

Two Case Reports of Progressive Pulmonary Hypertension with Type-1 Gaucher Disease: Efficient PAH-Specific Therapy and 1-Year Follow-Up

CASE REPORT

INTRODUCTION

Gaucher disease (GD), the most common lysosomal storage disorder, is a multisystem condition resulting from autosomal recessive mutations in the gene encoding glucocerebrosidase. Incomplete glucocerebrosidase activity leads to the accumulation of its main substrate, glucocerebroside (also called glucosylceramide).¹ According to the degree of neurological involvement in GD, 3 basic clinics are defined: acute neuropathic disease (type 2) and chronic neuropathic disease (type 3) are fatal in infancy and childhood, non-neuropathic disease (type 1) accounts for more than 90% of all cases, and the clinical course is highly heterogeneous. The clinical presentation of type 1 GD (GD1) varies from lifelong asymptomatic to early-onset forms that appear in childhood. The initial symptoms vary considerably, and patients can be diagnosed at any age. The most common symptoms are hepatosplenomegaly, anemia, thrombocytopenia due to hypersplenism, and often skeletal involvement.² Pulmonary involvement is a rare life-threatening disorder and pulmonary hypertension (PH) is the most serious pulmonary complication in GD1. Here, we present two cases of progressive PH in patients with GD1 responding well to pulmonary arterial hypertension (PAH) specific treatment. Both patients provided written consent for this case series.

CASE REPORTS

Table 1 displays clinical characteristics of two GD1 patients presenting with symptoms of PH. Both had shortness of breath and limited effort capacity and were referred to our cardiology clinic. Both patients had undergone splenectomy for thrombocytopenia in childhood. Despite the remarkable bone deformities in adulthood, GD1 was diagnosed at different stages of the disease and enzyme replacement therapy (ERT) was started late, and the clinical course was different. Both cases were diagnosed as PH after evaluation in our cardiology outpatient clinic and were further investigated.

Case 1

The first patient, a 63-year-old woman, was diagnosed with GD1 at an advanced stage of the disease and has been receiving ERT for the past 5 years. Her medical history included tuberculosis, early menopause, hip fracture and related operation, and oxygen therapy for the last 2 years due to bronchiectasis. She was also on treatment with oral anticoagulation (apixaban) and diltiazem due to atrial fibrillation (AF).

Her first evaluation in our center showed bilateral distention of jugular veins and mild bilateral pitting edema in lower extremities on physical examination. Expiratory sounds of the lungs were bilateral, and breath sounds were decreased on auscultation. Electrocardiography showed AF with a heartbeat of 96 bpm. Initial laboratory workup showed severely elevated NT-proBNP levels. Patient's functional capacity (FC) was New York Heart Association (NYHA) class III and

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Table 1. Clinical Characteristics of the Patients

	Patient 1	Patient 2
Current age (years)	63	42
Gender	Female	Male
Age at diagnosis of GD1 (years)	52	3
Age at splenectomy (years)	14	6
History of bone fractures	+	+
Baseline score (GD-DS3 *)	9 (severe disease)	6 (marked disease)
Age at first enzyme treatment (years)	57	36
Age at diagnosis of PH (years)	62	39
Genotype	N370S/ A341S	N370S/ p.N409S
Treatment of PAH	Phosphodiesterase type 5 inhibitor (Tadalafil 10 mg 2 × 1)	Endothelin receptor antagonists (Macitentan 10 mg 1 × 1)

*GD1-DS3, type 1 Gaucher disease severity score index; 0-3, mild disease; 3-6, moderate disease; 6-9, major disease; >9, severe disease which is used to assess the burden of disease, decide on treatment doses, and monitor response to treatment.¹³
GD1, type 1 Gaucher disease; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension

