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A novel *SLC44A* gene variant in a patient with neonatal cholestasis and liver failure

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ABSTRACT

SLC44A1 gene variants (MIM # 618868) are associated with a choline transporter deficiency with a rare autosomal recessive genetic disorder characterized by neurodegeneration, childhood-onset with ataxia, tremor, optic atrophy, and cognitive decline. Variants in the *SLC44A1* gene are considered to be responsible for the syndrome. We reported a four-month-old baby with neonatal cholestasis and liver failure, but neurological development and examination were normal. During the patient's initial physical examination, height, weight, and head circumference were < -2 SDS. He was alert, with eye tracking and a smile present, appeared icteric, and exhibited hepatosplenomegaly, with a history of second-degree consanguinity between his parents. The patient showed signs of neonatal jaundice, elevated transaminases, and episodes of hypoglycemia. After excluding biliary atresia, tyrosinemia, and other metabolic diseases, mitochondrial hepatopathy, vascular pathologies, and congenital infectious diseases through all standard examinations for neonatal cholestasis, a genetic analysis test and whole exome analysis were conducted. Molecular analysis of the whole exome revealed a novel inherited mutation, one inherited from each parent. This novel variant in the SLC44A1 gene is c.1632 + 1G > A. A thorough physical examination and laboratory tests should be conducted for patients presenting with neonatal cholestasis. Subsequently, whole exome analysis from the parents identified the same mutation as heterozygous c.1632 + 1G > A in the SLC44A1 gene. Genetic examinations should be considered in patients whose cause remains undetermined, particularly when there is a family history.

Conclusion: We describe a novel childhood-onset liver failure and metabolic disease caused by choline transporter deficiency with autosomal recessive inheritance.

1. Introduction

SLC44A1, a member of the choline-like transporter family, widely expressed in human tissues, is detected in both plasma and mitochondrial membranes and facilitates the choline uptake into the mitochondria, where the oxidation of choline to betaine takes place [1] Eugene Kennedy first identified the pathways predominant for de novo synthesis of phosphatidylcholine (PC) (cytidine diphosphate [CDP]- choline pathway) and phosphatidylethanolamine (CDPethanolamine pathway) in mammals. Choline transport like protein 1 (CTL1, *SLC44A1*) is believed to be the main choline transporter for the Kennedy pathway. The CTL1 protein is encoded by the *SLC44A1* gene [2]; [Michel and Bakovic], [3]). *SLC44A1* deficiency has been related to choline deficiency. [4,5,6].

Choline is involved in three main physiological processes: structural integrity and lipid-derived signaling for cell membranes, cholinergic neurotransmission, and methylation (as a significant source for methyl groups via its metabolite trimethylglycine). Choline is recently gaining increasing public attention. This is based on observations that 77 % of healthy men and 80 % of postmenopausal women were shown to have low choline and subclinical organ dysfunction (e.g., nonalcoholic fatty liver disease and muscle damage), which were resolved after three

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weeks of a choline-rich diet. [7].

The physiological relevance of *SLC44A1* as a choline transporter was addressed in several studies. The suppression of *SLC44A1* via siRNA results in the impaired growth of the cholinergic hybrid neuroblastoma cell line NG108–15 cells. These data are consistent with the role of *SLC44A1* in providing choline for incorporation into membrane phospholipids. [8].

[9] study on choline presents a wide phenotypic spectrum ranging from malodor to intellectual disability, epilepsy, anemia, neonatal cholestasis, nonalcoholic fatty liver disease or dysphagia, optic atrophy, dysarthria, and congenital myasthenic syndrome, emphasizing the central role of choline in human metabolism. [9] Here, we describe a case from families without any relatives, childhood-onset neonatal jaundice, and liver failure caused by homozygous mutations in the *SLC44A1* gene.

2. Case report

A 4-month-old male is admitted to Pediatric Gastroenterology in an external center due to prolonged jaundice and growth retardation in the second month of life. When the patient was four months old, he was referred to our center for further examination and treatment due to the development of liver failure. His jaundice started on the seventh day of life and lasted for ten days but recurred in the second month and continued. He was born to consanguineous parents(second-degree cousin parents) with a birthweight of 3150 g at term. He has no pathological findings detected in the prenatal and natal periods. His parents are alive and well, but his cousin died at age four due to Niemann-Pick disease, and his two cousins have mental retardation; the cause is unknown. On admission to the Pediatric Gastroenterology Department, his weight was 5.5 kg(10th percentile), height 55 cm (10th–25th percentile), and head circumference 36 cm (3rd percentile). On physical examination, the abdomen was distended in icteric appearance; the liver was palpable up to 2 cm below the dentition and slightly stiff; the spleen was palpable 4 cm. The patient had no edema and no signs of encephalopathy. The stool and urine color were normal. His cardiovascular examination showed a rhythmic S1-S2 and 1/6 systolic murmur. The central nervous system examination was normal. His tone was adequate, and tendon reflexes were positive. He was otherwise healthy, had no history of recurrent infections, and had a normal neurodevelopmental stages(grasp reflex was present, he could hold his head up); audiology and ophthalmologic examinations were normal.

