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CASE REPORT

TAVI in Patient Suffering from Niemann–Pick Disease (Acid Sphingomyelinase Deficiency) with Concomitant Situs Inversus and Dextrocardia

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ABSTRACT

Acid sphingomyelinase deficiency (ASMD)—also known as Niemann–Pick (NP) disease—is a rare, autosomal recessive disorder which is characterized by deficiency of the lysosomal enzyme acid sphingomyelinase (ASM), resulting in excessive storage of lipids in organs (i.e., spleen, liver, lung, bone marrow, lymph nodes, and vascular system). Only a few cases of moderate-to-severe valvular heart disease due to ASMD are described in the literature, mostly in adulthood. We report here the case of a patient with NP disease subtype B that was diagnosed during adulthood. NP disease in this patient was found to be associated with situs inversus. Specifically, a severe, symptomatic aortic stenosis was identified, and the need for surgical or percutaneous intervention was discussed. The heart team chose transcatheter aortic valvular implantation (TAVI), which was successfully performed with no complications on follow-up.

Keywords: Aortic stenosis; Transcatheter aortic valve implantation; Risk scores; Acid sphingomyelinase deficiency disease; Niemann–Pick; Situs inversus

Key Summary Points

Niemann-Pick (NP) disease is a rare storage disease with poor prognosis.

NP disease may negatively influence cardiac performance and morphology.

The association between NP and situs inversus is extremely rare, as is the occurrence of aortic stenosis.

Adoption of transcatheter aortic valvular implantation (TAVI) in aortic stenosis in a patient with aortic stenosis, situs inversus, and NP is feasible

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INTRODUCTION

Acid sphingomyelinase deficiency (ASMD), also known as Niemann–Pick (NP) disease, is a rare, autosomal recessive disorder that results from a deficiency of acid sphingomyelinase (ASM), a lysosomal enzyme that catalyzes the hydrolysis of sphingomyelin to ceramide and phosphocholine. The disorder is caused by a bi-allelic mutation in the sphingomyelin phosphodiesterase-1 (SMPD1) gene [1–3].

ASMD primarily results in the progressive accumulation of sphingomyelin, followed by excessive storage of lipids, sphingomyelin, and cholesterol in several organs of the body, such as the spleen, liver, lung, bone marrow, lymph nodes, central nervous system (CNS), and peripheral nerves [1–3]. First described by Albert Niemann in 1914 and differentiated from Gaucher disease by Ludwig Pick in 1927, NP disease is classified into four subtypes (Types A, B, C, D). Specifically, mutations in the SMPD1 gene cause NP disease types A and B [1–3]. The transcription of the protein involved in lipid transport is nearly abolished in type C1 (NPC1) or C2 (NPC2), while type D is a variant of NP disease subtype C [1–3].

Clinical manifestations range from rapidly progressive and fatal infantile neurovisceral disease to progressive chronic neurovisceral and visceral forms that are associated with significant morbidity and reduced life expectancy [4–8]. Common clinical features include hepatosplenomegaly, proatherogenic lipid profile, retinal stigmata, delayed growth and puberty, thrombocytopenia and leukopenia, lung failure, interstitial lung disease and pulmonary infections, fatigue, liver dysfunction or even cirrhosis due to sphingomyelin deposition, and progressive portal hypertension.

Alterations in cardiac structure and cardiac performance in patients with NP disease is recognized [4] and is often secondary to the pulmonary disease. These patients also develop a proatherogenic lipid profile (mixed dyslipidemia) in the early stages of the disorder, hence some may prematurely suffer from coronary artery disease. [5, 9, 10]. A systematic evaluation of morbidity and mortality in 103 patients with type B NP disease showed that 9% of the patients had coronary artery or heart valve disease [4]. The treatment of these patients remains challenging.

CASE REPORT

Written informed consent was obtained from the patient for the publication of this case report. The name and surname of the patient were removed.. The study was carried out in compliance with the 1964 Helsinki Declaration and its subsequent amendments.

