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A clinical and cardiovascular survey of Ehlers-Danlos syndrome patients with complete deficiency of tenascin-X

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ABSTRACT

Background: We recently described a new autosomal recessive type of Ehlers-Danlos syndrome (EDS) based on a deficiency of the extracellular matrix protein tenascin-X (TNX). TNX-deficient patients have hypermobile joints, hyperextensible skin and show easy bruising. Because of the reported cardiovascular abnormalities in other EDS types and the excessive haematoma formation after mild trauma in TNX-deficient individuals, we investigated whether cardiovascular or coagulation abnormalities occur in these patients.

Methods: We examined seven TNX-deficient patients. One of them had a mitral valve prolapse and died postoperatively after valve replacement, before the study was completed.

Results: Bleeding time and coagulation factors (INR, APTT, PT and fibrinogen) were all within the normal range. Ultrasonographic examination of the carotid and femoral arteries showed normal vessel wall compliance and distensibility. Echocardiography showed a slight billowing of the mitral valve in two patients from one family. All patients had normal diameters of aortic root and ascending aorta.

Conclusion: Although the patient group is small, there are no indications of generalised cardiovascular abnormalities in this type of EDS. We would recommend echocardiography for all these patients at the first evaluation and when a cardiac murmur appears.

INTRODUCTION

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of inherited connective tissue disorders characterised by hyperextensibility of the skin, hypermobility of joints and tissue fragility which results in easy bruising and (in the classical type) atrophic scars following superficial injury. Six well-defined types of EDS have been described[1] and the syndrome is generally regarded as a disorder of fibrillar collagen. Recently, we showed that deficiency of the extracellular matrix protein tenascin-X (TNX), encoded by the TNXB gene, causes a new type of EDS with autosomal recessive inheritance.[2] Patients with a complete deficiency of TNX showed marked joint hypermobility, skin hyperextensibility and easy bruising, resembling the classical type of EDS. The six patients studied showed a variety of other clinical manifestations (such as spina bifida occulta, IgA deficiency, gastrointestinal bleeding, arteriosclerosis, goiter) although it is not clear whether these are causally related to TNX deficiency.

TNX deficiency is associated with abnormalities in collagen and elastic fibres,[3,4] which are principal components of heart valves and large vessels. Cardiac abnormalities such as mitral valve prolapse and aortic dilatation are reported to be common features of certain EDS types,[1,5] although this has been questioned in a more recent paper.[6] Here we undertook an echocardiographic examination of six patients who were available for study and we investigated vessel wall properties of carotid and femoral arteries by ultrasonography. All these patients had excessive haematomas after relatively mild trauma or spontaneous haematomas. Although the most likely explanation for this phenomenon is vascular fragility due to connective tissue abnormalities, we wanted to exclude the possibility that the absence of serum TNX

caused abnormalities in coagulation. We therefore tested platelet function and performed screening coagulation tests.

MATERIALS AND METHODS

Patients

Six TNX-deficient patients were seen in our outpatient clinic. Three of them were identified through analysis of serum TNX levels in 151 Ehlers-Danlos patients. The other three were siblings. Initially we included seven patients; one of these patients died following cardiac surgery because of sepsis after a mitral valve replacement. These patients were described earlier.[2]

Clinical features

From the six patients medical history was recorded and physical examination was carried out with an emphasis on joint hypermobility, which was scored on a nine-point scale according to Beighton.[1] An electrocardiogram was performed in all patients.

Laboratory measurements

Blood was taken for measurement of screening coagulation tests (INR, APTT, PT and fibrinogen). Platelet function was tested by means of Ivy, simplate and aggregation tests. Von Willebrand factor was measured as a marker for endothelial function

Echocardiography

All patients underwent echocardiography, which was performed with standard equipment (GE ultrasound systems, Vingmed V, Horten, Norway, with second harmonic imaging (octave mode: transmit frequency of 1.7-1.9 MHz, receive frequency of 3.4-3.8 MHz)). Digitised measurements of the aortic root were taken in two-dimensional parasternal long-axis views at end diastole using the leading-edge technique at the four aortic levels described by Roman *et al.*:[7] at the annulus, sinuses of Valsalva, supra-aortic ridge and proximal ascending aorta. Echocardiographic evidence of mitral valve prolapse consisted of severe bowing of the anterior and/or posterior mitral valve leaflet(s) into the left atrium and with the coaptation point of the leaflets on the atrial side of the mitral annulus.[8] If the mitral valve leaflets showed bowing but the coaptation point was still on the ventricular side of the annulus or at the level of the annulus it was defined as 'billowing'.

