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Case Report

Challenging clinical management of a patient with Gaucher disease type IIIC homozygous for the D409H mutation, aortic valve calcification and porcelain aorta

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ABSTRACT

Background. Gaucher disease is a rare lysosomal storage disorder caused by glucocerebrosidase enzyme deficiency resulting in the cumulative deposition of glucocerebroside in macrophages, predominantly effecting bone marrow, liver and spleen. Gaucher disease type IIIC is a rare subtype that is characterized by cardiovascular involvement, eye-movement disorders, and late-onset neurological symptoms.

Case presentation. We present a 14-year-old adolescent boy diagnosed with Gaucher disease type IIIC at age four with a homozygous D409H mutation who developed severe aortic valve stenosis, extensive aortic calcification and a porcelain aorta despite enzyme replacement treatment since the diagnosis. Despite the challenges during the cardiac surgery, we successfully performed transcatheter aortic valve implantation (TAVI). The patient developed a complete atrioventricular block and required a pacemaker after the TAVI. He experienced further complications during the follow-up.

Conclusion. The case presents the challenges in the treatment of cardiovascular complications in patients with Gaucher disease and demonstrates the importance of individualized treatment approaches, as well as the potential advantages and complications of TAVI in difficult situations like this.

Key words: Gaucher disease type IIIC, D409H mutation, porcelain aorta, transcatheter aortic valve implantation (TAVI).

Gaucher disease is a rare autosomal-recessive lysosomal storage disorder caused by glucocerebrosidase enzyme deficiency.[1] Enzyme deficiency results in the cumulative deposition of glucocerebroside in macrophages, predominantly influencing the bone marrow, liver and spleen. It is classified into three main subtypes according to the patient's clinical presentation. Gaucher disease type IIIC (OMIM #231005) is a rare subtype and characterized by cardiovascular involvement, eye-movement disorders and late-onset neurological symptoms.[2] Cardiovascular involvement includes calcification in the aortic and mitral valves and the aorta.[3-6]

Porcelain aorta is characterized by nearly or completely circumferential calcification of the ascending aorta and/or aortic arch, poses significant challenges during cardiac surgeries such as aortic valve replacement and coronary artery bypass grafting. This extensive

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calcification blocks safe aortic cross-clamping or cannulation, increasing the risk of complications like aortic embolization, dissection, or rupture.[7] Although a porcelain aorta is commonly associated with atherosclerosis in adult patients, it may also appear as non-atherosclerotic in states such as systemic inflammatory diseases, radiation-related and chronic renal failure.[8] We present an adolescent patient with Gaucher disease type IIIC who developed significant aortic valve stenosis (AS) and porcelain aorta due to calcifications. He was managed with various catheter interventions and cardiac surgery. To the best of our knowledge, our patient is the first Gaucher type IIIC patient to undergo a TAVI procedure for severe AS and porcelain aorta due to calcifications.

Case presentation

The patient was diagnosed with Gaucher disease type IIIC at 4 years old by low glucocerebrosidase enzyme levels and the presence of Gaucher cells in the bone marrow histopathological examination. The glucocerebrosidase enzyme level was 0.87 nmol/s/mgp (normal range, 5-13.5). A homozygous D409H genetic mutation was identified. During the follow-up, despite periodic enzyme replacement therapy since the diagnosis, he had progressive AS due to calcifications. Echocardiography at 14 years showed an aortic valve with thick and immobile leaflets, severe AS with a mean gradient of 38 mmHg, left ventricular (LV) hypertrophy and mild thickening of the mitral valve and mild mitral regurgitation. Percutaneous left heart catheterization showed that the LV systolic pressure was 210 mmHg, and a 97 mmHg systolic pressure gradient was measured at the level of the aortic valve. After discussion with the cardiac surgeons, it was determined that a surgical prosthetic aortic valve replacement would be the initial treatment. However, when the median sternotomy was performed and the pericardium was opened, it was observed that the patient had extensive calcifications in the ascending aorta and the aortic arch, therefore, aortic cross clamping could not be performed. As the coronary buttons were also calcified, the patient was considered inoperable. Further discussions with the adult cardiologists led to the decision to perform transcatheter aortic valve implantation (TAVI). Cardiac computed tomography (CT) before the intervention showed that the aortic annulus diameter was 24x20 mm (+0.2 z score) with a circumference of 70 mm, and a surface area of 3.8 m^2. The left main coronary artery was located 10 mm away, while the right coronary artery was 14 mm away from the aortic annulus, sinus of Valsalva diameter was 25x26x26 mm (-0.8 z score) and the ascending aorta diameter was 17x20 mm (-0.7 z score). During the procedure, using the femoral artery access. Boston Scientific Amplatz Super Stiff™ guidewire was introduced into the LV. A 23-mm self-expandable Medtronic the Evolut™ R valve was placed over this wire in the appropriate aortic valve position. After TAVI, echocardiography showed no pressure gradient at the aortic valve and mild aortic regurgitation.