We report the case of a 65-year-old man who was substantially asymptomatic until 2 years prior to presentation with symptoms (2020) when he was accidentally discovered to have hepatosplenomegaly. Blood tests showed thrombocytopenia and relatively high values of B2—macroglobulin; renal function was preserved. More specific tests were then performed, including a genetic study for mutation(s) in the *JAK2 V617F* gene, which was negative, bone marrow biopsy, which revealed hypercellular bone marrow characterized by plentiful histiocytic foamy cells suggesting storage disease, and enzymatic tests, which revealed low ASM activity).

Additional genetic tests highlighted homozygous mutation c.1799 G > A in exon 6 of the SMPD1 gene, namely a substitution of an adenine base by guanine in the complementary DNA (cDNA) at nucleotide position 1779 that determines the replacement of histidine with arginine at amino acid position 600 of the protein, i.e., R600H. This mutation is associated to ASMD subtype B. Genetic tests also ruled out Fabry disease, Pompe's disease, and mucopolysaccharidosis type I.

With disease progression, the patient developed emphysematous chronic obstructive pulmonary disease (COPD), bronchiectasis, and recurrent pneumonia for which he was under pneumological follow-up and underwent periodical computed tomography (CT) scans. He also developed hypothyroidism due to chronic autoimmune thyroiditis, severe femoral osteoporosis and lumbar osteopenia, which caused walking deficits, and anxious—depressive

syndrome. In addition, situs viscerum inversus was diagnosed during examinations (Fig. 1).

In May 2022 the patient complained of dyspnoea with mild-to-moderate physical efforts and episodes of spontaneous vertigo. Subsequent cardiac magnetic resonance imaging (MRI) revealed dextrocardia, left ventricular moderate hypertrophy, and severe aortic stenosis. Ecocardiography outlined worsening of the cardiac function (left ventricle ejection fracton: 45%, which was lower than previous one [56%]) and new-onset septal dyssynergy. Calcific aortic sclerosis with severe stenosis was also identified (mean gradient: 56 mmHg, previous one: 35 mmHg) (Fig. 2).

The patient was admitted to our department on July 2022 for transcatheter aortic valve implantation (TAVI). Total body CT scan was performed to evaluate the patient's vascular accesses and their courses in the situs inversus totalis condition, with right-sided vascular system. A coronary angiography showed coronary arteries with inverted origin and course: common arterial trunk originated from the right coronary sinus and right coronary artery from the left, normal size, mild atherosclerotic burden, and right dominance. From the transesophageal echocardiography, we determined thickened, calcified aortic cusps, severe aortic stenosis, mild aortic insufficiency (peak gradient [PG] maximum = 80 mmHg; PG maximum = 60 mmHg). The aortic root (40 mm) and ascending aorta (42 mm) were dilated.

Taking into account the patient's clinical characteristics, TAVI was unanimously chosen as the intervention of choice. As a first step, we placed a temporary pacemaker in the right ventricle via the left femoral vein. A pigtail catheter was positioned at the non-coronary sinus.

In order to successfully carry out the procedure, we induced ventricular tachycardia of 180 beats per minute (bpm) so that we had a transient stasis of blood flux. After valve pre-dilatation with a 20 × 40-mm balloon (VACS II; Osypka Medical GmbH, Berlin, Germany), we inserted a 29-mm Portico-type transcatheter biological prosthetic valve (Abbott Laboratories, Chicago, IL, USA) at the aortic orifix level, which was 14 mm below the pigtail level. Valve post-dilation with a 23 × 40-mm balloon was performed in order to reduce periprotesic gradient and guarantee complete adherence of the valve (Fig. 3). At the end of the procedure, the temporary pacemaker was removed.

Post-procedure echocardiography and chest x-ray were performed to evaluate the presence of possible complications and confirm TAVI success. Specifically, the trans-thoracic two-dimensional echocardiogram showed normally

