Case Reports

Widespread Vasculopathy in a Patient with Morquio A Syndrome

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Morquio A syndrome (mucopolysaccharidosis IV type A), an autosomal recessive lysosomal storage disorder caused by a defective N*-acetylgalactosamine 6-sulfatase gene, leads to lysosomal accumulation of keratan sulfate and chondroitin 6-sulfate. This accumulation affects multiple systems and causes notable cardiovascular manifestations, such as thickening of the left-sided valves, ventricular hypertrophy, and intimal stenosis of the coronary arteries. There have been few reports of vasculopathy in this population. We present the case of a 58-year-old woman with Morquio A syndrome who was found to have aortic dilation on a routine screening echocardiogram. Magnetic resonance images revealed multiple tortuous, dilated arteries in her head, neck, and abdomen. The diffuse vasculopathy seen in this patient should prompt further study to determine whether this is an underreported phenomenon of clinical significance or an unusual finding in this rare disorder.* ***(Tex Heart Inst J 2017;44(6):420-3)***

Morquio A syndrome (mucopolysaccharidosis IV type A) is a rare autosomal recessive lysosomal storage disorder caused by homozygous or heterozygous pathogenic variants in the *N*-acetylgalactosamine 6-sulfatase gene (*GALNS*) that diminish enzymatic activity of *N*-acetylgalactosamine-6 sulfatase.[1] The disease is characterized by lysosomal accumulation of keratan sulfate and chondroitin 6-sulfate, which leads to various medical issues, such as short-trunk dwarfism, extensive skeletal manifestations, and joint hypermobility.[1] In addition, cardiac involvement, often of the left-sided valves, has been reported in this population,[2,3] but few cases of vasculopathy have been reported. We present the case of a woman with Morquio A syndrome who had aortic dilation with multiple tortuous, dilated arteries of the head, neck, and abdomen.

Key words: *Adult; aorta/pathology; cardiovascular abnormalities; heart valves/pathology; mucopolysaccharidosis IV/complications/diagnosis/diagnostic imaging/pathology*

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Case Report

In 2016, a 58-year-old woman with Morquio A syndrome was referred to our cardiology clinic for evaluation of systemic hypertension. In 2014, an echocardiogram had shown grade 1 diastolic dysfunction with mildly thickened mitral and aortic valves and no significant regurgitation or stenosis. At her primary care physician's office, the patient's systolic blood pressure ranged from 130 to 140 mmHg, and her diastolic pressure was approximately 70 mmHg. She had been taking metoprolol; on the basis of her previous echocardiographic results and mildly elevated systolic blood pressure, her primary care physician started her on verapamil, as well. Whereas the patient had no history of cardiovascular symptoms, she was in chronic pain from orthopedic issues related to Morquio A syndrome. Beginning at age 7 years, she walked with crutches, and, on occasion, used a wheelchair. Multiple fractures and orthopedic problems had necessitated operations for shoulder replacement, total knee replacement, bilateral hip replacement (twice), and cervical fusion of C1-C4.

The patient had been diagnosed with Morquio A syndrome on the basis of clinical and radiologic findings when she was 7 years old. In 1996, the diagnosis was confirmed by enzyme activity testing, which showed a profound deficiency of *N*-acetylgalactosamine 6-sulfatase activity in her fibroblasts (0 nmol/hr/mg protein). We first saw the patient in October 2015, at which time she began therapy with elosulfase alfa. Additional genetic testing revealed a duplication of the short arm on chromosome 17, consistent with Charcot-Marie-Tooth disease. There was no family history of vasculopathies or sudden cardiac death, but her father also had Charcot-Marie-Tooth disease.

At the current presentation, results of the patient's cardiovascular examination were normal. She was normotensive, 2+ distal pulses were present in each of her extremities, and her electrocardiogram showed sinus rhythm. Her echocardiogram revealed mildly thickened aortic valve leaflets and mildly dysplastic mitral and tricuspid valves, without significant valvular regurgitation or stenosis (Fig. 1). There was mild enlargement of the aortic root and ascending aorta, as well as moderate dilation of the sinotubular junction, which had not been seen on the previous echocardiogram. The size of her ventricles and her systolic function were normal. Because of the dilation of her aortic root and ascending aorta, she was continued on β-blocker therapy.

