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Case Report

Hepatopulmonary Syndrome in a Child with Trans Aldolase Deficiency: A Case Report

Gawahir Mukhtar[1]*, Khalid Al-mobaireek[2], Safa Eltahir[1], Mohammed Alzaid[1] and Wadha Alotaibi[1]

[1]Section of Pulmonary Medicine, Department of Pediatrics, King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia

[2]Section of Pulmonary Medicine, Department of Pediatrics, King Khalid University Hospital, Riyadh, Saudi Arabia

***Corresponding Author:** Gawahir Mukhtar, Pediatric Pulmonary unit, Department of Pediatrics, King Fahad. Medical City, Riyadh, Kingdom of Saudi Arabia.

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Abstract

Background: Transaldolase deficiency is a recently described inborn error of pentose phosphate pathway (PPP). This disorder is inherited as autosomal recessive, Patients may present in the neonatal or antenatal period with hydrops fetalis, hepatosplenomegaly, hepatic dysfunction, thrombocytopenia, anemia, and renal and cardiac abnormalities. Patients has characteristic dysmorphic features including triangular-shaped face, low-set ears, wide mouth, and thin lips. The most prominent features were skin abnormalities (wrinkle skin/cutis laxa). Hepatopulmonary syndrome (HPS) is considered to be one of the cardiopulmonary complications of liver disease, and it associated with portal hypertension. However, severe hepatic dysfunction is not required for a diagnosis of HPS. The triad of HPS includes liver disease or portal hypertension, hypoxemia, and intrapulmonary shunting.

Case Presentation: We report 9-year-old girl, from Saudi Arabia was diagnosed with transaldolase deficiency based on gene test at age of 2 years, who developed respiratory distress and hypoxia in early infancy and was later diagnosed with hepatopulmonary syndrome (HPS) after history of recurrent respiratory distress and respiratory failure that required high frequency mechanical ventilation. Patient currently on home oxygen 3L/min via face mask for the hypoxia, and supportive management for the chronic liver disease and anemia, plus multidisciplinary follow up care. No plan for liver transplantation as the data regarding the outcome in such cases are not available. To our knowledge this will be the second case of transaldolase deficiency and hepatopulmonary syndrome to be reported.

Conclusion: Hepatopulmonary syndrome should be considered as a cause of respiratory symptoms and hypoxia in patient with transaldolase deficiency and need to rule out other possible causes. At present, there is no treatment for the condition. Some patients with transaldolase deficiency might benefit from liver transplantation, however no available data for patients with hepatopulmonary syndrome.

Keywords: *Hepatopulmonary Syndrome; Transaldolase; Case Report; Saudi Arabia*

Introduction

Transaldolase deficiency TALDO deficiency is a rare an inborn error of the pentose phosphate pathway (PPP) 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) [1]. This disorder is inherited as autosomal recessive, Patients may

present in the neonatal or antenatal period with hydrops fetalis, hepatosplenomegaly, hepatic dysfunction, thrombocytopenia, anemia, and renal and cardiac abnormalities. The severity of presentation can vary from hydrops fetalis to slowly progressive liver cirrhosis. Patients has characteristic dysmorphic features including triangular-shaped face, low-set ears, wide mouth, and thin lips. The most prominent features were skin abnormalities (wrinkle skin/cutis laxa). The cardiac abnormalities include congenital heart defects, such as ventricular septal defect (VSD) and/or atrium septal defect (ASD), bicuspid aortic valve, aortic coarctation, and dextrocardia [2]. Hepatopulmonary syndrome (HPS) is considered to be one of the cardiopulmonary complications of liver disease, and it associated with portal hypertension (with or without cirrhosis). However, severe hepatic dysfunction is not required for a diagnosis of HPS. The triad of HPS includes liver disease or portal hypertension, hypoxemia, and intrapulmonary shunting [8].

