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Pulmonary Arterial Hypertension in Glycogen Storage Disease Type I

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Abstract

Pulmonary arterial hypertension (PAH) is a rare and highly fatal disease that has been reported in 8 patients with glycogen storage disease type I (GSDI). We describe an additional case of an acute presentation of PAH in a 14-year-old patient with GSDI, which was successfully treated with inhaled nitric oxide and sildenafil. We investigated the incidence of PAH in 28 patients with GSDI on routine echocardiography and found no evidence of PAH and no significant cardiac abnormalities. This study highlights that PAH is a rare disease overall, but our case report and those previously described suggest an increased incidence in patients with GSDI. Should cardiopulmonary symptoms develop, clinicians caring for patients with GSDI should have a high degree of suspicion for acute PAH and recognize that prompt intervention can lead to survival in this otherwise highly fatal disease.

Keywords

glycogen storage disease type I, pulmonary arterial hypertension, echocardiography, sildenafil

Introduction

Glycogen storage disease type I (GSDI) is an autosomal recessive disease with an incidence of approximately 1 in 100 000 newborns. Two main subtypes exist, with type Ia (von Gierke disease) caused by a deficiency of glucose-6-phosphatase and type Ib caused by defects in glucose-6-phosphate translocase. Abnormal accumulation of glycogen and fat and inadequate glucose production lead to hypoglycemia, growth retardation, hepatomegaly, lactic acidosis, hyperlipidemia, and hyperuricemia.[1] Prognosis has improved with continuous gastric feeding and the use of uncooked cornstarch to maintain euglycemia, but short stature, gout, renal dysfunction, osteoporosis, and hepatic adenomas are known complications.[1,2] Eight cases of pulmonary arterial hypertension (PAH) in patients with GSDI have been described,[3-9] but the incidence and etiology of PAH in patients with GSDI remain unknown.

Pulmonary arterial hypertension is a rare disease with an incidence of 2.4 to 7.6 cases/million cases. Pulmonary arterial vascular changes lead to increased pulmonary vascular resistance and right heart failure, and the typical annual mortality rate is 15%.[10] Transthoracic echocardiography serves as a noninvasive, accurate, sensitive, and specific screening tool for PAH.[11,12] An estimate of pulmonary arterial pressure is obtained from the tricuspid regurgitation (TR) jet velocity, with a peak velocity >2.8 to 2.9 m/s used as the cutoff for PAH.[13,14]

Here, we present the case of acute PAH in a 14-year-old boy with GSDI who acutely responded to treatment with inhaled nitric oxide and sildenafil. Additionally, the echocardiographic data from a cohort of 28 patients with GSDI followed at Duke University Medical Center were reviewed to investigate the incidence of PAH in these patients.

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Table 1. Case Report Laboratory Values Over Time.

	2 Months Prior to Acute PAH	Acute PAH Presentation	9 Years After Acute PAH
Glucose (60-115 mg/dL)	65	105	84
Bicarbonate (22-28 mg/dL)	27	22	28
AST (15-41 U/L)	18	39	32
ALT (3-35 U/L)	12	5	37
Lactic acid (0.7-2.2 mmol/L)	2.5	36	1.9
Cholesterol (100-200 mg/dL)	164	ND	178
Triglycerides (40-160 mg/dL)	274	ND	508

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ND, not done; PAH, pulmonary arterial hypertension.