To further delineate the degree of vascular involvement, we obtained magnetic resonance angiograms of the patient's head, neck, chest, abdomen, and pelvis and found extensive abnormalities. In addition to confirming dilation of her aortic root and ascending aorta (the latter of which was 35.78 mm in diameter) (Fig. 2), the images revealed severe tortuosity of the patient's entire descending aorta (Fig. 3) and abnormalities in her circle of Willis vasculature, including tortuous internal carotid and intracranial vertebral arteries, as well as prominent narrowing of the vertebral arteries (Fig. 4). In addition, she had dilation of the right subclavian artery, narrowing of the right carotid artery at the bifurcation of the brachiocephalic artery, narrowing at the origin of the left carotid artery, tortuous iliac arteries, and large, irregular femoral veins. Notable venous abnormalities included multiple areas of dilation involving the right subclavian vein, bilateral jugular veins, and bilateral femoral veins, as well as narrowing of the right brachiocephalic vein.

As of September 2017, the patient had reported no symptoms related to her cardiovascular issues. She was taking her β-blocker for hypertension control. The patient was seen by a geneticist, who did not consider additional testing for aortopathy or other vasculopathy to be indicated. In addition, the geneticist concluded that the vasculopathy was not causally related to the combined Morquio A syndrome and Charcot-Marie-Tooth disease phenotypes.

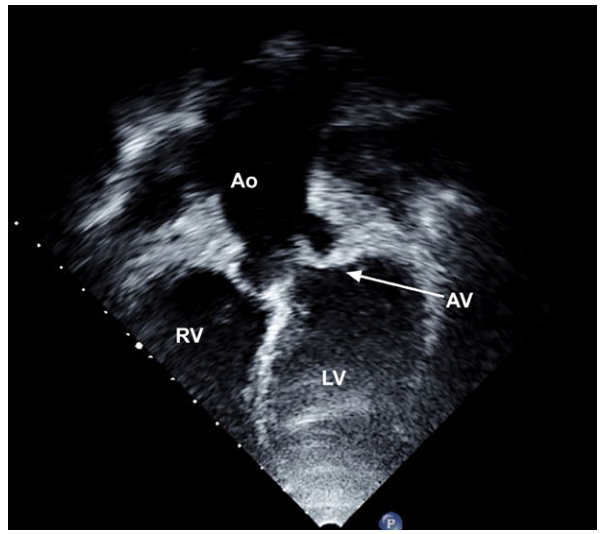

Fig. 1 *Transthoracic echocardiogram (apical 5-chamber view) shows mildly thickened aortic valve leaflets, mild dilation of the aortic root and ascending aorta, and moderate dilation of the sinotubular junction.*

Ao = aorta; AV = aortic valve; LV = left ventricle; RV = right ventricle

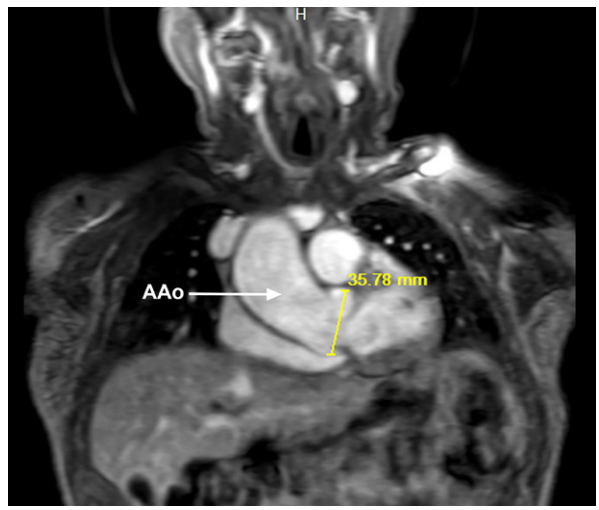

Fig. 2 *Magnetic resonance angiogram of the chest and neck shows a mildly dilated aortic root and ascending aorta (AAo).*

Discussion

Vascular findings are rare but well-described in patients with Morquio syndrome and have implications for cardiovascular monitoring in this cohort.[4,5] Given that long-term data on cardiovascular findings in patients with Morquio syndrome are scarce, our report on one of the oldest patients with the condition indicates that noninvasive imaging for the initial evaluation and monitoring of vasculopathy in these individuals may be appropriate. In addition, although we were unable to evaluate the potential impact of enzyme replacement therapy on our patient's diffuse vasculopathy, further studies are warranted to determine whether such therapy is beneficial and to better characterize the natural history of cardiovascular disease in this population.

