Coexistence of spinocerebellar ataxia autosomal recessive type 21 and Ehlers-Danlos syndrome spondylodysplastic type 3 in a patient

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List of key features

Liver failure
Hepatosplenomegaly
Joint contractures
Hypotonia
Global developmental delay

Introduction

Pediatric acute liver failure (PALF) is a rare condition that can be fatal if not diagnosed and treated early. Although many infectious, toxic, genetic, and metabolic conditions can lead PALF, the cause can not be found approximately in half of the cases. Elucidating the cause of PALF is important for initiation of appropriate medical treatment and selection of eligible patient for liver transplantation. Here in, we report a patient, admitted to hospital with acute liver failure, dysmorphic features, and neurodevelopmental retardation who subsequently diagnosed with Ehlers-Danlos syndrome spondylodysplastic type 3 (EDSSPD3) and spinocerebellar ataxia autosomal recessive type 21 (SCAR21).

Case

An 8-month-old girl was referred to our hospital with acute fulminant liver failure with a history of fever, vomiting, and altered consciousness for 2 days from another hospital. She was born with a normal spontaneous vaginal delivery after an uneventful pregnancy with a birth weight of 2080 g. She was the first child of first-degree cousin parents. Her medical history revealed hospitalization for bronchiolitis and acute gastroenteritis for several times. At 5 months old age, bone marrow aspiration was performed to elucidate the cause of thrombocytopenia and splenomegaly that revealed a normocellular bone marrow. Flat face, downslanting palpebral fissures, protuberant eyes, small mouth, jaundice, engorged superficial epigastric veins, hepatosplenomegaly, diffuse edema, wrinkled palms, thenar-hypothenar muscle atrophy, finger contractures, extremity contractures, joint laxity, inconsolable crying, hypotonia, delayed motor skills, unusual responds, and exaggerated deep tendon reflexes were noticed in physical examination (Fig. 1). Her blood tests revealed trombocytopenia (85 000/mm^3), hypoglycemia (49 mg/dl), hypoproteinemia-hypoalbuminemia (4.6 and 2.9 g/dl, respectively), increased alanine aminotransferase (270 U/l), aspartate aminotransferase (1080 U/l), alkaline phosphatase (978 U/l), international normalized ratio (INR) (3.7), lactate (25 mmol/l), and total-direct bilirubin

Fig. 1



Face photograph of the patient. Please note the downslanting palpebral fissures, protuberant eyes, and small mouth.

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(12.7 and 7.5 mg/dl, respectively). Gamma-glutamyl transferase (GGT) and creatine kinase levels were normal. Viral hepatitis was excluded with appropriate tests. Bone marrow smear showed nonspecific vacuolated cells, which raised suspicion for Niemann Pick types A, B, C, and Gaucher disease, but they were excluded by genetic studies. Arterial blood gas, blood-urine amino acid levels, urine organic acids, tandem mass spectrophotometry, and very long chain fatty acids were not specific for any metabolic disease. Alpha-1 antitrypsin, ferritin, autoimmune markers, and lipid profile were in normal ranges. Eye examination and echocardiography were also normal. Abdominal ultrasonography revealed splenomegaly. Brain MRI showed prominent cerebral sulcus, slightly enlarged III and lateral ventricles, and prominent white matter T2 intensities in the posterior parts. Also, inferior vermis was mildly hypoplastic, and the cisterna magna was wide. The pediatric end-stage liver disease score was 30 points. She was placed on the cadaveric list because she did not have a living donor. However, the patient, whose acute liver failure improved with supportive treatment including hemodiafiltration and plasmapheresis, was discharged after 25 days of hospitalization.

Genomic DNA was obtained from peripheral blood samples of the patient using standard protocols. Whole exome sequencing was performed on Illumina NextSeq 500 platform in order to elucidate the genetic cause. GnomAD, ExAC, and dbSNP data were used for variant filtering, and CADD, EIGEN, FATHMM-MKL, MutationTaster, dbscSNV, and GERP were used for in-silico pathogenicity prediction. Interpretation of variants was performed in accordance with the 2015 American College of Medical Genetics and Genomics (ACMG) standards and guidelines. A homozygous deletion [NM_001128225.2: c.483_491del; p.(Phe162_Ala164del)] in *SLC39A13* and a homozygous splice-site variant [NM_020680.3: c.1386 + 2T>C] in *SCYL1* were detected. The allele frequency of *SLC39A13* c.483_491del is %0.00000398, and this variant is not reported in the homozygous state in gnomAD (PM2). It is an in-frame variant that causes a change in the protein length and is not in a repeat region (PM4). Additionally, the variant has been previously associated with EDSSPD3 in the literature (PP5) (Giunta *et al.*, 2008). This variant is classified as uncertain significance according to the ACMG criteria. *SCYL1* c.1386 + 2T>C is a null variant affecting the splice-site (PVS1) and is not found in gnomAD (PM2). Based on this evidence, it is classified as likely pathogenic according to the ACMG criteria. Segregation analysis revealed that both parents were carriers of the same two variants. The patient died when she was 3 years old because of cirrhosis complications. Written informed consent was obtained from the patient's parents for publication.

