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CASE REPORT

Pulmonary Manifestations in a Patient with Transaldolase Deficiency

Nada Jassim • Mohammed AlGhaihab • Suhail Al Saleh • Majid Alfadhel • Mirjam M.C. Wamelink • Wafaa Eyaid

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Abstract Transaldolase deficiency is a newly recognized metabolic disorder. It is an autosomal recessive genetic disease (OMIM #606003). The effects of the defect in the TALDO gene are pleiotropic with a clinical presentation of growth retardation, dysmorphic features, cutis laxa, congenital heart disease, hepatosplenomegaly, pancytopenia, and bleeding tendencies. This is the first report of a child who was diagnosed at birth with transaldolase deficiency who subsequently developed hepatopulmonary syndrome.

Abbreviations

ASD II	Atrial septal defect secundum
AVM	Arteriovenous malformation
CEE	Contrast-enhanced echocardiography
CT	Computed tomography
HPS	Hepatopulmonary syndrome
99mTc-MAA scan	99Technetium macroaggregated albumin perfusion lung scanning
PDA	Patent ductus arteriosus
PPP	Pentose phosphate pathway
RR	Respiratory rate
SaO_2	Oxygen saturation
TALDO	Transaldolase
US	Ultrasonography
VSD	Ventricular septal defect

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N. Jassim · M. AlGhaihab · S. Al Saleh · M. Alfadhel · W. Eyaid (✉)
Department of Pediatrics MC 1510, King Abdulaziz Medical City, King Fahad National Guard Hospital, P.O Box 22490, Riyadh 11426, Saudi Arabia
e-mail: eyaidw@ngha.med.sa

M. AlGhaihab · S. Al Saleh · M. Alfadhel · W. Eyaid
King Saud Bin Abdulaziz University for Health and Science, Riyadh, Saudi Arabia

M.M.C. Wamelink
Department of Clinical Chemistry, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands

Introduction

The pentose phosphate pathway (PPP) is an important metabolic pathway in which glucose-6-phosphate (G6P) is converted into ribose-5-phosphate (R5P) through a series of reactions. Some of the reactions are reversible, while others are irreversible. The irreversible part of the pathway is rate-limited by the activity of G6P dehydrogenase (G6PD), whereas the reversible component is rate-limited by the activity of transaldolase (TALDO). The PPP serves a crucial role in cellular proliferation and growth by producing R5P, which is required for the synthesis of DNA and RNA. In addition, the PPP is an important source of NADPH (Perl et al. 2011).

Two little-known disorders of PPP are deficiencies in R5P isomerase and transaldolase, both of which affect the reversible, non-oxidative branch of the pathway. R5P deficiency is an exceedingly rare disease that has only been described once: The primary phenotype was leukoencephalopathy (Valayannopoulos et al. 2006). On the other hand, several patients have been reported with transaldolase deficiency since it was first described. In these patients, while liver involvement is prominent, the phenotype appears to be more pleiotropic (refer to Table 1; Eyaid et al. 2013).

Here, we report on an infant with the transaldolase (TALDO) deficiency. The infant developed respiratory

symptoms in early infancy and was later diagnosed with hepatopulmonary syndrome (HPS). To our knowledge, this is the first such case to be reported in the literature.

Case Report

A 17-month-old boy, the fifth child born to consanguineous parents, was diagnosed with transaldolase deficiency. Two siblings were similarly affected. The diagnosis was established by autozygome analysis and biochemical evaluations of urinary sugars and polyols (Family II, Patient 3) (Eyaid et al. 2013).

The child was born at 36 weeks gestation via spontaneous natural delivery. His Apgar scores at 1 and 5 min were 7 and 8, respectively. His growth parameters were within the normal ranges. He was observed to have a heart murmur and dysmorphic features, including triangular progeroid face, low set ears, short philtrum, and wrinkled skin, as well as hepatosplenomegaly. Therefore, additional evaluations were performed. These tests included echocardiography, which showed closed patent ductus arteriosus (PDA) and atrial septal defect secundum (ASD II) with small ventricular septal defects (VSDs). An ophthalmology evaluation and abdominal and head ultrasonography (US) were all normal. He experienced one incident of decreased hemoglobin and platelets that required transfusion. Other investigations, including the liver profile, were unremarkable. He was discharged at the age of 14 days.

At the age of 3 months, he presented to the emergency department with a 1-week history of fever and cough. At presentation, he was in moderate respiratory distress and was tachypneic (RR of 50/min) and had subcostal retractions. A chest examination revealed bilateral wheezes and crackles. The oxygen saturation (SaO_2) was 84 % in room air, and he thus required supplemental oxygen of 1 L/min via a nasal cannula. He was diagnosed with bronchiolitis with negative virology. He responded slowly to the supportive management, including oxygen, fluids, and inhaled bronchodilator therapy, and was hospitalized for 40 days on the basis that his hypoxia required supplemental oxygen. After release, he continued to have frequent admissions related to respiratory symptoms and bronchospasms, some of which occurred in the pediatric intensive care unit. However, no intubations were required. He has demonstrated occasional decreases in his hemoglobin to 90 g/L. These values normalize after transfusion.

