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Two Cases of Pulmonary Hypertension Associated with Type III Glycogen Storage Disease

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Abstract Glycogen storage diseases (GSDs) comprise a large, heterogeneous group of disorders characterized by abnormal glycogen deposition. Multiple cases in the literature have demonstrated an association between GSD type I and pulmonary arterial hypertension (PAH). We now also report on two patients with GSD type III and PAH, a novel association. The first patient was a 16-year-old girl of Nicaraguan descent with a history of hepatomegaly and growth retardation. Molecular testing identified a homozygous 17delAG mutation in *AGL* consistent with GSD type IIIb. At the age of 16, she was found to have PAH and was started on medical therapy. Two years later, she developed acute chest pain and died shortly thereafter. The second patient is a 13-year-old girl of Colombian descent homozygous for the c.3911dupA mutation consistent with GSD IIIa. An echocardiogram at age 2 showed left ventricular hypertrophy, which resolved following the institution of a high protein, moderate carbohydrate diet during the day and continuous gastric-tube feeding overnight. At the age of 12, she was found to have pulmonary hypertension. She was started on sildenafil, and her clinical status has shown marked improvement including normalization of her elevated transaminases. PAH may be a rare association in patients with GSD IIIa and IIIb and should be evaluated with screening echocardiograms for cardiac hypertrophy or if they present with symptoms of right-sided heart failure such as shortness of breath, chest pain, cyanosis, fatigue, dizziness, syncope, or edema. Early diagnosis of PAH is important as increasingly effective treatments are now available.

Keywords Amylo-1,6-glucosidase · Genetic · Hepatomegaly · Metabolic

Abbreviations

AGL	Amylo-1,6-glucosidase
GSD	Glycogen storage disease
PAH	Pulmonary arterial hypertension
VSD	Ventricular septal defect

Introduction

Glycogen storage diseases (GSDs) comprise a large, heterogeneous group of disorders characterized by abnormal glycogen deposition. GSD type III (OMIM 232400), characterized by deficiency of glycogen debrancher enzyme or amylo-1,6-glucosidase (AGL; EC 3.2.1.33), is further subdivided into groups including IIIa with hepatic and muscle involvement and IIIb an isolated hepatic form (Shin 2006).

Pulmonary arterial hypertension (PAH) is a rare disorder, with an estimated incidence of two to three per million per year (Gaine and Rubin 1998; Humbert et al. 2006), characterized by sustained increase in mean pulmonary artery pressure (above 25 mmHg at rest), a normal pulmonary capillary wedge pressure, and increased pulmonary vascular resistance. Before the advent of modern therapies, life expectancy for adults with idiopathic PAH was less than 3 years from diagnosis and less than 10 months for children (D'Alonzo et al. 1991). PAH may be heritable (HPAH), idiopathic (IPAH), associated with either drug or toxin exposures (fenfluramine derivatives) or other medical conditions including connective tissue diseases, HIV infection, congenital heart disease, sickle cell disease, and portal hypertension.

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Multiple cases have been described in the literature that demonstrate an association between GSD type I and severe pulmonary hypertension (Humbert et al. 2002b). To date, there have been no reported cases of GSD type III with PAH, although GSD III shares many clinical features with GSD I.

We present two patients, one with GSD IIIa and the other with GSD IIIb, and pulmonary hypertension.

Case Reports

The first patient was a 16-year-old girl of Nicaraguan descent who first presented to our pulmonary hypertension center with a 2-year history of progressive dyspnea on exertion with occasional cyanosis. At 8 months of age, she was noted to have hepatomegaly, but a liver biopsy performed at that time was reportedly normal. From the age of 11 months, there was evidence of growth retardation with both height and weight below the third percentile, but no further evaluation was undertaken.

On presentation at 16 years, a 2D echocardiogram was performed which demonstrated a dilated right ventricle with moderate right ventricular hypertrophy and slightly reduced right ventricular function. Her estimated right ventricular systolic pressure was 78 mmHg. The pulmonary regurgitation gradient was 36 mmHg. There was posterior bowing of the interatrial and interventricular septum consistent with at least systemic pulmonary arterial pressure. There was right to left shunting through a small interatrial communication.

