Cardiovascular findings in a boy with arterial tortuosity syndrome: case report and review of the literature

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Arterial tortuosity syndrome (ATS) is a rare hereditary, autosomal recessive, connective tissue disorder. Herein, we describe a five-year-old boy. He had hyperextensible skin, atypical facial features and inguinal hernia. We present his vascular imaging studies of kinking and tortuosity of the aorta and bilateral multiple peripheral pulmonary artery stenoses determined by conventional and magnetic resonance angiographic (MRA) examination. ATS must be considered in patients with connective tissue condition associated with diffuse arterial changes and involvement of the skin, joints and other organs. Vascular imaging studies, especially MRA, are useful in the screening of these vascular abnormalities.

Key words: arterial tortuosity syndrome, cardiovascular findings, magnetic resonance angiography, children.

Arterial tortuosity syndrome (ATS) is a rare hereditary, autosomal recessive connective tissue disorder. The clinical presentation is quite variable; the most common clinical features are tortuosity and elongation of the major arteries, pulmonary artery stenosis, pulmonary hypertension, hernia, dysmorphic facial features, and skin and joint laxity, suggesting a connective tissue disorder[1-4]. Here, we describe a five-year-old boy. He had hyperextensible skin, atypical facial features and inguinal hernia. We present the results of his vascular imaging studies of kinking and tortuosity of the aorta determined by conventional and magnetic resonance angiographic (MRA) examination. We also review the clinical findings of 47 patients with ATS reported in the literature.

Case Report

A five-year-old boy was referred to our department because of a murmur and increase in dyspnea, fatigue and cyanosis during his usual game activity. He underwent an operation at the age of one year because of right-sided inguinal hernia. According to the family history, he was the first child of healthy consanguineous parents. Two previous pregnancies of his mother ended with spontaneous abortion in the first trimester. His father also had hyperextensible joints, especially his shoulder joint, which had habitually dislocated in the past (4 times). Physical examination revealed that the patient's weight and height were appropriated for age. Peripheral pulses and blood pressure were normal in all extremities. He had a soft and hyperelastic skin. He was also noticed to have atypical facial features consisting of unilateral preauricular skin tag, downslanting palpebral fissures, beaked nose, and prominent upper lips. A third-degree systolic ejection murmur and fixed split and loud second heart sound were heard on the right and left second intercostal spaces. Chest radiography revealed that there was no cardiomegaly, but bilaterally increased bronchovascularity, prominent pulmonary conus and mild dilatation of the left pulmonary artery (LPA) were noted. Electrocardiography revealed indeterminate axis, pure R waves (8 mm) in the precordial V1 derivation and decreased R waves amplitude in the precordial V6

derivation. An echocardiographic examination was performed, and the size of ventricles and systolic function were found in normal ranges. Mild ventricular hypertrophy was revealed (interventricular septum thickness: 10 mm) and first-degree aortic regurgitation was demonstrated by echocardiography. Mild stenosis of both pulmonary arteries was also determined with a peak velocity of 2.5 m/seconds (sn). Echocardiography showed a mild dilation of the ascending aorta (22 mm) and an anomalous tortuous course of the aortic arch, with a systolic gradient of 37 mmHg measured in the distal part of the descending aortic arch. We thus suspected pseudocoarctation of the aorta.

Magnetic resonance (MR) imaging demonstrated a mild dilation of the ascending segment of the arcus aorta (23 mm), changing configuration of the distal arcus aorta, and tortuosity of the distal aortic arch. At the level of the diaphragm, the thoracic aorta had a severe right-sided kinking, tortuosity and elongation (Fig. 1). The course of the infradiaphragmatic abdominal aorta was normal. Conventional cineangiographic examination of pulmonary arteries showed multiple segments of sequential stenosis and dilatation in distal parts of both pulmonary arteries. The pressure gradients

