lathosterol while 7-dehydrocholesterol reductase (DHCR7) functions in the biosynthesis of cholesterol from 7-dehydrocholesterol. Cholesterol biosynthesis is impaired due to the defects of these both enzymes. The deficiency of DHCR7 enzyme leads to Smith–Lemli–Opitz syndrome (SLOS), while deficiency of SC5D enzyme causes a rarely seen disease termed as lathosterolosis [1–4]. Microcephaly, micrognathia, hypotonia, developmental delay, genital anomalies and skeletal anomalies have been reported in both SLOS and lathosterolosis. However, accompanying cardiac anomalies and cleft palate in SLOS and elevated liver enzymes in cases with lathosterolosis can be considered among the differential findings [5]. Even though lathosterolosis's genetic and biochemical processes have been identified, they vary in a wide range, and pathophysiological changes that have importance in the process of the disease are not still clearly known [1]. In the present study, we have reported an 8-month-old male case with a detected biallelic missense variant; c.656T>C p.(Leu219Ser), was identified in *SC5D* gene (Table 1).

Case presentation

An eight-month-old male patient was referred to the department of paediatric neurology for status epilepticus.

Table 1: Clinical and laboratory characteristics of the patients diagnosed with Lathosterolosis.

	Parnes et al. (1990)	Brunetti et al. (2002)		Ho et al. (2014)	Anderson et al. (2019)	Prasun et al. (2019)	Yaplito-Lee et al. (2020)	Current case
		Rossi et al. (2007)						
	Krakowiak et al. (2003)	Case 1	Case 2					
Molecular findings	Homozygous p.Y46S p.Y46S	Compound heterozygous p.R29Q and p.G211D	Compound heterozygous p.R29Q and p.G211D	Compound heterozygous p.K148E and p.D210E	Compound heterozygous p.P160R and p.D210E	Homozygous p.G211D	Compound heterozygous p.N71I and p.Q72*	Homozygous p.L219S
Gender	Male	Female	Female	Male	Male	Female	Female	Male
Cataract	+	+	NA	+	+	+	+	+
Microcephaly	+	+	+	+	+	+	+	+
Micrognathia	+	+	+	+	–	–	NA	+
Neurodevelopmental delay	NA	+	NA	+	+	+	+	+
Elevated liver enzymes	+	+	+	+	–	+	+	+
Age at diagnosis	Post-mortem	7 years	Aborted at 21 weeks	22 months	10 years	9 years	10 years	9 months
Lathosterol plasma level	NA	338 µmol/L	NA	81.6 µmol/L	219.8 µmol/L	31.4 mg/L (n<3)	54 µmol/L (n<10)	NA
Cholesterol level	NA	Normal	NA	Normal	Normal	NA	Normal	Normal
Brain MRI	NA	Normal	NA	Normal	NA	Normal	NA	Atrophic changes and volume loss
Genitalia	Undescended testicle, Penoscrotal hypospadias	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Limb anomaly	Syndactyly and hexadactyly	Postaxial hexadactyly and syndactyly	Postaxial hexadactyly and bilateral clubfeet	Postaxial hexadactyly of feet and bilateral Soft tissue syndactyly	Clinodactyly of both feet	Syndactyly	Partial syndactyly and clinodactyly	None

NA, not avaliable.

