We present images of an asymptomatic 14-month-old girl in whom a heart murmur was noted incidentally at 9 months of age during a mild bronchiolitic illness. She is the second-born child to nonconsanguineous white parents. There is no paternal family history of tall stature, sudden death, or cardiovascular or musculoskeletal problems. The father is 43 years old and 170 cm tall and had a normal echocardiogram. There is no family history of Marfan syndrome or Loeys-Dietz syndrome. The mother was adopted and her family history is not known. She is 46 years old, 161 cm tall, with well-treated hypothyroidism. Her echocardiogram showed normal intracardiac anatomy and only mild left ventricular hypertrophy. The other sibling, 4 years of age is well with normal echocardiographic findings.

Clinical Presentation and Examination

Our patient was born after an uneventful pregnancy following in vitro fertilization with intracytoplasmic sperm injection. Prenatal scanning was normal with no evidence of congenital heart disease. She was delivered by emergency cesarean delivery with breech presentation, with a birth weight of 3.045 kg. At birth, no murmur or abnormalities were noted except for a lip hemangioma, which has since regressed. She developed without concerns until the age of 8 months when she presented with bronchiolitis.

Examination at the age of 14 months showed the head circumference on the 50th centile (47 cm) and height on the 25th centile (76 cm). She had minimal dysmorphic features with full cheeks, short philtrum, ankyloglossia, no cleft palate but uvula singula, low-set ears, and a facial hemangioma. She had bilateral clinodactyly.

Cardiovascular examination was unremarkable except for a soft ejection systolic murmur best heard at the upper left sternal edge. Peripheral pulses were all palpable, and 4-limb blood pressure was normal (right arm, 99/56 mm Hg; left arm, 95/60 mm Hg; right leg, 109/78 mm Hg; left leg, 101/69 mm Hg).

Imaging Evaluation

Formal ophthalmological examination showed normal optic discs without tortuosity of the retinal vessels and no evidence of lens dislocation. Cranial and abdominal ultrasounds were normal. Radiography of the chest revealed widening of the superior mediastinum (Figure 1). Echocardiography revealed normal intracardiac anatomy with mild concentric left ventricular hypertrophy. The appearances of the aortic arch were extremely atypical with generalized dilatation and tortuosity with significant flow acceleration through the descending aorta (Movies I and II in the online-only Data Supplement). Both angiography (Figures 2 and 3; Movie III in the online-only Data Supplement) and contrast-enhanced computed tomography demonstrated a tight coarctation with tortuosity of the aortic arch and supra-aortic vessels, with abnormal origins of the right innominate and common origin of the left common carotid and subclavian arteries. At catheterization,
the peak-to-peak gradient across the coarctation site was 47 mm Hg (ascending aorta, 117/55 mm Hg; descending aorta, 70/40 mm Hg). The pulmonary vasculature was normal, and there was no patent ductus arteriosus.

Genetic Analysis

Comparative genomic hybridization was undertaken in view of the minor dysmorphic features and was normal. Further testing for fibrillin 1a, 1b, and 4, solute carrier family 2 member 10, transforming growth factor β-receptors 1 and 2, and smooth muscle aortic α actin 2 showed no abnormality. Myosin heavy chain 11 analysis identified a c.2075C>T transition in exon 17. This same transition was identified in the mother.

Management

A surgical repair of the coarctation was deemed necessary, regardless of the results of the genetic analysis. Planning of the operation was aided by reconstruction of the computed tomography images of the aorta as expected to be seen from the surgical access point (Figure 4). Our patient underwent successful surgical repair of the coarctation by a side-to-side anastomosis through a left posterolateral thoracotomy (Figure 5). The child was started on atenolol after the operation. A follow-up echocardiogram (Movie IV in the online-only Data Supplement) and contrast-enhanced computed tomography 6 months later showed satisfactory repair with nonprogressive dilatation of the aorta. Figure 6 shows a preoperative view for comparison with the postoperative view in Figures 7 and 8. The upper- and lower-limb blood pressures remain within normal range without significant gradient.

Discussion

Arterial tortuosity and severe ectasia of the major arteries are extremely rare, and presentation at such a young age suggests
an underlying genetic cause. Few genes and associated syndromes had been identified.

