Young Woman Affected by a Rare Form of Familial Connective Tissue Disorder Associated With Multiple Arterial Pulmonary Stenosis and Severe Pulmonary Hypertension

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A woman with skin findings of a connective tissue disorder, typical of Ehlers-Danlos syndrome, was admitted to the Cardiology Division because of signs of congestive heart failure. Electrocardiogram showed sinus tachycardia, signs of right ventricular enlargement and hypertrophy. Echocardiogram showed right ventricular dilatation, and severe tricuspid regurgitation with indirect signs of severe pulmonary systolic hypertension. Chest computed tomography revealed bilateral and diffuse involvement of the peripheral pulmonary arteries, with kinking and elongation of the pulmonary vessels associated with multiple stenoses and post-stenotic dilatation. On artery angiography an elongation of the aortic root with kinking and coiling of the carotid and vertebral vessels was also detected. This young patient exhibited features of arterial tortuosity syndrome, an uncommon connective tissue disorder, with peculiar dysmorphism and clinical signs overlapping Ehlers-Danlos syndrome. (Circ J 2008; 72: 164 – 167)

Key Words: Arterial tortuosity syndrome; Congestive heart failure; Ehlers-Danlos syndrome

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tenosis of the pulmonary artery (PA) may occur as single or numerous lesions located anywhere from the main pulmonary trunk to the smaller peripheral arterial branches. Associated defects are observed in most patients and include pulmonic valvular stenosis, ventricular septal defect, tetralogy of Fallot, and supravalvular stenosis. Several other congenital diseases have been also associated with pulmonary stenosis (eg, rubella and Noonan, William’s, Argille’s and Apert’s syndromes).1–3

Among the several connective tissue disorders, recently a new clinical and molecular entity was recognized as associated with tortuosity and elongation of the major arteries, and often associated with pulmonary stenosis, pulmonary hypertension, and aneurysms. Arterial tortuosity syndrome (ATS) is a rare hereditary disorder characterized by the same clinical skin–joint–vasculature signs of Ehlers-Danlos syndrome (ie, skin and joint laxity, contractures and dislocation, arachnodactyly, inguinal hernias and facial features, recurrent fever, bronchitis and pneumonia).4,5 This connective disorder frequently involves the arterial (systemic and pulmonary) circulation; aneurysms, and less frequently vascular stenoses, are the clinical manifestation of a structural abnormality of the arterial wall.6 Unfortunately, these patients may have major vascular and pulmonary complications, such as rupture of arteries and recurrent bronchitis and pneumonitis.7,8 ATS is typically transmitted in an autosomal recessive mode and the causal gene is still unknown.9,10

although Coucke et al recently mapped a gene for this syndrome to chromosome 20q13.11

Case Report

We report a rare case of a 20-year-old woman affected by ATS with the same clinical skin signs of Ehlersons-Danlos syndrome, admitted to our Cardiology Unit suffering from right chest pain, fever (38°C) and dyspnoea, with signs of right congestive heart failure (ascites and pedal oedema). In the family history her 21-year-old sister had already been found to have the same skin and vascular findings (Ehlers-Danlos signs with severe multiple peripheral arterial pulmonary stenosis).3

The electrocardiogram showed sinus rhythm of 100 beats/min, right axis deviation, increased P wave amplitude, incomplete right bundle branch block and signs of right ventricular hypertrophy and overload (Fig 1).

The echocardiogram color Doppler showed severe PA hypertension (110 mmHg). The right ventricle and atrium were both dilated, with moderate–severe tricuspid regurgitation. The inferior caval vein was enlarged, with mild respiratory excursion. The left ventricular diameter was reduced (Fig 2).