Case Report

A 14-year-old Pacific Islander male with GSDI diagnosed in infancy had shown normal growth and several years of excellent metabolic control (Table 1) on frequent cornstarch feedings. Baseline echocardiogram and electrocardiogram at 12 years of age were normal. He initially presented to the emergency department for emesis, leading to hypoglycemia, which was successfully treated with intravenous glucose prior to discharge home. However, 2 weeks later, he presented to the emergency department again with a 2-day history of breathing difficulty and palpitations. His evaluation showed sinus tachycardia at 148 beats/min, tachypnea with normal oxygen saturations, no fever, and a normal chest X-ray. Initial blood work was notable for a significantly elevated brain natriuretic peptide level of 877 pg/mL, mildly elevated creatinine of 1.1 mg/dL, and slightly elevated troponin at 0.07 μg/L (normal <0.04 μg/L). All other laboratory values were normal, and there was no significant leukocytosis, hypoglycemia, or evidence of liver dysfunction. He was admitted to the pediatric intensive care unit and quickly developed hypotension, bradycardia, and severe metabolic acidosis, requiring intubation, fluid resuscitation, and pressors. An emergent echocardiogram demonstrated an elevated TR jet velocity of 3.2 m/s, and he was started on inhaled nitric oxide at 20 parts per million and sildenafil 20 mg twice daily for suspected acute PAH. Infection was initially considered as a cause for his acute presentation, and an extensive infectious disease workup was performed for bacterial, fungal, and viral infections in blood, urine, respiratory, and cerebrospinal fluid (CSF) cultures. All infectious disease testing was negative, and antibiotics were discontinued shortly after admission. He remained afebrile without a significant leukocytosis throughout his stay, and infection was felt to be an unlikely etiology of his presentation. Instead, his rapid cardiopulmonary collapse, significantly elevated right heart pressures on echocardiogram, and clinical response to pulmonary vasodilators all suggested an acute onset of PAH. He was followed with serial echocardiograms, with a peak TR jet velocity of 3.4 m/s on hospital day 2. He clinically improved, and the inhaled nitric oxide was weaned off over 4 days. He was extubated on hospital day 8, and his echocardiogram on hospital day 15 showed a peak TR jet velocity of 2.9 m/s. Given his clinical improvement and declining TR jet velocity indicating normalizing pulmonary arterial pressures, a sildenafil wean was started, and sildenafil was discontinued on hospital day 20. He had developed renal failure initially requiring 6 days of dialysis and associated systemic hypertension, both of which normalized. He remained hospitalized for 1 month and required several subsequent months of outpatient rehabilitation for generalized weakness. He recovered fully over time, and echocardiogram obtained 1 year after his episode of acute PAH showed a high normal TR jet velocity of 2.8 m/s with no septal flattening.

Most recent follow-up at 23 years of age shows no recurrent evidence of PAH, with a normal echocardiogram and TR jet velocity of 2.0 m/s. He has no evidence of liver or kidney dysfunction (Table 1). He was recently diagnosed with systemic hypertension, for which he was started on low-dose lisinopril. He otherwise maintains good glucose control with cornstarch feedings five times per day.

Materials and Methods

Patients with GSDI who attend the Metabolic Diseases Clinic at Duke University Medical Center consented for participation in a GSDI natural history study, which was approved by the Duke Institutional Review Board. Of the 57 patients who consented for the GSDI natural history study, 29 had echocardiograms available for review. One patient's echocardiogram was eliminated for poor image quality, leaving a total of 28 patients for review. This cohort included follow-up data of 6 patients from a previous study by Kishnani et al at Duke University Medical Center examining PAH in GSDI.[7] All echocardiograms were reviewed in their entirety by 2 of the authors (R.D.T. and S.B.W.). Two echocardiograms were performed at outside institutions and reviewed by digital recording, and the rest were performed at Duke University Medical Center. Several specific features were documented for each echocardiogram: peak TR jet velocity (if present) in the parasternal and apical views, the presence of right ventricular hypertrophy, dilation, or dysfunction, the presence of septal flattening, increased right ventricular outflow gradient, and any additional structural abnormalities of the heart. These findings were then compared to the documented final report. In the event of significant discrepancies between the final clinical report and findings of research review, an independent assessment by a third reviewer was planned.

Results

Patient demographics are summarized in Table 2. Of the 28 patients in this review, 24 patients were diagnosed with GSDIa and 4 carried a diagnosis of GSDIb. The gender distribution was equal, with 14 males and 14 females. The median patient age at the time of echocardiogram was 24 years, with a range of

Table 2. Patient Demographics.

	GSD Type Ia	GSD Type Ib	Total
Age range (years)	3-51	4-28	3-51
Median age (years)	26	17.5	24
Males	13	1	14
Females	11	3	14
Echos reviewed			
Single echo	10	1	11
>1 echo	14	3	17

Abbreviation: GSD, Glycogen storage disease.

3 to 51 years. A total of 51 echocardiograms were reviewed, with 17 patients having multiple echocardiograms reviewed. The median time interval between echocardiograms was 35.9 months, with a range of 12 months to 12 years. The longest duration of follow-up over time by echocardiography was 18 years.