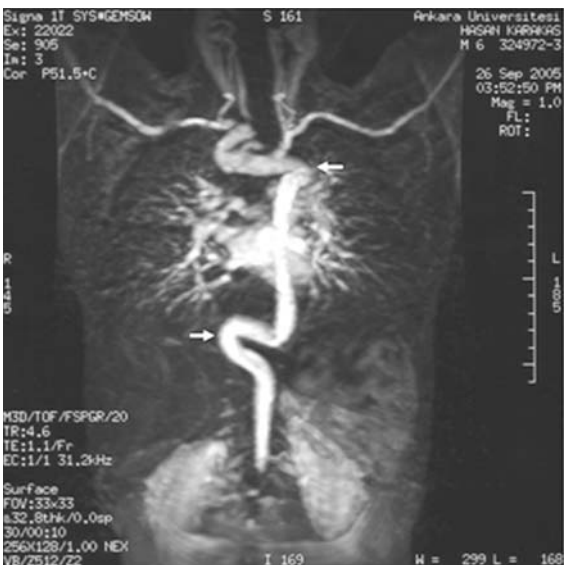

Fig. 1. Magnetic resonance imaging demonstrated the changing configuration of the distal arcus aorta and tortuosity of the distal aortic arch. At the level of the diaphragm, the thoracic aorta had a severe right-sided kinking, tortuosity and elongation.

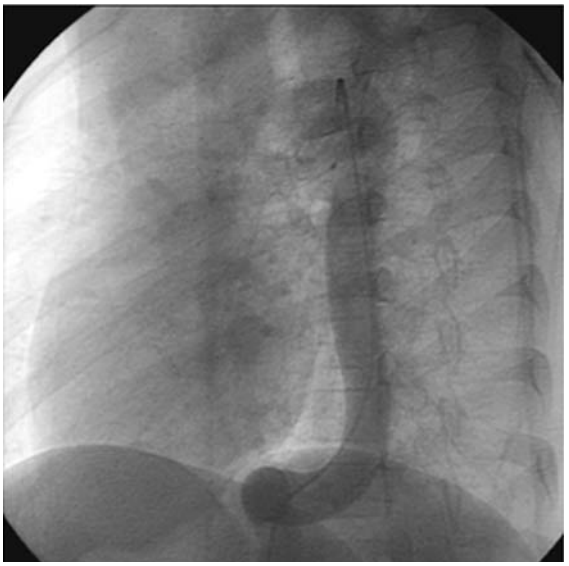

Fig. 2. Angiographic imaging demonstrated that the descending aorta in the distal part of the subclavian artery and infradiaphragmatic portion of the abdominal aorta had a severe tortuosity and elongation.

between the main pulmonary artery (MPA) and right pulmonary artery (RPA) and between the MPA and LPA were calculated as 52 mmHg and 50 mmHg, respectively. Angiographic imaging also demonstrated that the descending aorta in the distal part of the subclavian artery and infradiaphragmatic portion of the abdominal aorta had a severe tortuosity and elongation (Fig. 2). His external ocular examination and renal Doppler ultrasonographic examination were found normal.

We have followed the patient for five years with echocardiographic examinations. He underwent an operation at the age of eight years because of right-sided inguinal hernia. He is currently 10 years old and has recently suffered recurrent chest pain on physical activity. He had the same clinical findings that were previously described and there were no additional pathological findings. Chest radiography, standard resting electrocardiography and echocardiographic examinations did not change, except for mild increase in aortic regurgitation. An exercise-induced electrocardiography and a 24-hour Holter monitoring displayed no dysrhythmia or ischemic findings. Troponin–I level was measured several times and found in normal ranges. Cardiac catheterization revealed that no additional vascular abnormalities had developed

in major arteries in this period. In contrast to his earlier cardiac catheterization, multiple sequential dilatations rather than stenosis in distal parts of both pulmonary arteries were observed, and the pressure gradients between the MPA and its two branches had disappeared (Fig. 3). The pressure gradients between the MPA and RPA and between the MPA and LPA were calculated as 12 mmHg as 11 mmHg, respectively. The coronary arteries were found in normal dimension and location with three-dimensional reconstructed multidetector computerized tomographic imaging of the coronary arteries.

Discussion

Arterial tortuosity syndrome (ATS, OMIM 208 050) is a very rare connective tissue disorder associated with elongation, tortuosity, stenosis, and aneurysms of the large and middle-sized arteries. Connective tissue features including hyperextensible skin, hypermobility of joints and characteristic facial features have been also described in several families[1,2,5-14]. Inguinal herniae[6,8-11,13], arachnodactyly[5,6,8] and muscular hypotonia[8,10,13] have been sometimes observed (Table I). The symptomatology and clinical outcome appear to relate directly to the degree of arterial stenosis.