Familial thoracic aortic aneurysm has been described associated with a mutation in smooth muscle aortic α actin 2 (causing thoracic aortic aneurysm 6, Online Mendelian Inheritance in Man [OMIM] no. 611788) and myosin heavy chain 11 (causing thoracic aortic aneurysm 4, aortic aneurysm/aortic dissection, and patent ductus arteriosus, OMIM No. 132900). Myosin heavy chain 11 analysis identified a c.2075C>T transition in exon 17. This same transition was identified in the mother of our patient. This change converts a codon for alanine (GCG) to

Figure 5. Intraoperative view from left the posterolateral thoracotomy showing the distal end of the transverse aortic arch (**), the very tight coarctation (arrow), and the common trunk to the left common carotid artery and left subclavian artery (*) arising from the descending aorta.

Figure 6. Preoperative view of the aorta seen from above at the level of the coarctation (arrow) on an axial contrast-enhanced computed tomography image.

Figure 7. Comparative postoperative view of the aorta seen from above at the level of the previous coarctation (arrow) on an axial contrast-enhanced computed tomography image.

Figure 8. Reconstruction of contrast enhanced multidetector computed tomography images of the aorta seen from a left posterosuperior aspect 6 months after the surgical repair showing the absence of recoarctation at the site of repair (arrow).
a codon for valine (GTG; Ala692Val). Although not previously reported as either a mutation or a polymorphism, the alanine in that position is normally highly conserved in 15 of 16 species. However, the clinical phenotype is not compatible with thoracic aortic aneurysm 4, and the findings of the same variant in the mother, who has no evidence of aortic dilatation at the age of 46, would suggest that the variant identified is not pathological.

Loeys-Dietz syndrome is an autosomal-dominant aortic aneurysm syndrome with widespread systemic involvement (Loeys-Dietz syndrome, OMIM No. 609192). The different types are caused by mutations in the transforming growth factor β-receptor 1 and 2 genes. As stated above, these analyses did not show any abnormality, and the child did not have any of the other characteristic clinical features (hypertelorism, bifid uvula, or cleft palate).

Marfan syndrome (OMIM No. 154700) is a systemic connective tissue disorder characterized by abnormalities in the skeletal, ocular, and cardiovascular systems. Such clinical presentation would be extremely unusual. The findings of the normal fibrillin 1 analysis, which includes multiplex ligation-dependent probe amplification, would exclude Marfan in 70% to 90%. In addition, the lack of clinical features of Marfan syndrome means this is not a likely diagnosis.

Arterial tortuosity syndrome (OMIM No. 208050), associated with mutations in the SLC2A10 gene, is a rare, autosomal-recessive, connective tissue disorder characterized by tortuosity and elongation of the large- and medium-sized arteries with aneurysm formation and vascular dissection, as well as stenoses of the pulmonary arteries. It is usually associated with extravascular manifestations, including dysmorphism (down-slanting palpebral fissures, micrognathia, high-arched palate), hyperextensible skin, cutis laxa, hernia, skeletal abnormalities, and joint hypermobility. Arterial tortuosity syndrome shows clinical overlap with other connective tissue disorders characterized by vascular fragility such as the Loeys-Dietz and Marfan syndromes, which could be related to alteration of similar molecular pathways. In these disorders, aortic aneurysm is associated with increased transforming growth factor β signaling, altered collagen deposition, and elastic fiber disarray.

Conclusions

Such severe arterial tortuosity, stenosis, dilatation, and aneurysms of the medium- and large-sized vessels in this child were highly suggestive of arterial tortuosity syndrome, but genetic analysis of the transforming growth factor β-receptors 1 and 2 and solute carrier family 2 member 10 did not show any abnormality, and the patient does not present with its extravascular and dysmorphic features.

There remain many patients and families with aortic root dilatation and arterial tortuosity for which no underlying genes have been identified to date. This type of patient remains a challenge, particularly when they present so young and when the prognosis and the possible need for future surgery are unknown. Studies of the arterial tissue from such affected individuals and family may give further information in the future.

Disclosures

None.

References


Key Words: Aortic coarctation • Arterial tortuosity syndrome • Thoracic aortic aneurysm
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