At 12 months of age, a more intensive workup was performed for the prolonged hypoxia and difficulties in weaning off oxygen (0.5 L/min). Immunodeficiency and cystic fibrosis were ruled out. An upper gastrointestinal study and modified barium swallow were performed to rule out aspiration syndrome and gastroesophageal reflux. The results of these tests were unremarkable. A computed tomography (CT) of the chest showed bilateral diffuse ground-glass lung changes with atelectasis/consolidation in the right upper and lower and left lower lobes. The patient improved, was gradually weaned from oxygen, and was discharged to his home on room air. He was readmitted at 17 months of age in respiratory distress and was reassessed on the basis of an inability to wean him off the oxygen. He presented with pectus chest deformity, digital clubbing, and tachypnea, but with clear good bilateral breathing sounds. His SaO_2 was 66 % on room air, and he was therefore placed on 2 L/min of O_2. The arterial blood gas evaluation while on room air showed a pH of 7.365, PCO2t of 39.00 mmHg, PO2t of 36.1 mmHg, cHCO3- of 21.8 mmol, and base excess ecf of −3.6 mmol. The arterial-alveolar gradient (A-a gradient) was 65, where values greater than 15 suggest the presence of a shunt. A 99Technetium macroaggregated albumin perfusion lung scanning (99mTc-MAA scan) study was performed and revealed activity within the brain and the abdomen, suggesting that systemic shunting accounted for 36 % (this parameter is normally less than 5 %). Therefore, contrast-enhanced echocardiography (CEE, bubble echo) was performed. This test showed evidence of delayed positive bubbles, indicating intrapulmonary shunting. A series of repeated liver US examinations revealed a new finding of liver cirrhosis, which was confirmed by liver biopsy. The overall conclusion was a diagnosis of hepatopulmonary syndrome.

Discussion

Transaldolase (TALDO; EC2.2.1.2) deficiency (OMIM 606003) is a recently described inborn error of the pentose phosphate pathway (PPP). The reported systemic manifestations include dysmorphic features, developmental delay, congenital heart disease, hepatosplenomegaly, hepatic fibrosis, excessive bleeding, thrombocytopenia, hemolytic anemia, and renal complications (Wamelink et al. 2008; Tylki-Szymanska et al. 2009; Balasubramaniam et al. 2011). To our knowledge, no pulmonary effects associated with TALDO deficiency have previously been reported.

In this report, we describe a child with TALDO deficiency who had recurrent respiratory symptoms in the form of bronchospasm that required frequent hospitalization since infancy. We believe these symptoms are related to the primary genetic disease.

The patient started to develop signs and symptoms of respiratory distress, possibly secondary to systemic manifestations of the transaldolase deficiency, early in life. Alternatively, these symptoms may be secondary to reflux or aspiration. The subsequent progression of symptoms and hypoxemia was considered to be associated with the

development of HPS because his clinical picture and investigations failed to meet other differential diagnoses. He had one liver US study performed at the time of birth as part of routine investigation because he appeared dysmorphic. The results of this scan were normal. A second US was performed at the age of 17 months. This US showed liver cirrhosis, which was confirmed by a US-guided liver biopsy. A review of the literature indicates that HPS can occur without liver cirrhosis, as in case of non-cirrhotic portal hypertension, and when associated with HPS, the cirrhosis may be unrelated to the severity of liver dysfunction.

The results of the bubble echo analysis were positive for the left side of the heart within the 3–4 beats during which the root of pulmonary veins were visualized in the absence of any heart defect. This result supports the possibility of intrapulmonary shunting. This result was also supported by positive 99Technetium macroaggregated albumin perfusion lung scanning.

Hepatopulmonary syndrome was first described in 1884 by Fluckiger, who noted a relationship between the liver and the lung (Kennedy and Knudson 1977). In 1997, Kennedy and Knudson described "hepatopulmonary syndrome" (Yap et al. 1999). This syndrome is defined by a classical triad of chronic liver disease or portal hypertension, hypoxemia, and intrapulmonary shunting. It is a rare complication of chronic liver disease in children (Noli et al. 2008). The prevalence of HPS in adults with cirrhosis is reported to range from 4 % to 29 % (Gupta et al. 2001; Schenk et al. 2002; Noli et al. 2008). This syndrome has been measured in children with cirrhosis or severe portal hypertension, and the prevalence in this group is similar to that in adults (Barbe et al. 1995; Sasaki et al. 2000). The diagnosis of HPS in a child with liver disease is established by the demonstration of hypoxemia or an elevated alveolar-arterial oxygen gradient on arterial blood gas analysis and the presence of intrapulmonary shunting using contrast-enhanced echocardiography (CEE) or a 99mTcMAA perfusion scan (Krowka et al. 1990, 2000).

Hepatopulmonary syndrome is considered to be one of the cardiopulmonary complications of acute or chronic liver disease. It is most frequently associated with portal hypertension (with or without cirrhosis). However, severe hepatic dysfunction is not required for a diagnosis of HPS (Abrams et al. 1995).

One unanswered question is what triggered this child to develop HPS while his elder siblings did not, despite evidence that their livers were also cirrhotic. These observations suggest that the cause of the HPS is independent of the patient's liver condition, i.e., that both conditions are secondary to the primary genetic defect in the transaldolase enzyme as described above.

Currently, the only effective treatment for HPS is liver transplantation. This option was not pursued in our patient due to the lack of outcome data in patients with transaldolase deficiency.

Conclusion

Pulmonary involvement can be a consequence of transaldolase deficiency. Our patient had recurrent reactive airway disease and was confirmed to have hepatopulmonary syndrome. After excluding common causes, we propose that the recurrent attacks of cough, difficulty of breathing, and bronchospasm are pulmonary manifestations of the disease. We recommend that patients with transaldolase deficiency, who present with recurrent respiratory distress, be further investigated for possible development of HPS.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Contributions

Nada Jassim and Wafaa Eyaid: manuscript writing

Suhail Al Saleh, Majid Alfadhel, Mirjam M.C. Wamelink, and Mohammed AlGhaihab: interpretation of results and reviewing the paper

Take-Home Message

Patients diagnosed with transaldolase deficiency need to have regular follow-up evaluations of their hepatic and pulmonary function and should have early intervention to avoid adverse sequelae associated with this condition.

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