Cardiac catheterization was performed and demonstrated elevated mean pulmonary artery pressure (mean of 44 mmHg) with a normal mean pulmonary capillary wedge pressure (Table 1). Her cardiac index was low with extremely elevated pulmonary vascular resistance index at 24 u*m^2. There was no significant acute response to the administration of 100% oxygen via face mask, inhaled nitric oxide at 80 ppm, or intravenous epoprostenol at a maximum dose of 10 ng/kg/min. She was evaluated for causes of PAH and initially had elevated TSH and T4 that normalized on several serial repeat measurements.

Table 1 Cardiac catheterization data from patients 1 and 2 with normal reference values show elevated mean pulmonary artery pressure, normal mean capillary wedge pressure, and increased pulmonary vascular resistance consistent with the diagnosis of pulmonary hypertension in both patients. All data represent initial testing done on room air

	Patient 1	Patient 2	Normal values
Systemic blood pressure (mmHg)	110/68	83/50	109–114/64–68
Mean right atrial pressure (mmHg)	14	8	2–6
Pulmonary artery pressure (mmHg)	88/22	69/37	15–25/8–12
Mean pulmonary artery pressure (mmHg)	44	51	<20
Mean capillary wedge pressure (mmHg)	6	14	<15
Cardiac index (L/min/m^2)	1.6	2.9	3–5
Pulmonary vascular resistance index (u*m^2)	24	9	3

Liver biopsy was repeated at the age of 16 when she presented with pulmonary hypertension and marked hepatomegaly, which appeared out of proportion to her pulmonary hypertension. Liver biopsy showed marked glycogen storage affecting the hepatocytes with perisinusoidal and portal fibrosis and developing nodularity consistent with GSD. Further analysis of the liver showed elevated glycogen content with short outer branches and absence of debrancher activity consistent with type III GSD. Molecular testing showed that she had a homozygous 17delAG mutation in *AGL* consistent with GSD type IIIb. She was treated with albuterol, digoxin, furosemide, spironolactone, and continuous intravenous epoprostenol with some stabilization in her clinical symptoms.

At the age of 18, she presented to our emergency department with acute chest pain. She was tachycardic (heart rate 164 bpm) and tachypneic (respiratory rate 40 breaths/min), with a systemic arterial oxygen saturation level of 80%. One month before this presentation, her thyroid function tests were markedly abnormal with positive antithyroid peroxidase antibodies. Subsequent radioactive iodine scanning confirmed the diagnosis of Graves' disease. She was treated with propylthiouracil. She was admitted to the pediatric intensive care unit where she was found to be severely hypoglycemic with a glucose level of 6 mg/dL (normal 50–110 mg/dL) and to be hyperkalemic (8.6 mM/L; normal 3.6–5 mM/L). She was stabilized and put on BiPAP of 10/5 with inhaled nitric oxide at 20 ppm. Less than 10 h later, she complained of severe chest pain and became asystolic. Despite resuscitation attempts, she died.

The second patient is a 13-year-old girl of Colombian descent who was first noted to have poor weight gain and a large abdomen as an infant. A liver biopsy was performed at 14 months, which demonstrated glycogen accumulation, and she was diagnosed with GSD type III. Genetic testing of the *AGL* gene showed that she is homozygous for the c.3911dupA mutation consistent with GSD IIIa. An echocardiogram at age 2 showed left ventricular dilation (left ventricular end-diastolic dimension 3.28 cm, $z = 2.90$) with some hypertrophy in the presence of a large subaortic ventricular septal defect (VSD) with a large systemic to pulmonary shunt. She underwent repair of the VSD at 2 years of age, with a small residual restrictive VSD. Cardiac biopsy performed at the time of VSD repair showed subendocardial vacuolization of myocytes due to abnormal cytoplasmic glycogen deposits. Following the institution of therapy consisting of a high protein, moderate carbohydrate diet during the day, and continuous gastric-tube feeding overnight