The patient was born as 2nd live birth from the 2nd pregnancy of healthy father and mother who were first cousins. One sibling had undergone exitus at the age of one year; metabolic disease was considered, but a diagnosis was not established. Prenatal follow-ups encountered no complications. No perinatal complications occurred, and he had a birth weight of 3,100 g (−0.73 SD), a birth length of 51 cm (0.39 SD) and a head circumference of 34 cm (−1.43 SD). He was admitted to intensive care unit (ICU) monitoring with a clinical picture of status epilepticus in the course of SARS-coV-2 infection. At that time, the physical examination measured a weight of 7,400 g (−1.05 SD), a height of 73 cm (−0.72 SD) and a head circumference of 42 cm (−2.17 SD). He had no remarkable dysmorphic features except micrognathia, ptotic ear and thin-stranded hair (Figure 1). Laboratory tests revealed an alanine aminotransferase (ALT) level of 502 IU/L, aspartate aminotransferase (AST) level of 279 IU/L, alkaline phosphatase (ALP) level of 755 (normal range: 0–500) IU/L and gamma glutamyl transferase level of 651(normal range: 1–39) IU/L. However, a liver biopsy could not be performed. Viral hepatitis markers were negative. When cholesterol tests were evaluated, total cholesterol measured at 135 mg/dL, triglycerides at 165 mg/dL, high-density lipoproteins at 45 mg/dL and a low-density lipoprotein level of 127 mg/dL was detected. His electroencephalogram showed background slowing without epileptic activity or physiological components. The blood amino acid chromatography and tandem mass spectrometry (Tandem MS) results, ammonia, biotinidase, homocysteine, lactate, pyruvate, urine amino acid and urine organic acid levels were found to be normal in the analyses performed with respect to inborn metabolic diseases. Ophthalmological and hearing examinations were normal. The abdominal ultrasonogram was normal. The brain MRI revealed remarkable atrophic changes in both hemispheres, particularly in frontotemporal and bilateral temporal anteromedial regions, and enlargement of sulci and subarachnoid space consistent with volume loss. The extra-axial cerebrospinal fluid space was enlarged, there was enlargement of extra-axial space and sulci secondary to remarkable atrophy in bilateral frontal, anterior-superior areas and the parafalcine area, and decreased volumes of white and grey matters were encountered. A decrease in the volume of the brain stem and remarkably thin corpus callosum were noticeable (Figure 2). A regression was monitored in the levels of AST and ALT (138 and 144 IU/L, respectively), and the patient was discharged to be followed up by control examination. Whole exome sequencing was performed because of consanguineous marriage and sibling death in his medical history, high levels of transaminases, the encountered features consistent with suspected neurometabolic disease in the cranial imaging, the presence of mild developmental delay and absence of any feature as a result of the performed tests. A biallelic missense variant of c.656T>C p.(Leu219Ser) was identified in *SC5D* gene, and the mutation was consensually noted to be “detrimental” *in silico* prediction

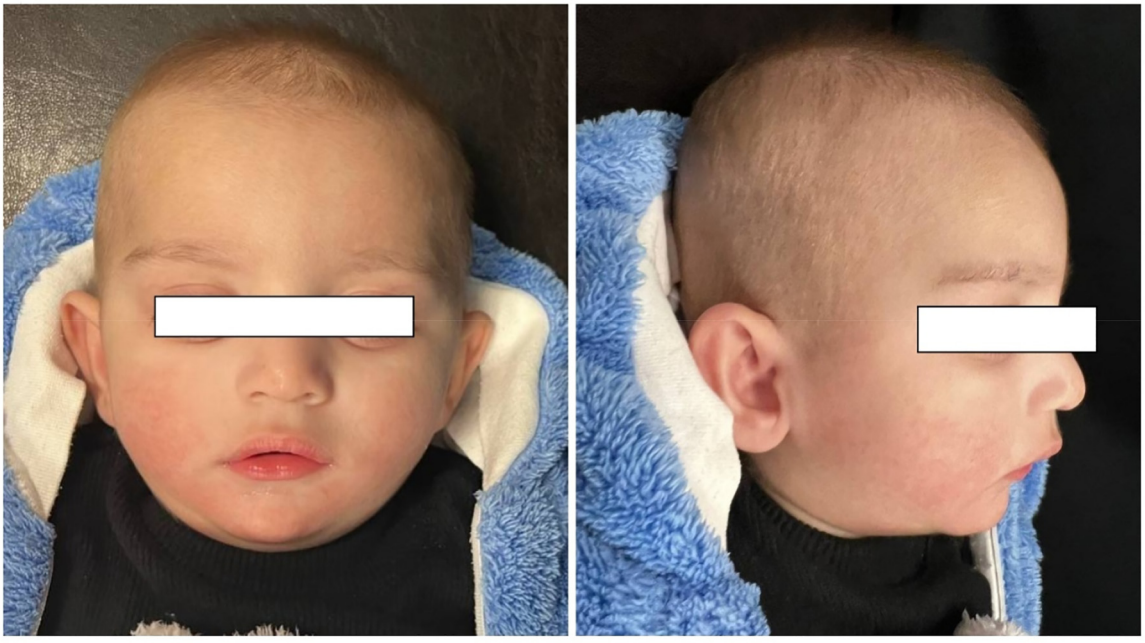

Figure 1: Facial appearance of the patient.