The patient was followed-up with periodic echocardiographic evaluations. After 18 months following the TAVI procedure, he complained of episodic dizziness. Electrocardiogram (ECG) showed a complete atrioventricular (AV) block. 24-hour ECG monitoring (Holter) revealed episodic 2:1 AV complete block with rare 1:1 transmission and an escape rhythm characterized by narrow QRS complexes. The average heart rate was 43 beats, minimum heart rate was 36 beats, and the maximum heart rate was 83 beats per minute. A transvenous pacemaker was implanted. The left subclavian vein was catheterized via an extrapleural approach and a transcatheter 58 cm Medtronic SelectSecure™ Model 3830 lead was implanted in the septal region. A Vitatron™ G20A2 pacemaker battery was placed in the left pectoral area.

Two months post-pacemaker installation, he experienced persistent fever, and echocardiographic assessment revealed a vegetation on the mitral valve. During the

medical treatment for infective endocarditis (IE) with intravenous antibiotics, echocardiography showed mitral cord rupture due to IE and severe mitral regurgitation. He underwent surgery again, and a redo-sternotomy was performed. This time he had femoral cannulation due to the presence of a calcified porcelain aorta. The femoral artery, femoral vein, and superior vena cava were selectively cannulated. The heart was fibrillated at 28 °C and the left atrium was accessed by performing a right atriotomy on the beating heart. The mitral valve was found to be significantly deformed with two of the chordae in the anterior leaflet being ripped. The mitral valve was excised and replaced with a 25 mm St Jude™ mechanical prosthetic valve. The surgery was successfully completed without complications. Figure 1 displays the patient's cardiac images in chronological order.

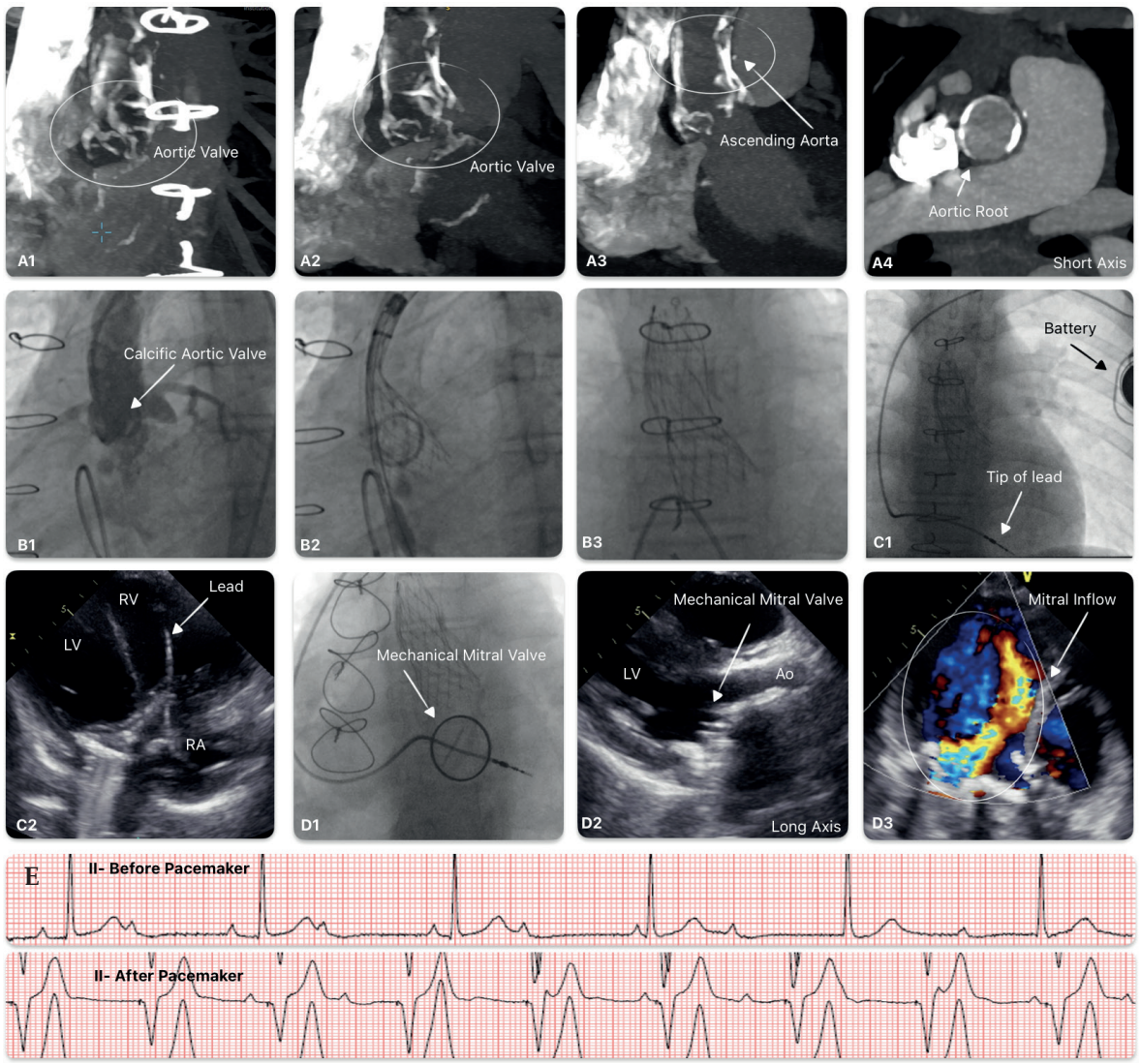

Fig. 1. Summary images of interventional procedures and imaging performed on the patient. **A:** Cardiac tomography images showing calcific aortic valve, aortic root and ascending aorta before the transcatheter aortic valve implantation (TAVI) procedure. **B:** Angiographic images of the TAVI procedure. **C:** Images showing the pacemaker implantation. **D:** Angiographic and echocardiographic image showing the prosthetic mitral valve and mitral stenosis in the prosthetic valve during the follow-up. **E:** Electrocardiographs before and after pacemaker implantation.