Table I. The Most Common Clinical Findings of Patients with Arterial Tortuosity Syndrome (References: 1-14)

1. Cardiovascular abnormalities
   a. Arterial tortuosity and lengthening: the major and middle arteries (aorta, carotid, coronary, pulmonary, vertebral, intracerebral, and renal arteries)
   b. Arterial aneurysms (aorta, carotid, coronary, pulmonary, and renal arteries)
   c. Arterial stenosis: peripheral stenosis of pulmonary arteries or severe pulmonary valve stenosis, severe renal arterial stenoses
   d. Ventricular hypertrophy
   e. Hypertension: pulmonary or systemic
2. Distinctive facial features: Downslanting palpebral tissues, beaked nose, soft nasal cartilage, blepharophimosis, long face, high-arched palate, cleft palate, prominent ears, micrognathia, strabismus
3. Skin findings: Cutis laxa, soft/thin/redundant skin or hyperextensible skin, ecchymosis
4. Joint findings: Joint laxity, contractures
5. Hernia: Inguinal, umbilical, gastric or diaphragmatic hernia
6. Others: Acrocyanosis, keratoconus, hypotonia, obesity, arachnodactyly, mental retardation, hip dislocation, hypothyroidism, myopia, chest deformities

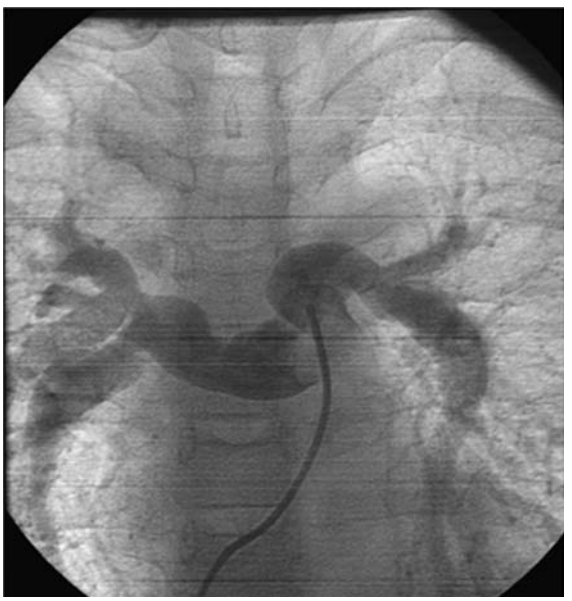

Fig. 3. Angiographic evaluation revealed multiple sequential dilatations in the distal parts of both pulmonary arteries.

In all ATS patients, the results of collagen type I and type III biosynthesis studies were normal on skin fibroblasts[6-8,12]. Histologic findings on autopsy of two affected children showed arterial changes with disruption of elastic fibers of the media and fragmentation of the internal elastic membrane as well as mucosal and transmural necrosis of the stomach, small bowel and colon and extensive necrosis of the liver[5,6]. The constellation of abnormalities suggests a genetic syndrome of connective tissue etiology[1-14].

Connective tissue diseases including Ehlers-Danlos syndrome, wrinkly skin syndrome, Gerodermia osteodysplastica, Marfan syndrome, cutis laxa, and Menkes disease present typical features consisting of hyperelastic or lax skin, laxity of joints, chest and spine deformities, herniae, and cardiovascular anomalies that mimic ATS. Clinical assessment, ultrastructural analysis of the skin, molecular studies of

the genes involved, analysis of the collagens produced in cultured fibroblasts, and quantification of the plasma levels of copper and ceruloplasmin may help differentiate among the different forms of the disease. Severe vascular involvement with tortuosity, elongation, aneurysms, or stenosis of the mid- and large-sized vessels are infrequent in these diseases, and when they are observed, ATS should be considered[12,13].

We could not undertake molecular studies of the genes involved or analysis of the collagens produced in cultured fibroblasts. However, the angiographic images of our patients were characteristic for ATS, as he had severe vascular involvement with tortuosity, elongation and stenosis of the mid- and large-sized arteries, which suggest ATS. We also noticed multiple sequential peripheric pulmonary arterial dilations rather than stenoses had persisted and aortic tortuosity had not increased over time.

Arterial tortuosity syndrome (ATS) is transmitted in an autosomal recessive mode. Gardella et al.[9] reported an Italian family with ATS. Five patients showed signs of disorganization of the extracellular matrix of fibronectin and of actin microfilaments in cultured skin fibroblasts. They performed the linkage analysis of the genes involved in Ehlers-Danlos syndrome and other connective tissue disorders and pointed out that ATS is a distinct clinical and molecular entity. In a genetic study including 11 ATS patients, Coucke et al.[15] described the mapping of the ATS gene to a small region on chromosome 20q13 that determines abnormalities of the elastin network in the major arteries.

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