Cardiology in the Young

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Aortic root dilation in a child with Marfan syndrome and mosaic Turner syndrome

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Brief Report

Cite this article: Groner A and Qadir A (2020) Aortic root dilation in a child with Marfan syndrome and mosaic Turner syndrome. *Cardiology in the Young* **30**: 1976–1977. doi: 10.1017/S1047951120003200

Received: 28 January 2020
Revised: 13 August 2020
Accepted: 9 September 2020
First published online: 7 October 2020

Keywords:
Mosaic Turner syndrome; Marfan syndrome; aortic root dilation

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Abstract

Patients with a known genetic cause of aortic root dilation usually have a single underlying aetiology, either a single gene defect as in Marfan syndrome or chromosomal anomaly as in Turner syndrome. However, it is possible, although unlikely, for a patient to inherit multiple independent risk factors for aortic root dilation. We describe such a patient, who inherited Marfan syndrome and a very unusual form of mosaic Turner syndrome. Long-term follow-up of this patient may provide insight into the natural history of this unique genetic combination.

Aortic root dilation and subsequent dissection is an important and commonly fatal medical condition in the adult population.[1] Research over the previous several decades has pointed to underlying connective tissue disorders as an important contribution to this patient population.[1] Many, although not all, connective tissue disorders have a known underlying genetic anomaly and much of their pathology is progressive with a start in childhood. Perhaps the best known and well described genetic cause of aortopathy is Marfan syndrome.[1] Turner syndrome is an additional cause of aortic root dilation, even independent of the presence of a bicuspid aortic valve.[2] Mosaicism attenuates many of the manifestations of Turner syndrome and may lessen the risk of aortopathy as well.[3]

A newborn infant, born at 37 weeks' gestation by vaginal delivery, was transferred to the Neonatal ICU shortly after birth due to ambiguous genitalia. Fluorescence in situ hybridisation panel showed a mosaic pattern of 45,XO (61%); 46,XY (22%); and 47,XYY (17%) cells. Further chromosomal analysis of 53 cultured cells showed a mosaic pattern of 2 abnormal cell lines 45,X (74%) and 47, XYY (26%), with no normal 46,XY cells observed, confirming the diagnosis of gonadal dysgenesis and mosaic Turner syndrome. Additional testing for Congenital Adrenal Hyperplasia showed normal levels of cortisol, adrenocorticotropic hormone, dehydroepiandrosterone, 17-hydroxyprogesterone, and 17-hydroxypregnenolone. It was determined through ultrasound imaging and Urology consultation that definitive testicles were present and the decision was made to raise the child as a male.

Cardiology referral was made after a murmur was noted at the 9-month well child visit. There was no history of cyanosis, feeding intolerance, tachypnea, sweating with feeds, or failure to thrive. An echocardiogram showed a dilated aortic root of 1.8 cm and ascending aorta of 1.3 cm, with approximate z-scores of +3 indexed to body surface area. There was no evidence of coarctation or ventricular dysfunction. The mitral valve appeared normal. The aortic valve annulus was of a normal diameter and shown to be tricuspid. Partial anomalous pulmonary venous return was suspected with a vein from the right upper lobe draining into the superior caval vein. Electrocardiogram at the time showed normal sinus rhythm, normal axes/intervals, and normal voltages.

At 14 months of age, the patient was scheduled to undergo a sedated MRI to better delineate his pelvic and gonadal anatomy. For a more detailed view of his venous anatomy and the extent of his aortopathy, cardiac MRI was extended to include this portion of his anatomy. The cardiac MRI showed dilation to 16 mm of the aorta at the level of the sinus of Valsalva. A small pulmonary vein from the right upper lobe was noted to be draining to the superior caval vein, although there were four pulmonary veins seen draining into the left atrium. The concurrent pelvic MRI was remarkable for undescended bilateral gonadal tissue (in addition to his two scrotal testes), a horseshoe kidney, and a small rudimentary uterus.

The early onset of aortic pathology and mosaicism prompted a referral for further clinical genetics evaluation. It was noted on physical exam that the child had an appreciable amount of joint laxity. Further inquiry of family history revealed that the child's mother had scoliosis, striae, and increased finger length. Further testing revealed that both the child and his mother were heterozygous for the pathogenic variant, c.4336 G > A, p.Asp1446Asn in exon 35 of the *FBN1* gene, confirming a diagnosis of Marfan syndrome. Therefore, he was started on losartan, an angiotensin II-receptor blocker, at an initial dose of 0.6 mg/Kg which was subsequently increased to a goal dose of 1.4 mg/Kg. He has been followed with yearly visits and is currently 6 years of age. His most recent echocardiogram, at 8 years of age, showed a dilated aortic root of

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2.5 cm, z-score + 3.66, and borderline/mildly dilated ascending aorta of 2 cm, z-score +2.14 (z-scores calculated using Pediatric Heart Network database values). This shows an approximate increase of 1 mm per year, respectively, for both since his diagnosis.

