

A case report of a patient with Ribbing disease underlines the connections between the skeletal and cardiovascular complications

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Abstract

A 69-year-old woman suffered from Ribbing disease, a hereditary X autosomal dominant disease with multiple sclerosing dysplasias. However, it is less known that the genetic mutation can often induce cardiovascular complications. The patient had a hypertensive cardiopathy and had been treated with percutaneous coronary angioplasty and stenting because of a myocardial infarction. She was seen because of dyspnea and we detected an aneurysm of the ascending thoracic aorta. The patient underwent surgical repair. In Ribbing disease an up-regulation of genes interferes with the production, processing, or formation of collagen type II and XI. These genetic effects are thought to be specific for osteoblasts and are responsible for the skeletal pathology. However, the defective synthesis of collagen can also induce cardiovascular complications which may be similar to those described in patients with type III Ehlers-Danlos syndrome, with type IV Marfan syndrome, and with osteogenesis imperfecta. Rheumatologists who treat patients with Ribbing disease should seek the advice of cardiologists for the occurrence of cardiovascular complications.

Introduction

A 69-year-old Turkish woman was born with the rare hereditary X autosomal dominant disease MIM ID 601477¹ which is called Ribbing disease (RD) and is characterized by sclerosing dysplasia with endosteal and periosteal bone growth confined to the diaphyses of the long bones.² Some have considered³ that the RD was an aspect of the hereditary diaphyseal dysplasia called Camurati-Engelmann disease,^{4,5} which is related to a mutation in chromosome 19q13.1-13.3 and in the most frequent form (type I) induces a malfunction of the transforming growth factor β 1.⁶ However, the RD and the Camurati-Engelmann disease are distinct disorders.⁷⁻¹⁰ In RD a mutation in the gene map locus in chromosome 20q13.3

has been detected.¹¹ However, not all affected individuals have mutations in one of the identified genes and other unknown genes can cause the pathology.⁹⁻¹¹ In humans the *COL9A2* gene encodes one of the three α chains of type IX collagen, a heterotrimeric molecule usually found in tissues containing type II collagen, a fibrillar collagen and the major collagen component of hyaline cartilage.^{11,12} Mutations in this gene are associated with epiphyseal dysplasia.¹³ In humans, another gene, *COL9A3*, encodes the collagen α 3 (IX) which also found in tissues containing type II collagen.^{11,14} Mutations in the *COL9A3* gene are also associated with multiple epiphyseal dysplasia.^{6,11-14} Briefly, mutations in the *COL9A2* and *COL9A3* genes occur in RD and interfere with the production, processing, or formation of collagen type II and XI. It is accepted that the up-regulation of these genes interferes with the function of osteoblasts and is responsible for the skeletal pathology. However, the defective synthesis of collagen can also induce cardiovascular complications.

Clinical characteristics of patients with Ribbing disease

Since 1980 we are treating 15 patients (3 families) with RD. These patients are of short stature (mean 142 cm, range 138 to 146) and have a slim body. The facial appearance is peculiar, since they have large eyes, thin pinched nose, and thin lips. The skin is thin and translucent, bruises easily and the veins are dramatically visible, particularly across the chest. There is severe dystrophy of the hair and nails. The symmetrical skeletal pathology begins in childhood and become severe at the age of 30-35. The hands (Figure 1) and feet are extremely misshaped. The large joints have normal stability, but small joints in the hands and feet show hyperextensibility.

Cardiac complications

Many patients with RD develop a severe left ventricular hypertrophy and hypertension.¹⁵ In 67% (10/15) of our patients we detected a moderate up to severe concentric left ventricular hypertrophy with relaxation dysfunction; the median age was 38 years (range 31-48). In 60% (6/10) of cases left ventricular hypertrophy was anticipated the occurrence of arterial hypertension by years. Angina pectoris occurred in 33% (5/15) of patients who can be younger than 30 years. Myocardial infarction occurred in 27% (4/15) of our patients and in 3 cases it was combined with severe concentric left ventricular hypertrophy (septum >22 mm) and anomalous coronary arteries (the peripheral epicardial arteries were short, ectatic, presented a corkscrew deformation, and had were multiple plaques). In addition to coronary artery disease the patients also had a dysfunc-

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tion of the microcoronary circulation. In patients with cardiovascular complications various cardiac arrhythmias (mostly atrial fibrillation and ectopic repetitive beats) are common. Other cardiovascular complications occurred in 27% (4/15) of cases: elongation and dilatation of the muscular portions of the thoracic and abdominal aorta (3 patients), fibroelastic degeneration of the mitral valve (3 patients), and of the aortic valve (2 patients). Renal failure related to arteriosclerotic changes of the renal arteries occurred in 2 patients. Lastly, spontaneous rupture of peripheral veins occurred in 4 patients and 2 patients were treated because of collapsed lungs. It is interesting to note that most of our patients with RD have arterial hypertension but other cardiovascular risk factors such as smoking (2/15 patients), diabetes mellitus (2/15 patients), dyslipidemia (2/15 patients) and obesity (1/15 patients) are uncommon.

