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Case Report
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A Child with Short-rib Thoracic Dysplasia Type 11 Presenting as Cholestasis: The Utility of Exome Sequencing

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Abstract

Short-rib Thoracic Dysplasia type 11 (SRTD) is a rare autosomal recessive disease characterized by skeletal abnormalities, hepatic, renal, pancreatic, cardiac and retinal involvement. The liver involvement as cholestasis is extremely rare. Here, we report a 4-year-old boy with recurrent cholestasis. A diagnosis of SRTD was made based on WDR34 mutation gene found by Whole-Exome Sequencing (WES). Our case provides a new insight toward considering WES as a first-line methodology for differential diagnoses of any child presenting with recurrent unexplained cholestasis.

Introduction

Short-rib thoracic dysplasia (SRTD) or Jeune syndrome or Asphyxiating Thoracic Dystrophy (ATD) are congenital disorders due to defects in primary cilium function. SRTD is known to be genetically heterogeneous with an autosomal recessive mode of inheritance with mutations identified in 14 genes to date (comprising 398 exons). It was first described by Jeune et al. [1] in 1955 in two siblings with severely narrowed thoracic cavities. SRTD has effects on cardiac, hepatic, pancreatic and renal function. The liver involvement t as cholestasis this syndrome is extremely rare.

The present paper describes a 4-year-old boy who has SRTD and cholestasis. A review of the literature is also provided.

Case Presentation

A 4-year-old boy presented with prolonged jaundice for 12 months. The parents described yellowish discoloration of eyes is intermittent and not associated with itching. There were no relieving or precipitating factors of jaundice. The perinatal history revealed that he had neonatal narrowed small chest required mechanical ventilation for 1 month and discharged on B2 agonist inhalers because of chronic lung disease. No history of fever, skin rash, joint pain, blood transfusion or recent travel. The family revealed no history of liver disease. The patient had normal developmental milestones. His past medical history was otherwise noncontributory. Physical examination revealed yellowish discoloration of eyes but no evidence of growth retardation. He had dysmorphic features; small chin, pointed nose and short arms and legs (Figure 1). Abdominal examination revealed no hepatosplenomegaly or ascites. Other systemic examination was otherwise unremarkable.

The laboratory findings showed in Table 1. Skeletal survey revealed short metacarpal and metatarsal bones (Figure 2 and 3). Abdominal ultrasound showed that the liver is mild coarse echo texture. There was evidence of mild hepatomegaly with fatty changes.

As there was no definitive infectious or metabolic cause of cholestasis, percutaneous liver biopsy was undertaken, which showed mild inflammation (grade 1 to 2) and fibrosis stage (1 to 2) with hepatocyte degeneration. Some of the portal tracts lack bile ductules. No inclusions or parenchymal nodules noted. There was evidence of paucity of bile duct. As the patient had episodic unexplained cholestasis, whole-exome sequencing was performed and showed mutations in the WDR34 gene. Genotype demonstrated short rib Thoracic Dysplasia type 11, therefore the diagnosis of SRTD type 11 was made. Ursodeoxycholic acid was prescribed and there was no progression of hepatic dysfunction during the 12-month follow-up period.

Discussion

SRTD or Jeune syndrome is a rare dystrophy of the skeleton, inherited as an autosomal recessive

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Figure 1: The child has dysmorphic features; small chin, pointed nose and narrow chest.

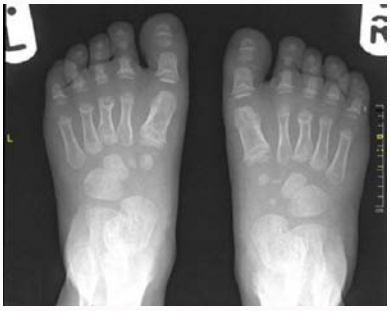

Figure 2: X-rays of the feet's demonstrated a short metacarpals and phalanges of 3rd, 4th and 5th fingers.

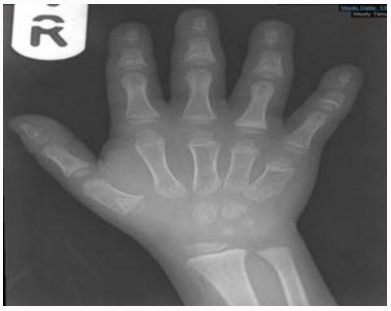

Figure 3: X-ray of the hands demonstrated a short second, third and fourth metatarsal bones.

condition. In spite of Jeune syndrome is non-motile ciliopathy with skeletal and multisystem organ, their clinical manifestations are not limited to musculoskeletal abnormalities. It has effects on cardiac, hepatic, pancreatic and renal function [2]. The etiology of hepatic disease, however, is unclear. Friedman et al. postulated that prolonged neonatal jaundice, polycystic liver disease, bile duct hyperplasia and congenital hepatic cirrhosis may be the cause of hepatic disease in adulthood [3].