6-minute walk distance (6-MWD) was 240 meters (m). Chest x-ray was remarkable with an enlarged pulmonary trunk and reduced peripheral vascularity in addition to cardiomegaly. Thorax computed tomography depicted diffuse bronchiectasis—bronchiolectasia areas in both lungs, which might be due to recurrent infections. While no findings of interstitial lung disease were observed in the lung parenchyma, areas of mosaic oligemia supporting the small airway disease were noticed. Resting oxygen saturation of 90% and a diffusing capacity of the lung for carbon monoxide (DLCO) of 42% were detected in pulmonary function tests. When perfusion and ventilation scans were evaluated; typical scintigraphic findings favoring pulmonary thromboembolism were not detected. Echocardiography revealed a normal left ventricular (LV) systolic function, severe enlargement of the right heart chambers and systolic functions were mildly depressed, severe tricuspid regurgitation was detected with an estimated systolic pulmonary artery pressure (sPAP) of 100 mm Hg. Cardiac catheterization findings were compatible with pre-capillary PH with normal capillary wedge pressure and increased pulmonary vascular resistance of 9.6 Wood units. With all these findings, she received the diagnosis of Group 5 PH according to the World Health Organization PH classification and was put on phosphodiesterase-5 (PDE5) inhibitor tadalafil. At the end of the first year of our treatment, her 6-MWD and FC were improved. The need for supplemental oxygen decreased significantly (Table 2).

Case 2

The second patient was a 42-year-old man with a previous diagnosis of GD1. Although diagnosed in childhood, ERT was introduced at the late stage of such a progressive disease and the regular use of ERT could not be ensured. Three years after the initiation of ERT, in the center where he had admitted with the complaint of palpitation, his LV ejection fraction was measured as 25-35% in echocardiography, and he was put on digoxin, angiotensin converting enzyme (ACE) inhibitor, spironolactone, and furosemide treatment and regular use of ERT was recommended.

Four months after the initiation of treatment, he admitted to our outpatient clinic with shortness of breath and flu-like symptoms to be evaluated with the diagnoses of heart failure (HF) and PH. His physical examination revealed moderate bilateral pitting edema in the lower extremities, jugular venous distention, decreased breath sounds, and fine crepitation rales in the lower lungs. Electrocardiography showed right bundle branch block and sinus rhythm. Initial laboratory analysis revealed severely elevated NT-proBNP levels (Table 2). Chest x-ray was remarkable for interstitial infiltrates concerning pulmonary edema, with an enlarged pulmonary trunk and cardiomegaly. He was put on IV furosemide and the treatment of HF was optimized by adding B-blocker treatment. In the re-evaluation of the patient whose edema symptoms were regressed and compensated, echocardiography showed moderate PH with depressed LV systolic function with an ejection fraction of 35% and NYHA class III FC, and a 6-MWD of 210 m. Despite the optimized HF treatment his dyspnea symptom persisted, therefore we performed cardiac catheterization. Catheterization revealed cardiac pressures consistent with pre-capillary PH and a negative vaso-reactivity test. We added endothelin receptor antagonist Macitentan and continued optimal HF therapy on top of ERT. At the end of first year of our treatment, his 6-MWD and FC were significantly improved. LV ejection fraction was 50% and the sPAP was 43 mm Hg in echocardiographic assessment (Table 2).

DISCUSSION

Herein we present two adult GD1 patients presenting with severe PH which is a rare complication of GD. Though clinical manifestations of GD1 are well addressed, data on cardiac involvement and/or PH are a few and mostly based on individual case reports and clinical observations. Only 1-2% of patients with GD1 exhibit overt pulmonary manifestations in the form of interstitial lung disease or pulmonary vascular disease (i.e., severe PH and/or hepatopulmonary syndrome).¹ A historical echocardiographic

Table 2. Time Course of Clinical Status, Exercise Capacity, and Hemodynamic Results