Fig. 2



Skeletal radiographs of the patient show wide and irregular metaphyses of long bones and metacarpals.

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Discussion

SCAR21 is characterized by recurrent liver failure and neurological symptoms. The condition is also known as CALFAN syndrome (low GGT cholestasis, acute liver failure, and neurodegeneration) (Lenz *et al.*, 2018). Schmidt *et al.* (2007) first showed the association of *SCYL1* pathogenic gene variants with spinocerebellar ataxia and motor neuron disease on mice in 2007. *SCYL1* encodes a protein that plays a role in intracellular transport between the Golgi and the endoplasmic reticulum, maintenance of Golgi integrity, and also facilitates the nucleo-cytoplasmic transport of tRNA (Burman *et al.*, 2008; Burman *et al.*, 2010; Chafe and Mangroo, 2010). In 2015, clinical findings of deleterious *SCYL1* variants were first described in three cases from two different families (Schmidt *et al.*, 2015). It was observed that all three patients had recurrent acute liver failure in infancy. These episodes ended in middle childhood and all patients remained with residual hepatic fibrosis and hepatosplenomegaly. All three patients also manifested early motor delay and cerebellar dysfunction in early childhood (Schmidt *et al.*, 2015). Seven patients from five different families were examined in 2018, and it was observed that cholestasis with low GGT, acute liver failure, and neurodegeneration were common features in *SCYL1* variations. In the literature review, it was determined that there were 16 patients reported to date (Schmidt *et al.*, 2015; Lenz *et al.*, 2018; Li *et al.*, 2019; Shohet and Cohen, 2019; Spagnoli *et al.*, 2019; Chavany *et al.*, 2020). The history of recurrent acute liver failure was reported in 15 of 16 patients. Unlike other patients, one patient who had recurrent respiratory problems without known acute fulminant hepatic failure history was reported (Spagnoli *et al.*, 2019). On the other hand, the presence of chronic liver disease was also reported in SCAR21. Hepatic fibrosis may develop after recurrent acute liver failure attacks in infancy, and thus, chronic liver failure and necessity of liver transplantation may occur in patients with SCAR21. The neurological and developmental findings of our patient were compatible with SCAR21 as described in the literature (Schmidt *et al.*, 2015; Lenz *et al.*, 2018; Li *et al.*, 2019; Shohet and Cohen, 2019; Spagnoli *et al.*, 2019; Chavany *et al.*, 2020). She had a delay in developmental milestones in addition to truncal ataxia and tremor in the extremities that became evident after the age of 1 year.

Ehlers-Danlos syndrome spondylodysplastic type 3 (EDSSPD3; MIM 612350) is a rare autosomal recessive disorder caused by deleterious variants in the *SLC39A13* gene (MIM 608735). EDSSPD3 is characterized by joint hypermobility, hyperelasticity of skin with atrophic scars, bluish sclerae, osteopenia, short stature, platyspondyly, widened metaphyses, finger contractures, tapered fingers with wrinkled palms and thenar/hypothenar muscle atrophy (Giunta *et al.*, 2008). The facial dysmorphism is characterized by a flat face, downslanting palpebral fissures, protuberant eyes, and a small mouth (Kumps *et al.*, 2020). Myopia, keratoconus, bifid uvula, delayed tooth eruption, and hypodontia may be accompanying features of the disorder (Kumps *et al.*, 2020). Affected individuals were reported to have increased urinary lysyl pyridinoline/hydroxylysyl pyridinoline ratio of approximately 1, whereas both lysyl hydroxylase and prolyl 4-hydroxylase activities were normal (Giunta *et al.*, 2008). Giunta *et al.* (2008) described six patients of two families with EDSSPD3 carrying a homozygous in-frame deletion in *SLC39A13* [NM_001128225.2: c.483_491del; p.(Phe162_Ala164del)]. We identified the same *SLC39A13* variant in our patient who presented with a phenotype, including facial appearance, growth retardation, hypotonia, limb contractures, joint laxity, and widened metaphyses, consistent with EDSSPD3 (Figs. 1 and 2).

Skeletal abnormalities were reported both in EDSSPD3 and SCAR21. Short stature and other skeletal findings of our patient were compatible with EDSSPD3, which made the assessment of *SCYL1* variation effect on the skeletal system difficult.

Our patient is the first case described with concomitant EDSSPD3 and SCAR21. We also report a novel, pathogenic *SCYL1* variant. SCAR21 syndrome should be considered in the differential diagnosis of acute liver failure, especially in recurrent and chronic liver diseases with normal GGT levels.

Acknowledgements

Informed consent has been obtained from patients that grants permission for the publication of images as part of this work.

Conflicts of interest

There are no conflicts of interest.

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