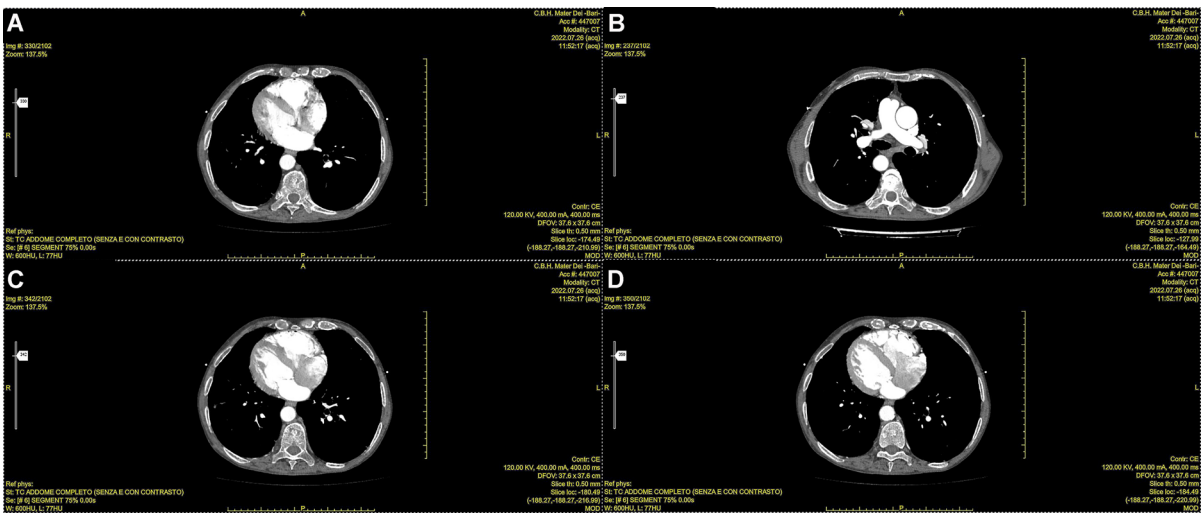

Fig. 1 Computed tomography (CT) scans of the thorax showing the situs inversus. Specifically, the CT scans outlined the inversion of the sites of heart and great vessels

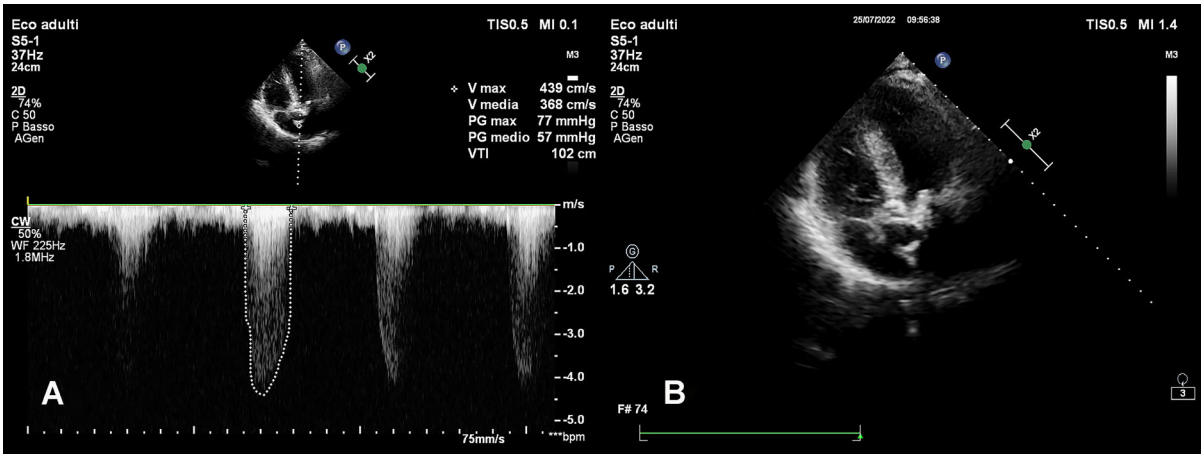

Fig. 2 Echocardiographic evaluation. **a** Mean and maximum gradient at the aortic root level, **b** B-mode identification of the aortic root and valve via apical view