In Jeune syndrome, hepatic complications characterized by increases in transaminase levels and hepatomegaly, resulting in portal hypertension [4]. In our patient, there were no clinical and radiological findings of portal hypertension. Pawlowska et al. [5] reported three

Table 1: Laboratory results.

Test	Results	Normal range
Alanine transaminase	79	9 to 2 IU/Liter
Alkaline Phosphatase	460	156 to 369 IU/Liter
Albumin	40	38 to 47 gram/Liter
Aspartate aminotransferase	56	21 to 44 IU/Liter
Gamma glutamyl transpeptidase	103	6 to 16 IU/Liter
Direct bilirubin	3.2	0.80 to 3.40 mmol/Liter
Total bilirubin	4.9	0.8 to 6.8 mmmol/Liter
Total Cholesterol	5.4	2.90 to 5.40 milimole/Liter
White blood cell count	6.4	4.0 to 12.0 × 10^9/Liter
Hemoglobin	12.1	11 to 14.5 gram /DL
Platelet	406	150 to 450 × 10^9/Liter
Blood urea nitrogen	5.3	3.2 to 7.9 milimole /Liter
Prothrombin time	12	11 to 14 seconds
International normalized ratio	1	0.8 to 1.2
Partial thromboplastin time	36	26 to 41 seconds
Hepatitis C Antibody	Nonreactive	-
Anti-Hepatitis B core	Nonreactive	-
Hepatitis B surface Ag	Nonreactive	-
Herpes simplex virus 1/2 IgM	Negative	-
Herpes simplex virus 1/2 Antibody	Negative	-
Cytomegalovirus Polymerase chine reaction	Not Detected	-
Hepatitis C virus(RNA) (Qualitative)	Not Detected	-
Epstein Barr virus PCR	Not Detected	-
Alpha-1-Antitrypsin	1.81	0.88 to 1.74 gram/Liter
Ceruloplasmin level	0.53	0.22 to 0.58 gram/Liter
Vitamin E	6.1	5.0 to 20.0 meligram/Liter
Total 25-OH Vitamin D	55.6	Less than 25 (deficiency) 25 to 49 (suboptimum) 50 to 125 (optimum)
Tandem MS	Unremarkable	
Ammonia	51	10 to 47 micromole/Liter

cases with neonatal cholestasis and concluded that newborns with ATD and cholestasis had very poor prognosis. Labruene et al. [6] reported three children who had clinical and laboratory evidence of liver disease and documented that treatment with ursodeoxycholic acid controlled the progression of hepatic dysfunction. In our patient, there was no progression of hepatic dysfunction during follow-up period.

Jeune syndrome patients typically present with a narrow bell-shaped rib cage, a distended abdomen, and short arms and legs [7]. In our patient, clinical and radiological examination often shows skeletal abnormalities. Jeune syndrome patients can show various kinds of ocular involvement such as retinitis pigmentosa. Thirty percent of Jeune syndrome patients are thought to have renal insufficiency [2]. We did not detect any eye or renal problems in our patient. Anesthesia is very important in this syndrome because those patients need respiratory evaluation, as it can have fatal consequences, especially in younger patients [8]. In our patient, there was no anesthesia complication during liver biopsy.

Whole Exome Sequencing (WES) is sensitive, specific and efficient for discovery in SRTD and can be considered a first-line methodology for mutation identification in affected individuals with recurrent unexplained cholestasis [9]. Exome sequencing identifies DYNC2H1 mutations as a common cause of asphyxiating thoracic dystrophy without major polydactyly, renal or retinal involvement.

To the best of our knowledge and PubMed review, our report is the first case of such a hepatic association of SRTD with no gastrointestinal, renal, pancreatic, cardiac or retinal involvement.

Conclusion

SRTD or Jeune syndrome is a rare dystrophy of the skeleton, inherited as an autosomal recessive condition. WES is sensitive, specific and efficient for discovery in SRTD and can be considered a first-line methodology for mutation identification in affected individuals with recurrent unexplained cholestasis.

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