She had been evaluated using right cardiac catheterisation and pulmonary arteriography (Table 1) at 2 years of age and then again at 16 years, with the diagnosis of stenosis/hypoplasia of the major right end left PA and severe stenosis at the origin of the lobar PA segments. Right ventricular angiography showed bilateral arterial pulmonary obstruction with numerous sites of stenosis and post-stenotic dilatation of the peripheral pulmonary arterial tree (Figs 3, 4). The patient and her sister both had an arterial anomaly, with elongation of the aortic arch and kinking and coiling of
carotid and vertebral vessels detected by aortic and carotid artery angiography (Figs 5, 6). To confirm the examination an ultrafast chest computed tomography scan was performed, which demonstrated the pulmonary stenosis and aneurysms and/or kinking of major arterial vessels, with narrowing at the bifurcation of the PA, extending into both the right and left branches with a combination of main and peripheral stenosis at numerous sites (Figs 7, 8); pulmonary

**Table 1 Hemodynamic Data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Pulmonary systolic pressure</td>
<td>110 mmHg</td>
</tr>
<tr>
<td>Pulmonary diastolic pressure</td>
<td>36 mmHg</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure</td>
<td>10 mmHg</td>
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<tr>
<td>Cardiac output</td>
<td>5.5 L/min</td>
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**Fig 1.** ECG on admission.

**Fig 2.** Echocardiogram on admission.
perfusion scintigraphy was normal.

The patient had undergone a genetic study at another institution and it was positive for a mutation in GLUT10; in the present study genomic DNA was extracted from peripheral blood leukocytes by a standard technique. A set of 400 highly polymorphic microsatellite markers (ABI PRISM Linkage Mapping Set Version 2; Applied Biosystems, Foster City, CA, USA) with an average spacing of 10 centimorgans was analyzed on a capillary sequencer (ABI3100; Applied Biosystems) and then the DNA sample was analyzed. The data were processed using Genescan and Genemapper software (Applied Biosystem). Patient DNA
was analysed with microsatellite markers from the Genethon genetic map. Markers were investigated on an ABI3100 capillary sequencer, and alleles were numbered according to length, with the shortest allele being assigned number. MLINK was used to calculate 2-point lod scores between the ATS locus and the markers.

**Discussion**

ATS is a rare autosomal recessive disorder characterized by tortuosity, elongation, stenosis and aneurysm formation in the major arteries, because of disruption of the elastic fibers in the medial layer of the arterial wall. It is caused by mutations in *SLC2A10*, which encodes the facilitative glucose transporter GLUT10; GLUT10 deficiency is associated with upregulation of the TGFβ pathway in the arterial wall, a finding also observed in another syndrome, Loey-Dietz syndrome in which aortic aneurysms are associated with arterial tortuosity. A correct diagnosis gives information useful in preventing rapid progression of the disease, for example, because of pregnancy in affected females, and enables stratification of patients for the risks of aneurysmal rupture. Furthermore, a correct diagnosis is important for familial screening. In the family tree of the present case, a 21-year-old sister had the same skin and vascular findings (the same Ehler-Danlos type skin features), with severe multiple peripheral arterial pulmonary stenosis and elongation of the aortic root, carotid and vertebral vessels; so 2 siblings have clinical manifestations of the syndrome.

Mild to moderate unilateral or bilateral stenoses do not require surgical relief, and numerous stenotic areas are unsuitable for correction, even with intra-operative balloon angioplasty. Well-localized obstruction of a severe degree in the main PA or its major branches may be alleviated by percutaneous transcatheater balloon angioplasty, often accompanied by endovascular stent implantation or bypassed with a tubular conduit. Recently, the effectiveness of angioplasty, with stent implantation or cutting balloon therapy, was evaluated for peripheral pulmonary stenoses, but despite successful dilatation, only modest improvement of the clinical status after the procedure was reported.[12,13] The natural history of peripheral pulmonary stenoses, and of arterial abnormalities as in the present case, are well known, but the consequence could be relevant, considering the severity of the pulmonary arterial stenoses and of pulmonary hypertension and the risk of arterial rupture. In fact, it is difficult to speculate about the prognosis and therapy of these patients because there are no data about the course of this rare disease. Therefore, this case interestingly underlines that the clinical features of 2 different uncommon syndromes can coexist and overlap in the same patient.

**References**