Vessel wall compliance

Cross-sectional compliance (CC) and distensibility coefficients (DC) are defined as the absolute and relative change in volume for a given change in pressure, respectively. Since arterial volume cannot be measured directly, simplified models have been used which assume that arteries have a circular shape and that the arterial length does not change during the cardiac cycle. With this simplification, CC and DC of separate arteries can be assessed by measuring diameters and diameter changes ultrasonographically using a vessel wall movement detector (Wall Track System, Maastricht, the Netherlands) as described by the group of Hoeks and Reneman.[9,10] Measurements were performed by one person according to a protocol described by Van den Berkmortel *et al.*[11] Traces were recorded at the following sites: 1) the right and left common carotid arteries (2 cm proximal of the bulb); 2) the right common femoral artery (at least 1 cm proximal of the bifurcation into the deep and superficial femoral artery).

RESULTS

All TNX-deficient patients had hyperextensible skin, hypermobile joints and easy bruising, as reported earlier. There were no signs of atrophic scarring. One of the patients had coexisting congenital adrenal hyperplasia. Three patients complained of recurrent (sub)luxation/dislocation of joints and two patients had chronic joint pain.

One patient had a mild systolic murmur at the apex; the other patients had normal heart sounds. The electrocardiogram showed no abnormalities. Echocardiographic analysis showed no evident mitral valve prolapse, but two patients of the same family had billowing of the mitral valve. The diameter of the ascending aorta and aortic root was normal in all six patients available for study. Initially we included seven patients in this study. This seventh patient had a mitral valve prolapse that was complicated by a *Staphylococcus aureus* endocarditis in 1990. Mitral valve replacement was performed in July 2002. During surgery, the tissues of the patient appeared fragile and bled easily. Unfortunately, the patient died 16 days postoperatively due to sepsis. The mitral valve showed excessive tissue and a chorda rupture of the anterior mitral valve leaflet; microscopically there were myxoid degenerative changes. We did not observe fragmentation and clumping of elastic fibres in this mitral valve as we recently found for the dermal elastic fibres in these patients.[4] There were no signs of neovascularisation or inflammation. As large arteries are also rich in elastic fibres we examined the vessel wall compliance and distensibility of these arteries; these results were comparable with those of earlier measurements from healthy controls.[12] Screening coagulation tests and platelet function tests were also normal.

DISCUSSION

There are several reports showing a high prevalence of cardiovascular abnormalities in EDS patients. Aortic rupture as seen in the vascular type of EDS is the most serious complication but also in the classical type of EDS cardiovascular complications were observed (Leier *et al.*)[5] In

hypermobility syndrome patients, Grahame *et al*. found mitral valve prolapse to be more frequent in patients with a high hypermobility score, but echocardiography was only performed with the M-mode technique.[13] A more recent study by Dolan *et al*. showed no evidence of increased frequency of mitral valve prolapse in patients with EDS.[6] This apparent discrepancy can be explained by a possible bias in the study by Leier *et al*. because a substantial number of the reported patients in that study initially presented to a cardiologist.[5] In our study, two patients of the same family had billowing of the mitral valve and one unrelated patient had a mitral valve prolapse. Because of the small patient group it is too preliminary to conclude that there is an association between TNX-deficient type EDS and cardiac abnormalities. In addition, billowing and prolapse of the mitral valve are not uncommon in the general population. Studies show a prevalence of 1 to 2%.[14,15]

At this point, no general recommendation can be made as to whether all EDS patients should be subjected to echocardiography. Former studies show that cardiac abnormalities and aortic root dilatation occur in all subtypes of EDS[5,16,17] but studies on the prevalence of cardiac abnormalities within the specific EDS subtypes and studies concerning long-term outcome of the cardiovascular abnormalities have not been carried out. The EDS type based on TNX deficiency described here can easily be discriminated from the other types, because of the absence of atrophic scarring and family history. We would recommend echocardiography for these patients at the first evaluation and when a cardiac murmur appears. If there is a mitral valve prolapse with coexisting mitral insufficiency patients should be followed yearly or every other year according to the severity of the disorder. In case of interventions patients should be treated according to the endocarditis prophylaxis.

We recently found that dermal elastic fibre structure is disturbed in TNX-deficient patients.[3,4] Whether these patients suffer from a more generalised elastinopathy remains to be investigated. Our measurements of arterial vessel wall mechanical properties showed no evident abnormalities nor did we observe abnormal elastic fibres in the mitral valve that was available for study. In large blood vessels there is co-expression of TNX and tenascin-C (TNC), which is another member of the tenascin gene family.[18] TNC could possibly compensate for the absence of TNX leading to normal vessel wall properties.

One of the clinical features of the TNX-deficient patients is easy bruising. This could be caused by mechanical fragility of the vascular connective tissue. Since a 140 kDa TNX fragment is present in plasma, this could theoretically affect the intrinsic coagulation properties. We found, however, no impaired coagulation in these patients.

In conclusion, we would recommend echocardiography for patients with EDS due to TNX deficiency, at the first evaluation and when a cardiac murmur appears.

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