None of the echocardiograms reviewed showed evidence of PAH. Of the 6 patients in our review described previously by Kishnani et al,[7] 2 had been noted to have estimated systolic pulmonary artery pressures >20 mm Hg (TR jet velocity >2.2 m/s). However, on follow-up, none of the patients showed abnormalities or progression to PAH on echocardiogram. The maximum TR jet velocity in the entire cohort was 2.5 m/s, and none of the echocardiograms showed septal flattening. There was no right ventricular dilation, hypertrophy, or dysfunction. One patient had moderate aortic insufficiency and severe mitral insufficiency, and 2 patients had mild aortic insufficiency. Finally, 1 patient had a slightly elevated right ventricular outflow gradient ranging between 1.9 and 2.1 m/s on serial echocardiograms, but there was no evidence of obstruction or pulmonary hypertension. There were no other significant structural abnormalities among our patient cohort, and there were no major discrepancies between the results of our review and the final documented echocardiogram reports.

Discussion

None of the patients with GSDI in our cohort showed evidence of PAH. Given the low incidence of PAH in general, this result is not surprising. However, we add another case report to the previously described 8 cases of PAH in patients with GSDI, further strengthening the well-described association between these two rare diseases.[3-9] The complex pathogenesis of PAH is largely unknown, but recent progress has been made in identifying some genetic causes for familial PAH, and clinical testing for mutations in *BMPR2*, *ALK1*, *ENG*, *SMAD8*, and *CAV1* genes are now available. PAH is associated with congenital heart disease in the setting of a systemic to pulmonary shunt, connective tissue diseases, human immunodeficiency virus, portal hypertension, toxins and drugs, hemoglobinopathies, and several other conditions.[15,16] Pediatric PAH is associated with several genetic syndromes, including GSDI and III, but the etiology of PAH in GSD remains unclear.[15-17] Given the common association of PAH in both GSDI and GSDIII, it is possible that a common mechanism leads to PAH in both diseases.

Table 3. Reported Cases of Pulmonary Arterial Hypertension in Patients With GSDI.

Author	Age at PAH Diagnosis (years)	Sex	Shunt[a]	Survival	Pathology (Pulmonary Arteries)
Pizzo[3]	16	F	Yes	No	Intimal fibrosis, medial hypertrophy, plexiform lesions
Hamaoka et al[4]	12	F	No	No	Fibrous occlusion, plexiform lesions
Hamaoka et al[4]	16	M	Yes	No	ND
Ohura et al[5]	21	F	No	No	ND
Bolz et al[6]	4	F	No	No[b]	Intimal fibrosis
Kishnani et al[7]	24	F	No	No	ND
Humbert et al[8]	25	M	Yes	Yes	ND
Ueno et al[9]	17	M	No	Yes	NA
Torok et al	14	M	No	Yes	NA

Abbreviations: GSDI, glycogen storage disease type I; NA, not applicable; ND, not done; PAH, pulmonary arterial hypertension.
[a]Portal vein or intestinal vein surgical shunt to inferior vena cava.
[b]Patient had an atrial septal defect and died 4 years after PAH diagnosis.

Characteristics of the 9 current case reports of PAH in patients with GSDI, including our case, are listed in Table 3. Patients with GSDI were typically diagnosed with PAH in the second to third decade of life, except 1 patient described by Bolz et al, who was diagnosed with PAH at 4 years of age and died 4 years later. This patient had an atrial septal defect, which typically does not lead to PAH until adulthood. However, the combination of an intracardiac shunt and GSDI was felt to accelerate PAH progression.[6] PAH is more common among females, with a 1.6- to 1.7-fold increase in idiopathic PAH and a 2- to 2.7-fold increase in incidence compared to males in familial PAH.[18] For PAH-associated diseases, the gender distribution is thought to be more heavily influenced by the epidemiology of the underlying condition,[19] and in the reported cases of PAH in patients with GSDI, 5 were females, and 4 were males. Three patients underwent surgical shunt placement from the portal or intestinal vein to the inferior vena cava, which was previously performed to promote growth in patients with GSDI. Some have questioned if blood returning directly to the lungs without passing through the hepatic circulation increases the risk of PAH. As previously mentioned, portal hypertension is associated with PAH, but none of the reported patients showed evidence of portal hypertension. Regarding

survival, only the 3 most recent patients with GSDI and PAH survived, with the rest succumbing typically months after being diagnosed with PAH.