Case Report

Familial history of the patient

All maternal relatives have RD with arterial hypertension. Three grandparents, the parents, several uncles and aunts (maternal side) and two sisters died of infarction when they were <60-year old.

Personal history of the patient

Both hands (Figure 1) and feet have the typical deformities of the RD. The patient has multiple skeletal problems and received two total hip prostheses (right at the age of 45, left at the age of 47) because of necrosis of the femoral heads. Severe hypertension (up to 230/120 mm Hg) was diagnosed at the age of 40 and was treated with amlodipine and carvedilol; at the age of 58 a combination with candesartan 32 mg and hydrochlorothiazide 12.5 mg was added,

and with this therapy blood pressure was lowered to an average of 142/86 mm Hg. At this time the echocardiogram (ECG) revealed left ventricular hypertrophy with negative T waves (Figure 2). Echocardiography, performed when the patient was 65-year old, found a severe concentric hypertrophy (systolic IVS 24 mm) with normal LVEF (65%), reduced longitudinal shortening (<8 mm) and marked relaxation dysfunction (E/A 0.5, DTI 236 ms, E/E' 19). The patient complained of dyspnea (Class II-III NYHA) without chest pain. When the patient was 66-year old she had a non-ST segment myocardial infarction (NSTEMI). Ventriculography detected a severe left ventricular hypertrophy, a slightly reduced LVEF (<52%) with a hypokinetic contraction of the inferior wall. Coronarography detected diffuse coronary stenoses, with up to 60% stenosis of the RIVA and RCA; the RIA was very long and both the RIVA and RIA were characterized by a cork-screw tortuosity. Figure 3 shows some aspects of the coronary pathology in this patient. The patient was treated with percutaneous transluminal coronary angioplasty/bare metal (PTCA/BM) stenting of the proximal and medial RIVA. The TIMI Risk Score was 2. The patient was treated with clopidogrel 75 mg/day (for 8 months) and with aspirin 100/mg/day (indefinitely) and (even in the absence of dyslipidemia) rosvastatin (20 mg/day). The antihypertensive medications remained unchanged.

Patient's clinical status

The 68-year-old woman was 146 cm tall and weighed 45 kg. She had thin lips and nose. There were typical RD deformities of hands (Figure 1) and feet, hyperkiphosis of the thoracic region of the spine, and total hip prostheses. Both knees presented moderate arthritic pathology. The respiration rate was 18/min. The lungs were clear. When breathing normal air the peripheral oxygen value was 98%. The carotids were palpable with 1/3 loud systolic murmur. Blood pressure was 145/89 mm Hg, pulse 76/min, regular. The jugular venous pulse was <4 cm H₂O. Hearth: the left ventricular impulse was bulging; the heart sounds were rhythmic, the 2nd sound was accentuated over the aorta; a 2/6 loud systolic murmur could be heard over the aorta and the apex. There was moderate venous varicosis of the legs, without signs of thrombophlebitis.

Laboratory

Blood sedimentation rate BSR 18 mm (1st h), normal hematological status, normal hepatic values, creatinine 106 µMol/L (reference value <80) with glomerular filtration rate (GFR) 43 mL/min (MDRD formula, reference value >69), negative D-dimers, NT-proBNP level 290 pg/mL (reference <200).

Stress-echocardiography

The resting ECG (Figure 4) shows a relevant left ventricular hypertrophy with *giant T waves*. This electrocardiographic pattern is usually seen in rare cardiomyopathies with a marked apical hypertrophy. At rest the echocardiogram detected a left ventricle with normal dimensions (EDV 40 mm), severe concentric hypertrophy (systolic IVS 25 mm), normal LVEF (63%), reduced longitudinal shortening (8 mm) and asyneresis of the medial and apical segments of the inferior wall with a normal contraction of the other segments; the relaxation phase was abnormal (E/A 0.5, DTI 257 ms, E/E' 21); the left atrium was enlarged (LAVi 35 mL/m², reference value <24); the ascending aorta was enlarged, up to 51 mm. The exercise was stopped because of dyspnea at a low heart rate (92/min). The ECG was unchanged. In the echocardiogram, the left ventricular dimensions and the dyskinesia were unchanged, and the LVEF was almost unchanged (70%).