When the patient was admitted to our clinic, symptomatic treatment of liver failure was initiated, intravenous fluid replacement containing high dextrose (10 μg/kg/min) with fluid restriction, decontamination treatment (laxative agent lactulose and oral gentamicin), hyperammonemia treatment (sodium benzoate 500 mg/kg/day), coagulopathy treatment (Vitamin K replacement for three day and fresh frozen plasma) and *N*-acetylcysteine (7 mg/kg/h) treatment for hepatocyte damage, were started. The patient's biochemical tests, hemogram, and coagulation tests were taken, and the investigations for the etiology were planned. The patient's PELD score was 45, and the Child-Pugh score was 9 B (Peld score and Child-Pugh score are staging systems used to estimate the severity of liver disease in patients with cirrhosis and correlate with the patient's prognosis. A Peld score of 20 or above and a Child-Pugh score of b-c indicate a poor prognosis). The results of routine laboratory tests are presented in Table 1.

In metabolic tests for the etiology of the patient, no significant elevation was found in tests for galactosemia (galactose-1-phosphate uridyl transferase, galactose-1-phosphate, total galactose, free galactose), succinylacetone was negative (1.97mcgmol/L), biotinidase was within normal limits, organic acid excretion in the urine was normal. Enzyme activities for lysosomal storage diseases were within normal limits. Thyroid function tests for congenital hypothyroidism were within normal limits (TSH 2.76 mU/L and T4 1.42 ng/dL). His ferritin, transferrin saturation, and lipid levels were normal range. In viral serology,

Table 1
Laboratory tests in the patient.

Tests	Results	Normal Range
Aspartate aminotransferase	413 U/L	31 U/L
Alanine aminotransferase	317 U/L	34 U/L
Gamma-glutamyl transferase	65 U/L	38 U/L
Alkaline phosphatase	719 U/L	281 U/L
Total serum protein	6,2 g/dl	6.4–8.3 g/dl
Albumin	4 g/dl	3.5–5.2 g/dl
INR	4.2	
Direct bilurubin	39 mg/dl	0.6 mg/dl
T.bilurubin	45 mg/dl	0.9 mg/dl
White blood cell count	10.1 μL	5.5–15.5/μL
Hemoglobin	9.2 μL	11–14 g/dL
Platelets count	162 μL	150–450/μL
Amnoia	182	120
Lactat	32	20
Glucose	54 mg/dl	60 mg/dl
Ferritin	663	333
Afp	125	≤7

Hepatitis A-B-C IgM negative, EBV VCA IgM negative, and CMV DNA were analyzed from the anti-CMV IgM positive patient. CMV DNA from 49 IU/L was repeated weekly, but there was no increase in the patient's viral load.

The patient's anti-toxoplasma IgG 1/256 positive, IgM negative, IgG avidity index was 57 %, but the mother's pregnancy follow-up was done regularly; TORCH infection was not considered because the patient had no history of congenital toxoplasmoses such as hydrocephalus, chorioretinitis, and other clinical findings associated with other TORCH infections.

Systemic scanning was initiated to detect additional findings in the patient's current condition and perimembranous VSD was detected in his echocardiography. It was interpreted as irregular liver contours and increased echogenicity, splenomegaly, and moderate ascites on abdominal ultrasonography. Abdominal USG was not compatible with biliary atresia(bile ducts are present and normal width, the gallbladder is present, triangular cord sign is negative). Transfontanel USG was normal. Ear, nose, and throat examination was routine; he could pass the hearing test. Eye examination was normal. In the patient who was examined in detail for eye involvement of metabolic diseases, there was no cataract or crystal deposition, and neurodevelopmental tests were normal.

Alagille syndrome, tyrosinemia, mitochondrial hepatocytes, and other metabolic diseases were investigated in the differential diagnosis, but no specific diagnosis was established during that hospitalization. A liver biopsy could not be performed on the patient because of the progressive worsening of the clinical picture and unresolved coagulopathy, which did not respond to fresh frozen plasma and other clotting factors. A whole exome sequence analysis was sent to investigate the patient's genetic diseases. Homozygous c.1632 + 1G > A variant in the *SLC44A1* gene was detected in the patient. Preparation for liver transplantation was planned for the patient, the cadaver was listed, and the donor from a living donor was studied, but a suitable donor could not be found.