In the search for the mechanism of PAH in GSDI, increased levels of pulmonary vasoconstrictors such as serotonin, purine, histamine, and catacholamines have been proposed.[4] The most focus has been placed on serotonin, which is a vasoconstrictor produced by the enterochromaffin cells of the intestine and rapidly metabolized by endothelial monoamine oxidase in the liver and lung.[8] Genetic variation in the serotonin transporter and a serotonin receptor have been noted in the platelets and lung tissue of patients with PAH, and transgenic mice overexpressing the serotonin transporter develop PAH.[15] Humbert et al demonstrated elevated plasma serotonin levels in both patients with severe PAH and patients with GSDI, and plasma serotonin was significantly elevated in 1 patient with both PAH and GSDI. However, the level of serotonin alone did not predict the development of PAH, as only 1 of the patients with GSDI with elevated serotonin had PAH.[8] Also, selective serotonin-reuptake inhibitors are widely used clinically and have not been correlated with development of PAH.[11] Perhaps instead of causing PAH, an elevated serotonin level may serve as a marker of diseased tissue or altered signaling in the lungs and/or liver, as these are the sites of serotonin metabolism.

Considering the multiple genetic mutations which may lead to GSDI, we hypothesize that these variations could lead to different alterations in cell signaling, which may or may not lead to PAH. Perhaps some mutations leading to GSDI affect the glucose metabolism in the liver and also affect the pulmonary vasculature, making these patients more likely to develop PAH. Additionally, it is quite possible that the development of PAH is multifactorial, and triggers such as systemic illness, poor metabolic control, or decreased hepatic circulation contribute to the development of PAH in some patients with GSDI. In our patient, baseline echocardiogram was normal without evidence of PAH, but he had an episode of hypoglycemia 2 weeks prior to his acute presentation with pulmonary hypertension, which perhaps served as a trigger for his acute presentation.

While the etiology of PAH in GSDI remains unclear and the prognosis typically grim, in our case report and 2 of the previously reported cases, medical management of PAH led to survival. In the previous reports, 1 patient was treated with exercise limitation, warfarin, and diuretics,[8] and 1 was treated with the prostacyclin analog beraprost sodium, with subsequent transition to sildenafil.[9] In our case report, the patient was managed transiently on inhaled nitric oxide and sildenafil. Inhaled nitric oxide was weaned off within the first week of admission, and sildenafil was weaned off within 3 weeks of his admission, suggesting a transient pulmonary hypertensive crisis. It is quite possible that PAH is acute and transient in these patients due to acute triggers such as poor metabolic control. Many acute therapies were not available for pulmonary hypertension in the past, and it is not surprising that earlier, patients with GSDI and PAH succumbed.[3-7] The use of new agents such as inhaled oxide, prostacyclin analogs, and phosphodiesterase type 5 inhibitors such as sildenafil may enable stabilization and recovery without the need for lifelong therapy.

Given the available treatment options for PAH in patients with GSDI, clinicians must have a high index of suspicion for this diagnosis when patients with GSDI complain of shortness of breath, tachypnea, fatigue, chest pain, syncope, or edema, especially in the second decade of life. Chest X-ray, electrocardiogram, and echocardiogram should be ordered promptly in addition to basic laboratory chemistries to assess for signs of PAH.[16] Early detection and treatment of PAH in these patients could prevent progressive worsening or a sudden, severe pulmonary hypertensive crisis and can lead to improved outcomes.

In conclusion, PAH is a rare but highly fatal disease that has been associated with GSDI. Given the rarity of both GSDI and PAH, the exact incidence of PAH in patients with GSDI is difficult to quantify, and clinical collaboration among institutions will be required to further address this question. Additionally, further work is needed to explore the causes of PAH in patients with GSDI, which is likely multifactorial and could be related to genetic variations within GSDI and overall metabolic control. Finally, clinicians caring for patients with GSDI should have a high degree of suspicion for PAH, should cardiopulmonary symptoms develop, as prompt intervention can lead to survival in this otherwise highly fatal disease.

Authors' Note

All authors were involved in the concept and design and/or the interpretation of data for the manuscript, were involved in drafting or critical revision of the manuscript, and approved the version to be published.

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Declaration of Conflicting Interests

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