In a study of 27 British patients with Morquio A syndrome who died between 1975 and 2010, the mean life expectancy was 17.4 ± 9.5 years before 1990, and it improved to 30.7 ± 10.8 years after 1990. Notable causes of death in these patients were respiratory failure in 63%, cardiac failure in 11%, and myocardial infarction in 4%. No patients in the series died of complications related to vasculopathy.[6]

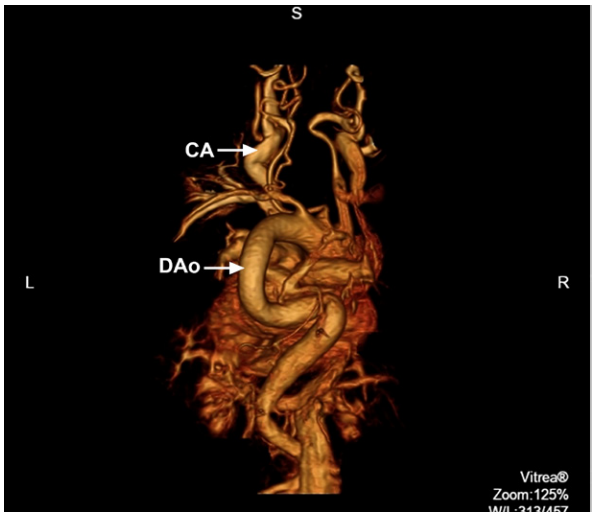

Fig. 3 *Three-dimensional magnetic resonance angiogram of the heart shows marked tortuosity along the length of the descending aorta.*

CA = carotid artery; DAo = descending aorta

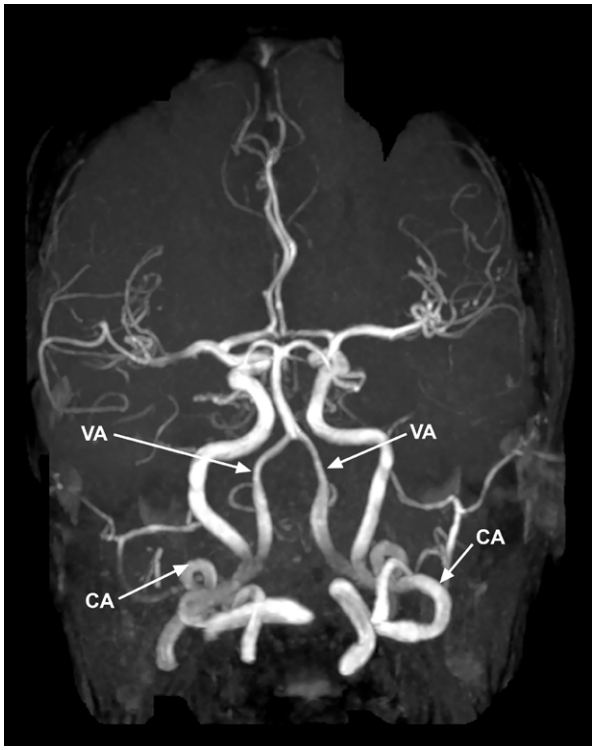

Fig. 4 *Magnetic resonance angiogram of the brain shows the circle of Willis vasculature with tortuous internal carotid and intracranial vertebral arteries. Note the prominent narrowing of the vertebral arteries.*

CA = carotid artery; VA = vertebral artery

Patients with Morquio A syndrome generally have a normal appearance at birth, and symptoms develop as keratan sulfate and chondroitin 6-sulfate accumulate in their tissues. Affected organ systems include the musculoskeletal, pulmonary, ophthalmologic, cardiac, and auditory systems.[1] With regard to the cardiac system, the left-sided valves are most often involved. Typical findings include thickened and shortened mitral valve chordae, thickened and rolled mitral valve edges, and fused aortic valve cusps.[2] In a study of 10 patients with Morquio A syndrome, 5 developed left-sided valvular dysfunction.[3] Additional cardiac findings have included hypertrophy of the myocardium and intimal sclerosis of the coronary arteries.[2,7] Vascular disease has also been described in these patients, although it was not present to the extent seen in our patient.[4,5,8]

There appears to be a subset of patients with Morquio A syndrome who develop vascular disease, but the actual mechanism of the vascular changes is not known. One potential explanation is that collagen dysplasia of the vessels occurs secondary to the progressive changes in the collagen related to the skeletal system. This possibility is supported by histologic evidence of chondroitin 6-sulfate deposition in the aorta of a deceased Morquio A patient with severe cartilage disease.[9] In addition, arterial vasculopathy may be due to disorders involving the elastin pathway—including Morquio A syndrome—that result in impaired elastogenesis.[10] Regardless of the mechanism of vasculopathy, more patients with Morquio A syndrome are surviving to older age, and there is hope that successful enzyme replacement therapy will further prolong life[6]; therefore, using the tools available to uncover underappreciated late sequelae is important. The current recommendation regarding cardiac screenings for these patients is to obtain electrocardiograms and echocardiograms every 3 years[1]; however, this testing strategy would have missed the widespread disease in our patient. Further investigation is needed to determine whether vasculopathy is an underreported phenomenon of clinical importance or an unusual presentation of disease in patients with Morquio A syndrome.

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