(Slonim et al. 1982), the cardiac hypertrophy resolved and her clinical status progressively improved. Continuous normoglycemia was maintained and normal developmental milestones were achieved, with normal height, weight, and pubertal development. At the age of 12, she complained of shortness of breath and had an echocardiogram demonstrating tricuspid regurgitation jet. She then underwent cardiac catheterization and was found to have pulmonary hypertension. Resting pulmonary artery pressure was more than two-thirds of the systemic arterial pressure with an elevated mean right atrial pressure. Mean pulmonary capillary wedge pressure was normal. There was a mild response to the administration of 100% oxygen with the pulmonary artery pressure decreasing by 10 mmHg. In addition, when nitric oxide was administered at 80 ppm, her mean pulmonary arterial pressure fell from 52 to 35 mmHg. At rest, her pulmonary vascular resistance index was high at 9 u*m^2 which decreased to 5 u*m^2 with acute vasodilator testing. Superior vena cava saturation was 83% with no step up to the pulmonary artery which was 75%, with a Qp:Qs of 1.6 indicating no significant left to right shunt through the small residual VSD. Therefore, her pulmonary hypertension could not be attributed to the residual VSD. She was started on sildenafil 20 mg p.o. three times daily for PAH, and her clinical status has shown marked improvement. In addition, she had a history of elevated transaminase levels in the range of AST 1,042 U/L and ALT 813 U/L (normal 12–38, and 7–41 U/L, respectively) with no other evidence of synthetic liver dysfunction. Following treatment with sildenafil, the transaminase levels decreased to 149 U/L (AST) and 147 U/L (ALT) within 3 months and have normalized, 37 U/L (AST) and 34 U/L (ALT), after 3 years of sildenafil therapy. Interestingly, there was no overt clinical evidence of right heart failure or right ventricular systolic dysfunction by noninvasive testing before medical treatment with sildenafil to explain the decline in transaminases following treatment.

Discussion

While GSD type I has been repeatedly associated with pulmonary hypertension, there are no reports in the literature of PAH associated with type III GSD. The underlying connection between PAH in GSD I and GSD III remains to be elucidated and should be independently confirmed. The fact that we observed PAH with both GSD type IIIa and IIIb suggests that cardiac involvement is not required for PAH since cardiomyopathy may occur in type IIIa, but is not observed in type IIIb GSD.

In one study, patients with type Ia GSD were found to have elevated serotonin levels as did individuals with PAH when compared to age-matched controls (Humbert et al. 2002a). Moreover, one individual with both type Ia GSD and PAH had dramatically elevated plasma serotonin concentrations. Since not all patients with GSD I or GSD III go on to develop PAH, there must be additional factors required.

We hypothesize that there could be a diffusible substance produced by or not cleared by the diseased liver that causes pulmonary vasoconstriction. This is one mechanism hypothesized in cases of portopulmonary hypertension in which portosystemic collaterals allow humoral substances, normally metabolized by the liver, access to the pulmonary circulation (Panos and Baker 1996). Alternatively, there could be an intrinsic problem in the underlying pulmonary vasculature due to glycogen accumulation. As in portopulmonary hypertension, lung pathology from patients with type I GSD seems to consistently demonstrate pathological changes that are indistinguishable from those seen in classic idiopathic PAH (Humbert et al. 2002b; Pizzo 1980).

In conclusion, while PAH may be a rare association, the diagnosis should be considered in patients with GSD III if they present with cardiorespiratory symptoms such as shortness of breath, chest pain, cyanosis, fatigue, dizziness, syncope, or edema. Moreover, cardiac involvement in GSD is well established, and screening echocardiograms are recommended to examine at wall thickness, ventricular mass, in addition to systolic and diastolic function in GSD III patients (Kishnani et al. 2010). At the time of screening echocardiogram, we suggest examination for signs of elevated pulmonary arterial pressure such as right atrial or right ventricular enlargement, systolic flattening or posterior bowing of the interventricular septum, and measurement of the tricuspid regurgitation jet. Therapeutic drugs including prostacyclin, endothelin-receptor antagonists, and phosphodiesterase inhibitors, like sildenafil, have shown promising results in patients, including children and infants, with PAH (Suesaowalak et al. 2010). Recognizing elevated pulmonary arterial pressure early can be especially important, as increasingly effective treatments are now available for PAH.

Synopsis

Pulmonary hypertension association with glycogen storage disease IIIa and IIIb.

References to Electronic Database

Glycogen storage disease type III: OMIM 232400. Amylo-1,6-glucosidase: EC 3.2.1.33. HUGO-approved gene symbol: *AGL*.

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