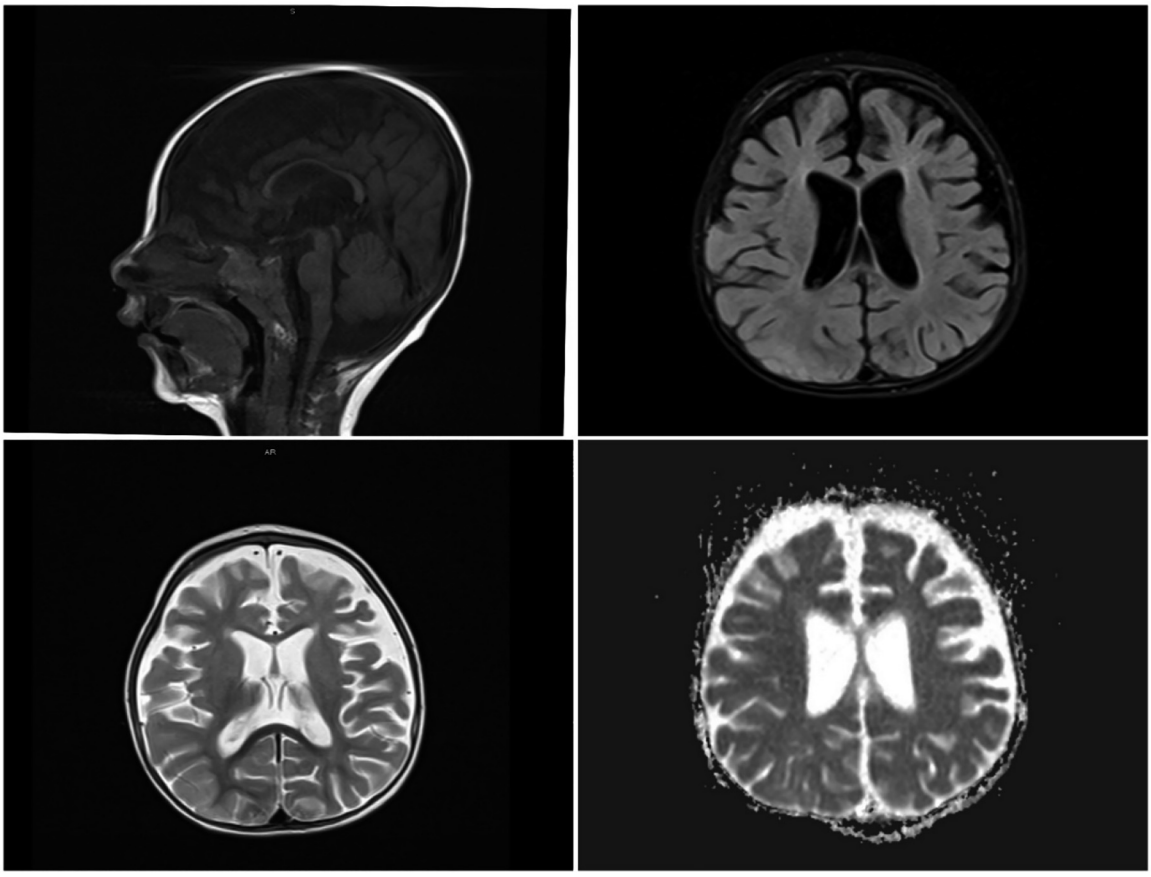

Figure 2: Cranial MRI images of the patient performed at the age of eight months.

databases and evaluated to be of uncertain significance according to the ACMG 2015 criteria (Table 2). At the beginning of 2022, the same variant was detected in another patient who presented with hypotonia and microcephaly during diagnostic testing (https://www.ncbi.nlm.nih.gov/clinvar/variation/1333349/?new_evidence=true).

The patient received simvastatin therapy for six months, but treatment was discontinued due to elevated liver enzymes. He was able to sit without support but unable to walk at the age of two years. The initial ophthalmological examination was normal, but a bilateral cataract was diagnosed by the ophthalmological examination at the age of two years. Liver parenchyma had a non-homogeneous appearance in the ultrasound, and no mass was encountered. The enzyme levels were as follows: ALT 655 IU/L, AST 321 IU/L, gamma glutamyl transferase 913 U/L, alkaline phosphatase 837 and bilirubin levels were within normal limits.

Discussion

Lathosterolosis is a metabolic disease characterised with multiple congenital anomalies in the axial and appendicular skeletons, urogenital anomalies, as well as central nervous system and liver involvement. Clinical features

Table 2: Bioinformatics analysis of the variant.

Gene	Variant	Type zygosity	Clinvar	ACMG	Mutation taster	SIFT	PROVEAN	gnomAD
SC5D (NM_006918.5)	c.656T>C p.Leu219Ser	Missense Homozygous	UCS	UCS (PP3 + PM2)	Disease causing	Damaging	Damaging	0

ACMG, American College of Medical Genetics and Genomics Guidelines; Mutation taster, (http://www.mutationtaster.org/); SIFT, sorting intolerant from tolerant; PROVEAN, protein variation effect analyzer; genomAD, genome aggregation database (https://gnomad.broadinstitute.org/); UCS, uncertain significance.

develop due to both a deficiency of cholesterol and the accumulation of lathosterol, which is the precursor product. Even though its genetic and biochemical processes have been identified, pathophysiological changes that have importance in the process of the disease are still not clearly known [1].