It should be noted that the patient was born with ambiguous genitalia and his mother elected to have surgical correction as an infant to identify him as male gendered. While he was noted to have two testes within what was identified as scrotal tissue on ultrasound, his pelvic MRI showed bilateral pelvic gonadal tissue (described as "undescended testes") and a rudimentary uterus. Guidelines from the 2016 Cincinnati International Turner Syndrome meeting defined Turner syndrome as phenotypically female.[4] However, with respect to our patient with 45,X chromosomes ranging from 61% (fluorescent in situ hybridisation) to 74% (cell culture) of cells, rudimentary uterus and bilateral pelvic gonads we feel that gender may not be fully indicative of the underlying pathophysiology.

To our knowledge, this is the first case of aortopathy in a child with concomitant Marfan syndrome and mosaic Turner syndrome. Two prior case reports have described children with non-mosaic Turner syndrome and Marfan syndrome. These include a 15-year-old girl who was found to have Marfan syndrome and 45, XO in all 16 cells studied, who exhibited dilation of the ascending aorta noted on echocardiogram, as well as other manifestations of the 2 syndromes. This included arachnodactyly, scoliosis, vertebral abnormalities, protrusio acetabulae, ectopia lentis, short stature, and primary amenorrhoea[5]. Additionally, Ornek et al. described the anesthetic management of a 3-year-old girl with both syndromes. This patient's cardiac abnormalities included significant mitral insufficiency, mitral valve prolapse, minimal mitral valve stenosis, and an atrial septal defect. She did not show evidence of aortic dilation[6].

The mechanism of aortopathy in Marfan syndrome is thought to be related to abnormal or deficient synthesis of the extracellular matrix protein, fibrillin-1, and resultant dysregulation of transforming growth factor-beta[7]. Elevated transforming growth factor-beta has been correlated with larger aortic roots and more rapid aortic root growth in patients with Marfan syndrome and levels can be used to predict cardiovascular events.[8] Additionally, use of transforming growth factor-beta antagonists has been found to prevent aortic aneurysm and even other non-cardiac sequelae in a mouse model of Marfan syndrome.[9] The literature has varied with regard to the most effective treatment for preventing aortic root dilation and dissection, specifically in regard to the use of beta-blockers versus angiotensin receptor blockers. It was shown that among children and young adults with Marfan syndrome, there were no differences in the rate of aortic dilation, corrective surgery, dissection, or death after 3 years of therapy with losartan or atenolol.[10] Still, losartan may be seen as a more attractive option given the reduced side effect profile when compared to beta-blockers.

In contrast, less is known about the aortopathy associated with Turner syndrome at the molecular level, although recent reports suggest a link with tissue inhibitors of metalloproteinases.[11] However, it is clear that Turner syndrome is an independent risk factor for progressive proximal aortic dilation.[2] Aortic dilation is itself a risk factor for dissection and not surprisingly aortic dissection occurs at a higher incidence in those with Turner syndrome when compared to the general population.[12] This risk is further increased by the presence of a bicuspid aortic valve or hypertension, which are common sequelae of Turner syndrome.

Discussion

The aortopathy seen in our patient could represent a manifestation of his Marfan syndrome, mosaic Turner syndrome, or a product of the combination of the two syndromes. Notably, aortic root dilation is more consistent with Marfan syndrome, but ascending aortic dilation is more typical of Turner syndrome. Therefore, it is possible that both are contributing to the underlying findings. Interestingly, this child also displayed partial anomalous pulmonary venous return, another cardiac manifestation associated with Turner syndrome. Given that the best treatment of aortic dilation associated with Turner syndrome is unknown, losartan was not initiated until the diagnosis of Marfan syndrome was made. More work needs to be done to assess if there is an additive risk of dilation and dissection in patients with multiple predisposing syndromes in order to optimise their treatment and follow-up care.

Acknowledgements. None.

Financial Support. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflicts of Interest. None.

Ethical Standards. The authors assert that all procedures contributing to this work comply with the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975 as revised in 2008.

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