	Patient 1		Patient 2	
	PAH Pre-treatment	Post-treatment	PAH Pre-treatment	Post-treatment
NYHA class	III	II	III	II
6 MWD (m)	240	325	210	490
Cardiac rhythm on ECG	AF	AF	SR	SR
Laboratory findings				
Hemoglobin (g/dL)	11.4	12.2	17.2	14.6
WBC (K/ μ L)	11.2	7.7	8.67	7.27
Platelets (K/ μ L)	251.000	260.000	253.000	290.000
AST (0-34 U/L)	11	16	26	16
Creatinine (0.57-1.1 mg/dL)	0.57	0.41	0.67	0.68
Total cholesterol (mg/dL)	110	139	182	195
Ferritin (μ g/dL)	434	260	1943	1444
NT-ProBNP (0-125 pg/mL)	3106	1912	2465	156
TSH (mU/L)	2.3	1.89	2.49	2.45
Echocardiographic evaluation				
Left ventricular EF %	Normal	Normal	35%	50%
Right ventricular EF %	Mild depressed	Mild depressed	Mild depressed	Mild depressed
TRV (m/s)	4.96	4.3	3.6	3.1
TAPSE (mm)	13	18	11	14
RV S' (m/s)	7	12	5	7
sPAP (mm Hg)	100	90	62	43
Right heart catheterization findings				
Pulmonary artery pressure (mm Hg)	65/25-40	-	71/26-44	-
Right ventricular pressure (mm Hg)	65/5	-	70/7	-
Right atrial pressure (mm Hg)	6	-	8	-
Pulmonary artery wedge pressure (mm Hg)	11	-	10	-
Cardiac output by Fick (L/min)	3	-	3.9	-
Pulmonary vascular resistance (Wu; Wood unit)	9.6	-	8.72	-
Mixed venous oxygen saturation (MVo ₂) %	52.1	-	72	-
Arterial oxygen saturation (SaO ₂) %	92.3	-	96.7	-
Left heart catheterization	No pulmonary artery coronary compression	-	No pulmonary artery coronary compression	-
Coronary angiography	Normal coronaries	-	Normal coronaries	-

NYHA, New York Heart Association; 6MWD, 6-minute walk distance; ECG, electrocardiography; AF, atrial fibrillation; SR, sinus rhythm; WBC, white blood cell; AST, aspartate aminotransferase; NT-ProBNP, N-terminal pro b-type natriuretic peptide; TSH, thyroid stimulating hormone; EF, ejection fraction; TRV, tricuspid regurgitation peak velocity; TAPSE, tricuspid annular plane systolic excursion, RV S', right ventricular systolic motion; sPAP, systolic pulmonary artery pressure.

study published in 1998 has depicted a ranging prevalence of PH 7% to 30% in adult GD1 patients regarding the use of ERT therapy. Type 1 GD patients on ERT therapy had lower prevalence of PH than those untreated (7.4% vs. 30%, consecutively).³

Several mechanisms may explain the relationship between GD1 and PH. One of the major causes associated with PH in GD1 patients is splenectomy. As systemic involvement typically includes hypersplenism and splenomegaly, most patients undergo splenectomy in the early course of the disease. However, removal of the spleen causes Gaucher cells

to accumulate in other tissues such as lung tissue leading to hepatopulmonary syndrome, which occurs with interstitial lung disease, pulmonary capillary occlusion, or abnormal vascular shunt development.⁴ Other mechanisms that may explain the relationship between splenectomy and PH are dysfunctional pulmonary endothelium, intimal fibrosis, medial hypertrophy, plexiform lesions, and post-splenectomy thrombocytosis.⁵ As in our cases risk factors for severe PH include asplenic patients naive to ERT, asplenic patients treated sub-optimally with ERT, female gender, glucocerebrosidase mutations other than N370S, positive family history, and an ACE I gene polymorphism.¹