Computed tomography of the chest

The ascending aorta was enlarged up to 52 mm and in relation to the small body surface of the patient the enlargement was severe. The aortic arch (32 mm), descending aorta (27 mm), suprarenal abdominal aorta (22 mm) and infrarenal aorta (17 mm) had a normal



Figure 1. Hands of the patient. Typical deformities of a Ribbing disease: symmetric changes with abnormal length of the fingers (especially the 2nd and the 3rd) and enlargement the distal phalanx of the thumb. Also, swelling and altered axis of several joints.

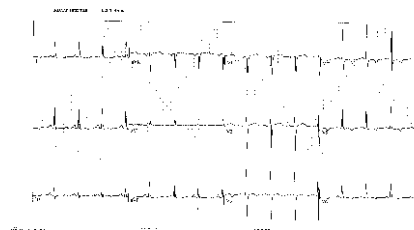


Figure 2. 1st ECG of the patient. The ECG shows sinus rhythm with a normal PR interval, global left ventricular hypertrophy, negative T waves from V3 to V5, and normal QTc-interval.

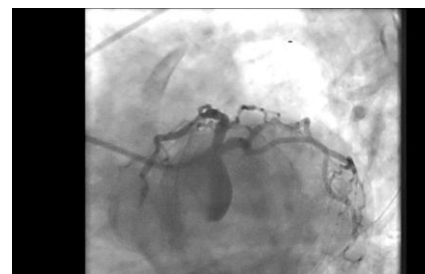
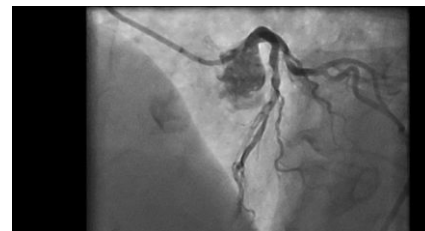


Figure 3. Coronary pathology of the patient. A) The RCA shows a 60% stenosis in the middle portion and multiple non-significant stenoses in other parts. B) The RIA shows a cork-screw like tortuosity of the coronary arteries, often seen in patients with Ribbing disease.

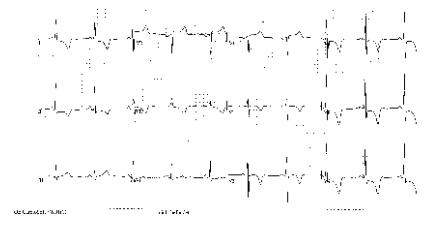


Figure 4. 2nd ECG of the patient. The follow-up ECG (1 year later) shows sinus rhythm with a normal PR interval; global left ventricular hypertrophy is more evident and there are "giant negative T waves" from V2 to V6; the QTc-interval is normal.

size; the iliac arteries were normal. Figure 5 shows the computed tomography (CT) of the ascending and descending thoracic aorta.

Therapy

We attributed the dyspnea to the diastolic dysfunction of the hypertrophied left ventricle. Spironolactone was added to the cardiovascular medication and the dyspnea slowly improved. The aneurysmatic pathology of the ascending aorta was treated surgically (open surgery with implantation of an aortic conduit). The recovery was uneventful. The histology of the resected segment of the aorta revealed elastic fiber fragmentation and cystic medial necrosis.

Discussion

This case brings evidence for the profound connections between skeletal and cardiovascular complications in RD, which may be similar



Figure 5. Aortic aneurysm of the patient. The CT shows a marked enlargement (diameter up to 52 mm) of the sinus portion of the thoracic aorta. Related to the patient's body surface the enlargement is highly pathologic.

to those described in patients with type II Ehlers-Danlos syndrome, in patients with type IV Marfan syndrome, and sometimes patients with osteogenesis imperfecta.

Conclusions

Although it is impractical to draw a general conclusion regarding the patterns of gene expression in RD, it is certain that mutations in the *COL9A2* and *COL9A3* genes interfere with the synthesis of collagen type II and XI. These defects alter the osteoblast-specific factor 2 and induce the skeletal pathology. However, as shown in this case, the defective synthesis of collagen may also affect the cardiovascular system and induce severe complications. Patients with RD should not only be followed for their skeletal pathology but also checked for the occurrence of cardiovascular complications.

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