Case Report

9-year-old girl was diagnosed with transaldolase deficiency based on gene test at age of 2 years (homozygous mutation in the TALDO1 gene (602063) on chromosome 11p15). She was outcome of uneventful pregnancy, full term and normal vaginal delivery. She was admitted to NICU for 18 days for work up because of dysmorphic features (including triangular progeroid face, low set ears, short philtrum, and wrinkled skin, as well as telangiectasia all over her face and chest. She was found to have CHD (ASD and mild tricuspid regurgitation) and hepatosplenomegaly. At age of 1 year, she developed epistaxis and petechial rash all over back and lower limb, so admitted to hospital and found to have pancytopenia, hepatosplenomegaly and liver derangement. Her initial CBC showed thrombocytopenia with platelet ranging from 50-80 with severe anemia. She had prolonged PT and APTT. Corrected mixing study consistent with factor deficiency. Factor analysis was consistent with chronic liver disease. Factor V111 was normal. Almost all other factors including factor V, factor V11 and fibrinogen were normal. Bone marrow aspiration and biopsy were done to rule out bone marrow failure and they showed cellularity of 70% and active trilineage with hematopoiesis. No evidence of any abnormality. Flow cytometry and Cytogenetic studies were performed in the bone marrow. The flow cytometry showed no immune phenotypic evidence of clonal abnormality. Cytogenetic panel to rule out any leukemia were all negative. The bone marrow chromosomal analysis revealed 46XX, which is normal female karyotype. There were no other abnormalities. Patient was admitted frequently due to jaundice and coagulopathy with history of recurrent respiratory distress and thrombocytopenia and was labeled as chronic liver disease. Gene study for Shwachman diamond syndrome was negative. Serology tests for hepatitis and metabolic tests were all normal. Ultrasound echogenic showed echogenic liver. Liver function test showed high liver enzymes. At age of 2 years she became oxygen dependent after history of recurrent respiratory distress and respiratory failure that required high frequency mechanical ventilation. She also experienced an incident of decreased hemoglobin and platelets that required transfusion. More intensive workup was performed for the prolonged hypoxia and difficulties in weaning off oxygen (2 L/min). Cystic fibrosis and immunodeficiency were ruled out. An upper gastrointestinal study and modified barium swallow were performed to rule out aspiration syndrome and gastroesophageal reflux. The results were normal studies. Putting in mind the diagnosis of hepatopulmonary syndrome, a computed tomography angiography (CTA) of the chest were requested by pulmonology team and it showed evidence of dilated sub pleural pulmonary vessels with features of chronic cirrhotic hepatic changes, bilateral diffuse ground-glass lung changes with atelectasis in the right upper and lower and left lower lobes. In further assessment, a 99Technetium macroaggregated albumin perfusion lung scanning (99mTc-MAA scan) study was revealed accumulation of the tracer in the liver, kidneys and both lungs. The activity within the lung and the abdomen, suggesting that systemic shunting accounted for 43% (this parameter is normally less than 5%). A series of repeated liver US examinations revealed developing of liver cirrhosis, which was confirmed by liver biopsy. The result of whole exome sequences came confirming the diagnosis of transaldolase deficiency.

Cardiac assessment and echocardiogram showed ASD 11, mild tricuspid and mitral valves regurgitation. The plan was to do bubble echo which will show evidence of delayed positive bubbles, indicating intrapulmonary shunting. However, the cardiology team post ponded the test because the patient was clinically unstable and it was invasive procedure.

The blood gas evaluation in room air showed a pH of 7.372, PCO_2t of 23.8 mmHg, PO_2t of 63.7 mmHg, cHCO_3^- of 16.7 mmol, and base excess ecf of -11.4 mmol. The arterial-alveolar gradient (A-a gradient) was 56.28 mmHg, and the estimated normal gradient for her age is 6 mmHg, where values greater than 15 mmHg suggest the presence of a shunt.

Patient currently on oxygen 3 L/min via face mask for the hypoxia, supportive management for the chronic liver disease and anemia inform of ursodeoxycholic acid, vitamin K, ADEK and iron. She has multidisciplinary follow up including pulmonology, gastroenterology and hematology. No plan for liver transplantation as the data regarding the outcome in such cases are not available.