However, with these symptomatic and supportive treatments, there was no regression in coagulopathy and cholestasis, the patient with progressive liver failure resulted in ascites and pulmonary hemorrhage due to liver failure and mortality during the 15-day follow-up period. In this period of the patient, the same variant in *SLC 44A1* was studied from the mother and father, detected as heterozygous c.1632 + 1G > A variant in the parents' genetic analysis supports the diagnosis. Fig. 1 shows the case and parent photographs.

3. Discussion

This mutation OMIM # 618868 is inherited as autosomal recessive; neurodegeneration, ataxia in childhood, tremor, dystonia, spasticity,

Fig. 1. Photograph of case and parents.

cerebellar atrophy, and optic atrophy, causing neonatal jaundice, although rare, can cause liver failure in the neonatal period.

The literature detected early developmental delay in 2 of 5 reported individuals. Several individuals presented with transient hepatic abnormalities (neonatal jaundice, elevated transaminases, and episodes with hypoglycemia) To the best of our knowledge, our case is the first case presented with severe liver insufficiency. The first characteristic neurological findings can be detected between the ages of 2–8. Fagerberg et al. reported that patients aged 13 to 22 years had clinical features including severe ataxia, dysarthria, dystonia, tremor, fascial dyskinesia, bilateral optic atrophy, and cognitive decline. (Fagerberg CR et al. [10]). Common cranial MRI findings for affected individuals were bilateral periventricular and cerebellar white matter hyperintensities and cerebellar atrophy. Also, low signal intensity in globus pallidus was detected. (Fagerberg CR et al. [10]).

Our patient's neurological examination was normal, and cranial MRI was normal. This can be explained by his younger age compared to the patients shared in the literature.

The choline transporter-like protein 1 (CTL1) is a highly conserved Na + −independent, intermediate-affinity transporter of various cell types. [3,2]. It is present as a primary 3.5 kb transcript that is broadly expressed in various tissues and regions of the brain. This gene is universally expressed, including the liver [4,6]. CTL1 is considered a universal choline transporter across both the plasma membrane and the mitochondrial membrane.

[11] The CTL1 protein is encoded by the *SLC44A1* gene [2,3,11]. The regulation of *SLC44A1* expression has been reported in various models. Following facial nerve transection, *SLC44A1* transcripts are upregulated, suggesting that the protein may activate choline uptake for membrane synthesis in motor neurons following nerve injury [12] This effect is consistent with the mitochondrial localization of one of the two major choline metabolic pathways in hepatic tissues and corresponds to the oxidation of choline to betaine. Moreover, *SLC44A1* could be involved in the transport of choline both into and out of the mitochondria since a complex series of reactions also contribute to a substantial release of free choline and phosphocholine from mitochondrial phospholipids which likely become available for phospholipid synthesis in the endoplasmic reticulum [11].

SLC44A1 gene defects have a clinically heterogeneous course. Due to the small number of cases, individual clinical features may vary. The existence of cases with reversible hepatic fibrosis in the literature indicates that the liver is one of the main organs involved. Affecting mitochondrial function may explain the heterogeneous presentation. We have shown that biallelic pathogenic variants in the SLC44A1 gene result in childhood-onset liver failure. WES analysis was performed, and no other variant that could explain the clinical picture was detected.

Segregation analysis was performed; it was shown that the parents were carriers. This mutation is thought to explain the clinical picture in the patient.

In conclusion, in patients presenting with neonatal jaundice and coagulopathy, biliary atresia, alagille syndrome, galactosemia, tyrosinemia, and other metabolic and mitochondrial diseases are excluded, choline transport defects should be included in the differential diagnosis.

Informed consent

His parents or legal guardians of patients provided signed informed consent.

Disclosure of Ethical Statements

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Approval of the research protocol

N/A.

Registry and the Registration No. of the study/trial

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Animal studies

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Dogan Barut: Writing – original draft, Resources, Conceptualization. **Emine Burçe Dörtkardeşler:** Investigation, Formal analysis. **Miray Karakoyun:** Writing – review & editing, Data curation, Conceptualization. **Ebru Canda:** Writing – review & editing, Methodology, Investigation. **Huseyin Onay:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Sema Aydogdu:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors have no relevant financial or non-financial interests to disclose.

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Data availability

No data was used for the research described in the article.

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