The *SC5D* gene that has been identified in the genetic basis of the disease is located in the 11q23 region, and the homozygous or compound heterozygous mutations have been associated with lathosterolosis. A biallelic missense variant in the *SC5D* gene was also detected in our patient [3]. If the presence of distinctive facial features and limb anomalies creates the suspicion of a cholesterol biosynthesis defect, normal cholesterol or 7-dehydrocholesterol levels cannot rule out the diagnosis of a cholesterol synthesis defect like lathosterolosis [6]. The lipid profile of our patient did not show any features, but the plasma cholesterol profile could not be evaluated by gas chromatography-mass spectrometry (GC-MS). Also, no skeletal anomaly was observed.

Lathosterolosis is a rarely seen disease, and only seven cases had been reported in the literature before today; our case is the eighth reported case in the literature while he is only the first case reported from Turkey.

The clinical and laboratory features of lathosterolosis were first described in the literature in 1990 by Parnes et al. [7]. Parnes et al. described clinical features of the disease in a male infant with intrauterine developmental retardation, hypotonia, congenital cataract, undescended testicle, penoscrotal hypospadias, syndactyly and polydactyly. The clinical features were similar with Smith–Lemli–Opitz syndrome, but this patient was differentiated from SLOS by the histopathological examination that showed intracellular accumulation of mucopolysaccharides and lipids in tissue macrophages, as well as Kupffer cells and non-neuronal cells of the central nervous system. The genetic studies of that case were conducted in 2003 by Krakowiak et al., and the patient was diagnosed with lathosterolosis [4].

However, the first confirmed genetic cause of lathosterolosis was defined by Brunetti-Pierri et al. in 2002 as a pathogenic variant in the *SC5D* gene. Brunetti et al. did not encounter 7-dehydrocholesterol in the plasma sterol profile by gas chromatography/mass spectrometry (GC/MS) method in a male case with dysmorphic facial features, axial hypotonicity, polydactyly, syndactyly and high levels of liver enzymes, whereas they had observed a peak of lathosterol. The fibroblast cultures of the proband also suggested a block in cholesterol biosynthesis at the level of *SC5D*. They have found the two missense mutations c.88G>A; p.(R29Q) and c.632G>A; p.(G211D) in the DNA of the proband. Each parent was heterozygous for one of these two mutations, indicating that the proband was a compound heterozygote and suggesting that the disease has an autosomal recessive pattern of inheritance [3].

After Brunetti et al. described the genetic and clinical features of the disease, new cases were reported in 2014, 2019 and 2020 by Ho et al., Yaplito-Lee et al., Anderson et al. and Prasun et al., respectively [6, 8–10]. The clinical features of the disease may vary. For instance, hepatosplenomegaly and cirrhosis leading to liver failure were noted in the period of infancy in some cases, while biopsy results indicated the diagnosis of cirrhosis in advanced ages in other cases [4, 7, 10].

Cataract was detected at the age of four years in the case reported by Ho et al. despite a normal ophthalmological examination in the early term similarly to our case [6].

Except the 10-year-old male case reported by Anderson et al., high levels of liver enzymes and/or parenchymal disease were present in all the case including our patient [9].

Kamino et al. evaluated 60 preterm newborns in their 2019 study and reported that early plasma lathosterol levels were associated with increased axial and radial diffusivity, and increased volume of the subcortical white matter while each 1 μmol/L increase in early plasma lathosterol levels was considered to be related with a 2.0-point decrease in Bayley Motor Scores. This study demonstrates the relationship between lathosterol levels and the development of subcortical white matter [11].

Conclusions

Lathosterolosis is a very rare cholesterol metabolism disorder, and it is obvious that the disease can be presented with a wide range of clinical features in newly reported cases. The case reported in our study was differentiated from other reported cases by admission due to the complaint of seizures and the absence of limb anomalies. The remarkable atrophy in the white matter and very thin corpus callosum were noticeable in the cranial imaging. The common feature reported in all the cases was delayed neuromotor developmental milestones. Lathosterolosis should be taken into consideration in cases with cataract, delayed neuromotor developmental milestones and high levels of liver enzymes.

Learning points

(1) Lathosterolosis is a rarely seen disease and only seven cases had been reported in the literature before today.

(2) Patients can present with a wide range of clinical features.
(3) Lathosterolosis should be taken into consideration in cases with cataract, delayed neuromotor developmental milestones and high levels of liver enzymes.

What is new?

The case reported in our study was differentiated from other reported cases by admission due to a complaint of seizures and the absence of limb anomalies. The remarkable atrophy in the white matter and very thin corpus callosum were noticeable in the cranial imaging.

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