Fifteen months after the prosthetic mitral valve replacement, he started to complain about a chronic cough and intermittent dyspnea. Echocardiographic evaluation showed aortic and mitral valve stenosis and pulmonary venous hypertension. An average 15 mmHg gradient was measured at the level of the aortic valve; and an average 16 mmHg gradient was measured at the level of the mitral valve with continuous wave Doppler. The mean pulmonary pressure was calculated as 35 mmHg based on mild pulmonary insufficiency flow. No significant aortic valve insufficiency was observed. Surgery and other transcatheter treatment options were postponed due to a high risk of complications and family concerns. Currently, the patient is stable and has no dyspnea with intensive oral diuretic treatment, including oral furosemide, chlorothiazide and aldactone combinations.

Informed consent was obtained from the patient and his family to share patient clinical information and imaging photographs anonymously for scientific purposes.

Discussion

Gaucher disease type IIIC is a rare variant of Gaucher disease that is determined by a distinctive phenotype with homozygous D409H mutation. The presence of this mutation has been associated with the development of oculomotor apraxia and cardiac calcification.[2,9] Our patient with Gaucher disease type IIIC had extensive calcifications on the aortic valve, ascending aorta and aortic arch resulting in a porcelain aorta. It has been reported that in patients with Gaucher disease type IIIC, calcifications may involve intracardiac structures like mitral and aortic valves, and may also extend into the aorta.[2-5,10,11] Our patient had both AS and a porcelain aorta due to calcifications, but did not have a mitral valve involvement, however mitral valve was also involved due to IE.

It has been reported that the existence of calcific aortopathy may increase the possibility of developing ischemic heart disease over an extended period of time.[12] Our patient did not present with findings of ischemic cardiomyopathy. This may be due to the fact that he is still in the pediatric age group and does not have additional comorbidities which are usually present in adults. Porcelain aorta is typically associated with atherosclerosis and systemic inflammation in older adults. However, the condition can also occur at a young age due to infectious and genetic factors, such as Gaucher disease, aortitis, and Singleton Merten syndrome, in children.[13]

In patients with porcelain aorta, difficulties in aortic cross-clamping and embolization risk during the cardiac surgery have led to the consideration of the TAVI procedure as an alternative and appropriate choice.[14-17] Porcelain aorta may be considered a relative contraindication for surgical valve replacement when there is severe AS.[17] However, in children, the best course of action is to perform surgery as the initial treatment due to the patients' longer lifespan and the lack of cumulative experience with TAVI in children. Therefore, our initial decision was to perform surgery in our patient.

The presence of a porcelain aorta is a separate factor that can predict an increased risk of pacemaker requirement after TAVI.[18] Our patient also required a pacemaker implantation due to the development of a complete AV block, 18 months after the TAVI procedure. Therefore, in patients with porcelain aorta, especially after the TAVI procedure, close monitoring of the symptoms and performing periodic ECG and Holter examinations is essential.

In patients with a porcelain aorta who needs cardiac surgery (aortic and/or mitral valve replacement), it is usually difficult or impossible to perform aortic cross-clamping due to extensive calcifications or significant deposits of plaque throughout the ascending aorta, requiring the use of innovative approaches.[19,20]

In patients with severe AS and a porcelain aorta, TAVI has become a crucial therapeutic method. It provides a less intrusive option compared

to conventional surgical methods. However, during the patient follow-up, complications may occur that are predictable, such as pacemaker requirement, or unpredictable, such as mitral cord rupture as in our case.

In conclusion, cardiac involvement may be an important cause of mortality and morbidity in patients with Gaucher disease. Therefore, close cardiac follow-up should be performed. We presented the challenges in the treatment of cardiovascular complications in patients with Gaucher disease type IIIC and demonstrated the importance of individualized treatment approaches, as well as the potential advantages and complications of TAVI. To the best of our knowledge, our patient is the first Gaucher disease type IIIC patient who receieved TAVI procedure for severe AS and porcelain aorta due to calcifications.

Ethical approval

Informed consent was obtained from the patient and his family to share patient clinical information and imaging photographs anonymously for scientific purposes.

Author contribution

The authors confirm their contribution to the paper as follows: Study conception and design: MÖ, EA, HD, HHG, İE, MG, EBK; data collection: MÖ, EA, İE; analysis and interpretation of results: MÖ, EA; draft manuscript preparation: MÖ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declares that there is no conflict of interest.

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