Patients with GD1 are considered to be immunocompromised due to splenectomy and impaired secretion of inflammatory cytokines in Gaucher macrophages. There have been case reports of various infections, including tuberculosis, in patients with delayed or untreated treatment.⁶ Our patients could contribute GD1 literature in several aspects. First case was a late diagnosed GD1 patient at the age of 52 though she had had the splenectomy at the age of 14 years. The 38-year time gap has led to the severe recurrent lung infections and bone involvement. Though she was suffering from dyspnea she was not referred to cardiology until the development of palpitations. She was followed without echocardiographic evolution for many years though cardiac involvement is highly frequent in GD1 patients. Cardiac involvement other than PH in GD, restrictive cardiomyopathy and calcifications of the valves and aortic arch, has been reported mostly in GD3 and childhood. Cardiac involvement is restrictive in nature in most of the cases. There are case examples of diastolic dysfunction, LV hypertrophy, and restrictive cardiomyopathy due to infiltrative damage to the myocardium.^{7,8} Dilated cardiomyopathy was described in the literature only in a young pregnant woman with a diagnosis of GD1 who had never received ERT. That patient has survived the postpartum period without any problems and was discharged with digoxin and diuretic use.⁹ However, LV recovery data in follow-up are missing, but previous case reports suggest that high-dose ERT may also improve cardiac symptoms of HF and low LV ejection fraction.¹⁰ Our second case is the second case of dilated cardiomyopathy in an adult GD1 patient in the literature. He was diagnosed as GD1 in early childhood; however, ERT therapy was initiated more than 30 years later. Specific ERT is the mainstay of GD management, which significantly reduces both the morbidity and mortality of the disease. Early initiated ERT not only prevents splenectomy but also significantly reduces the development of PH after splenectomy which is the major modifiable risk factor for severe PH in GD1.

Another important aspect of our patients is the significant improvement of clinical course with PAH specific therapy. Use of PAH specific agents with anti-remodeling and vasodilator actions as adjuvant to ERT improves hemodynamic and functional status while prolonging life. There is limited data in the literature regarding the treatment of PH in patients with GD1. Case reports suggest PAH therapies such as prostacyclins, PDE5 inhibitors (sildenafil),¹¹ and endothelin receptor antagonists (macitentan)¹² improve symptoms in GD1-associated PH. Accordingly, our patients' symptoms alleviated after 1 year of vasodilator therapy (with tadalafil in the first and with macitentan in the second patient). We preferred to use tadalafil in the first patient as GD1 is a disease of liver. Though patient's liver function tests were within normal limits, we aimed not to increase the burden of liver involvement and also not to deepen the anemia in such a patient on oxygen therapy. To the best of our knowledge, our first case is the first presentation of the efficacy of tadalafil in GD1 associated with PAH. This patient is also a good case to mention the importance of

family screening as her 53-year-old asymptomatic sister has received GD1 diagnosis during family genetic screening and still symptom-free without ERT. For the second patient we preferred Macitentan, a second-generation ERA with lower hepatic adverse effects compared to Bosentan. Adding ERA to the treatment of our second patient may raise a question due to the co-existence of HF and precapillary PH. However, there were two facts to be considered while adding this therapy. First, despite the optimal medical HF therapy for the last 4 months, his dyspnea was persisting. Second, findings were consistent with precapillary PH in the cardiac catheter which was conducted while he was on optimal medical HF treatment. We all well-know that PH due to HF deteriorates with ERA. However, his clinical symptoms did not worsen with the initiation of ERA which might be a clue for the precapillary-PH in this patient. Eventually, in metabolic storage diseases such as GD1, the accumulating substances not only affect the pulmonary arteries but also the myocardium, pulmonary veins, etc. Therefore, the clinical picture, and response to therapy may vary depending on the dominant organ or tissue involvement.

CONCLUSION

In conclusion, adult GD1 patients could present with PH and/or HF. Splenectomy, late diagnosis, and late treatment are probably the major contributors of PH in these patients. Even the late course of disease presenting with PH, optimal ERT, and PAH-specific treatment are beneficial in clinically and hemodynamically. Therefore, physicians should be aware of the risk of PH and cardiac involvement in GD1 patients especially in those with late or suboptimal treatment. Regular echocardiographic assessment should be a part of the routine clinical follow-up not to miss the development of PH and cardiac complications. There is still need for large-scale prospective studies or registries to increase our knowledge regarding the best treatment strategy for this rare and clinically important disease process.

Informed Consent: Both patients provided written consent for this case series.

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