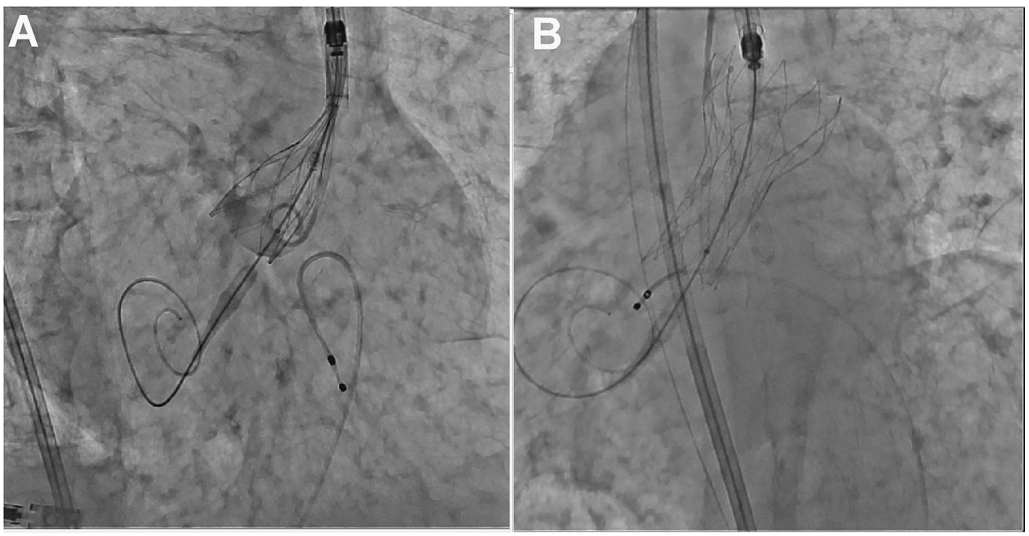

Fig. 3 Percutaneous implantation of the prosthetic aortic valve. **a** Initial release of the bioprosthesis, **b** final result after the complete release of the bioprosthesis

positioned bio-prosthesis, absence of trans-prosthetic gradient (medium gradient: 5 mmHg), and mild-to-medium peri-prosthetic leak.

On August 2022 the patient was safely discharged from the hospital to his home.

DISCUSSION

In this case report we describe the unique case of a patient with NP disease, situs inversus, and severe aortic stenosis who successfully underwent the TAVI procedure.

Cardiovascular diseases are common in persons with ASMD phenotypes, both at an early age and during adulthood; consequently, a well-designed cardiologic follow-up is usually necessary for these patients [6–9, 11, 12]. The cardiac diseases which may develop include valvular heart disease, heart failure, and coronary artery disease. The latter is presumably related to the atherogenic lipid profile found in most patients affected with type B NP disease,

while heart failure may be caused by pulmonary failure or ischemic heart disease, while the precise mechanism for valvular heart disease is not known. Several cases of severe mitral insufficiency and aortic stenosis have been reported in the literature, both in children and in adult patients similar to the case reported here [6–9, 11, 12].

Patients with ASMD suffering from cardiac valvular defects can be treated with medications and/or by surgery, but new therapeutic strategies should be considered. Specifically, TAVI may be considered the treatment of choice in persons with severe aortic stenosis in relation to the complex clinical features of these patients. While data on complications in patients with ASMD who underwent valve replacement surgery are reported in the literature [7], no data currently exist on the use of TAVI in patients with ASM. Indeed, the need for a comprehensive registry for the clinical management of NP patients could be beneficial.

Only a few cases of patients affected by ASMD who were diagnosed with severe aortic stenosis have been reported in the literature [9]. Most of these patients were treated by aortic valve repair and developed complications up to the exitus. However, a few cases of patients with situs inversus who underwent TAVI are also described in literature [13–15].

Our patient presented with two rare pathological conditions, namely, situs inversus and NP disease, together with concomitant comorbidities. Although clinical experience with such a case has not been described in the literature, our team considered him to be eligible for TAVI, which was successfully performed.

Although further studies are required, we do consider TAVI as a possible treatment of choice to repair severe aortic stenosis in patients suffering from ASMD.

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Disclosures. Daniele De Feo, Anna D'Anzi, Vincenzo Pestrichella, Pietro Scicchitano, Carlo Lafranceschina, Vito Caragnano, Fabio Tiecco, Antonella Scialpi, Giuliana Laronga, Marco Matteo Ciccone, and Sabino Iliceto have nothing to disclose.

Compliance with Ethics Guidelines. Written informed consent was obtained from the patient for the publication of this case report. The name and surname of the patient has been removed. The study was carried out in compliance with the 1964 Helsinki Declaration and its subsequent amendments.

Data availability. Data will be available on request by contacting the corresponding author.

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