Discussion

Transaldolase (TALDO) is one of the key enzymes in the pentose phosphate pathway (PPP), deficiency lead to an inborn error of PPP. The disorder is caused by mutations in the TALDO gene, first described in 2001 [2] presenting primarily with liver disease and variable clinical course. Patients show common symptoms like hydrops fetalis, dysmorphic features, liver dysfunction (cirrhosis), hemolytic anemia with renal involvement, and heart problems. The severity of presentation can vary from hydrops fetalis to slowly progressive liver cirrhosis. Any patient presenting with hepatosplenomegaly, liver dysfunction (cholestasis, elevated transaminases, coagulopathy), anemia, and/or thrombocytopenia and dysmorphic features associated with skin abnormalities (cutis laxa/wrinkled skin) should be investigated for TALDO-D. The biochemical profile indicates an elevated level of polyols (erythritol, arabitol, ribitol, sedoheptitol, and perseitol) and C7 sugars (sedoheptulose, mannoheptulose, and sedoheptulose-7P) in urine and/or plasma, although in older patients, erythritol or arabitol can be within normal range [2]. Genetic analysis of the TALDO1 gene can confirm this diagnosis and can be of value for prenatal diagnoses and counseling of families. Prenatal diagnosis can be done by measuring polyols and C7 sugars in amniotic fluid [3].

Eyaid., *et al*. (2013) reported the largest case series on Transaldolase Deficiency, consisting of 12 patients from six Saudi families. All patients had cardiac defects, dysmorphic facial features, cutis laxa, hepatosplenomegaly, thrombocytopenia, and anemia. The dysmorphic facial features included a triangular face, low-set ears, prominent philtrum, infraorbital creases, wide mouths, and thin lips. Transaldolase Deficiency was thus diagnosed in all the patients. Molecular analysis confirmed a homozygous mutation in the TALDO1 gene in all the affected patients [4].

Hepatopulmonary syndrome (HPS) was first described in 1884 by Fluckiger, who noted a relationship between the liver and the lung [5]. Kennedy and Knudson described hepatopulmonary syndrome in 1997 [6].

Jassim., *et al*. (2014) reported the first case of transaldolase with hepatopulmonary syndrome in a child who was diagnosed at birth with transaldolase deficiency who subsequently developed hepatopulmonary syndrome [1]. This syndrome is a rare complication of liver disease acute or chronic in children, and it includes the triad of liver disease or portal hypertension, hypoxemia, and intrapulmonary shunting [7]. The diagnosis of HPS in a patient with liver disease is established by detection of hypoxemia or an elevated alveolar-arterial oxygen gradient on arterial blood gas analysis and the presence of intrapulmonary shunting which can be demonstrated by contrast-enhanced echocardiography (CEE) or a 99mTcMAA perfusion scan [8].

In this report, we describe a child with TALDO deficiency who had recurrent respiratory symptoms in the form of respiratory distress and hypoxia that required frequent hospitalization and mechanical ventilation since infancy. We believe these symptoms are related to the diagnosis of hepatopulmonary syndrome because her clinical picture and investigations failed to meet other differential diagnoses. Her a computed tomography angiography (CTA) of the chest showed evidence of dilated sub pleural pulmonary vessels with features of chronic cirrhotic hepatic changes. In further assessment, a 99Technetium macroaggregated albumin perfusion scanning (99mTc-MAA scan) study was revealed activity within the brain and the abdomen, suggesting the present of systemic shunting. The arterial-alveolar gradient (A-a gradient) was greater than 15 mmHg which also suggest the presence of a shunt [7]. Unfortunately contrast-enhanced echocardiography

(CEE, bubble echo) was not done as patient was not clinically stable for the procedure. Patient currently taking supportive treatments for the chronic liver disease and anemia, and oxygen therapy for the hypoxia. Liver transplantation is not option for this child as there is no available data regarding the outcome in patients with same problem.

Conclusion

Hepatopulmonary syndrome should be considered as a cause of respiratory symptoms and hypoxia in patient with transaldolase deficiency and need to rule out other possible causes. Multidisciplinary care with input from a pulmonology, gastroenterology, cardiology and hematology is crucial to the successful management of these patients, all working together with the child and the family to optimize care and quality of life. At present, there is no treatment for the condition. Some patients with transaldolase deficiency might benefit from liver transplantation, however no available data for patients with hepatopulmonary syndrome.

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