Case Report

Cardiovascular Features in a Case of Ehlers-Danlos Syndrome

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SUMMARY

Diagnosis of Ehlers-Danlos syndrome was made in a 37-year-old man on the basis of hyperextensibility of the fingers joints, hyperelasticity and fragility of the skin, molluscoid pseudotumor, calcified subcutaneous spheroids, microscopic alterations of the dermis, megacolon, intestinal bleeding and bilateral inguinal hernia.

A history of anginal pains, a loud ejection type systolic murmur over the aortic area and electro- and vectorcardiographic signs of unusually severe left ventricular hypertrophy simulated aortic valve stenosis. Cineangiograms of the left ventricle confirmed the existence of high degree concentric hypertrophy. Pressure, oxygen saturation, flow measurements, and cineangiography, however, excluded aortic stenosis and other hemodynamic factors as causes of the hypertrophy. Finding of sudden narrowing of the aorta at the level of the arch reasonably accounted for the systolic murmur.

Cardiac anomaly is interpreted as dependent upon a primary myocardial disease, possibly related to the tissue disorders of the Ehlers-Danlos syndrome.

Additional Indexing Words:

Left ventricular hypertrophy Aortic arch abnormalities

VISCERAL abnormalities associated with the Ehlers-Danlos syndrome are being recognized frequently. Although heart involvement is considered to be rare,¹⁾ several cardiac and vascular anomalies,²⁾ such as atrial septal defect,³⁾ Fallot's tetralogy,⁴⁾ bifid pulmonary artery and aortic arch anomaly,⁵⁾ sinus of Valsalva aneurysm,⁶⁾ valvular abnormalities,^{7), 8)} multiple arterial lesions⁹⁾ have been reported in patients with this syndrome.

The occurrence of the findings described below seems to have been unobserved so far.

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CASE REPORT

The patient, a 37-year-old workman, was admitted to the University General Hospital of Milan on November 23, 1971 for cardiac evaluation because of slight dyspnea on effort and episodes of substernal pain. During the preceding 5 years he had several separate chest pains, with radiation to the jaw and to the left upper extremity, related to physical exertion and relieved by rest. A year before, a diagnosis of aortic stenosis was made on the basis of a cardiac ejection murmur and left ventricular hypertrophy. There was no history of rheumatic fever, diphtheria or scarlet fever. Cyanosis was never observed.

Physical examination revealed an intelligent man of normal stature, with broad nasal bridge. His skin was of normal texture, thin and hyperelastic, and could be pulled easily for 2 or 3 inches about the neck, sternum and elbows. On release it snapped back to resume its former position, without leaving any wrinkles. A few fine "cigarette-paper" scars were noted on the hands. The joints were definitely hyperextensible. A molluscoid pseudotumor was evident over the scrotum.

The Ehlers-Danlos syndrome was suspected. A review of the past history uncovered other possible manifestations of this disease. In fact, at the age of 14, an operation was performed for repair of bilateral inguinal hernia, with subsequent normal healing of the wounds. At the age of 30, the patient was hospitalized because of repeated episodes of rectal bleeding. Such episodes ceased spontaneously and the cause of them remained undefined.

In the family history none of the family members had manifestations of Ehlers-Danlos disease. The patient's father and daughters were examined and found to be normal.

Ocular defects were not observed. The chest appeared slightly deformed, the ribs of the lower left part of the chest being pulled forwards giving a slight thoracic asymmetry. The blood pressure was 110/70 mm.Hg, the pulse 70 beats per min. and regular. The lungs were clear to auscultation. Examination of the heart revealed regular rhythm and normal sounds. No thrill was palpable. A grade 4/6 systolic ejection murmur was heard at the left sternal border and transmitted to both carotid arteries. The right abdomen was soft. Mild tenderness was found in the left abdomen which, in its upper quadrant, appeared distended with increased resonance to percussion. There were no abnormal neurological findings.

Routine laboratory studies, including urinalysis, serological test for syphilis, hemogram, blood urea nitrogen, cholesterol, fasting blood sugar, serum sodium, enzymes (SGOT, SGPT, LDH), erythrocyte sedimentation rate, were within normal limits. The guaiac test on the stools was repeatedly positive. A coagulation study was normal. Protein-bound iodine was 6.5 μ g. per cent. The nitroprusside screening test for homocystinuria was negative. Examination of chromosomes of leukocytes cultures from peripheral blood revealed a normal male karyotype, 46, XY. A biopsy of skin was taken from the right antecubital area. Histological examination showed a normal epidermis. In sections stained with hematoxylin and eosin no great degree of abnormality was seen in the dermis. In sections stained for elastic tissue there appeared to be an increase in the number of elastic fibers and an obvious lack of uniformity. A chest roentgenogram showed normal lungs and mild cardiac enlargement. Rounding of the heart's apex in the frontal projection

Fig. 1. Twelve-lead electrocardiogram. In the precordial leads the 1 mV. calibration signal is reduced to 5 mm. The voltage of RV_4 is 85 mm. The combined voltage of $SV_2 + RV_4$ is 115 mm.

Fig. 2. Transverse plane QRS loop. From the 1 mV. calibration signal it is evident that the magnitude of the maximum QRS spatial vector strikingly exceeds the normal upper limits. The abnormally large ST vector and the $Ts\dot{E}$ loop are discordant to the $QRSs\dot{E}$ loop

and cardiac backward displacement in the lateral view were evident. This view showed also calcified subcutaneous spheroids in the posterior wall of the chest. A roentgenologic study of the gastrointestinal tract was carried out. The barium filled stomach was found to be displaced downward and to the right by the great distention of the airfilled left tract of the colon. The latter was likely responsible for the thoracic and abdominal asymmetry previously mentioned. On barium enema a dilated and elongated double loop of sigmoid in the pelvis and huge transverse and descending colon were evident. The electrocardiogram (Fig. 1) revealed signs of unusually severe left ventricular hypertrophy: the voltage of the R wave was 85 mm. in V_5 . A similar pattern was shown by the vectorcardiogram: the maximum QRS vector in the transverse plane loop (Fig. 2) exceeded 5 mV.

On the basis of the anginal pains, of the clinical, electrocardiographic and vectorcardiographic patterns, the possibility of aortic valvular stenosis was considered and a hemodynamic evaluation was decided. The results of pressures, oxygen saturation and flow measurements are reported in Table I. No systolic pressure gradient was detected between the left ventricle and the aorta. The dye dilution curves, with injection of 5 mg. of indocyanine green into the right atrium and withdrawal from the femoral artery, had normal configuration. Cineangiograms from the left ventricle and the aortic root revealed a very hypertrophic left ventricle with an obviously restricted chamber both in systole and diastole, as shown in Fig. 3, A and B, respectively. For a better definition of the aortic arch, aortography was also performed. The aortograms showed normal origin of the coronary arteries,

Table I. Results of the Right and Left Heart Catheterization

Pressures mm.Hg			Oxygen Saturation %	
Right atrium	s.	6	Superior vena cava	74
	d.	2		
Right ventricle	s.	36	Right atrium	73
	e. d.	6		
Pulmonary artery	s.	36	Right ventricle	73
	d.	15		
	w.	18	Pulmonary artery	74
Left ventricle	s.	104	Left ventricle	96
	e. d.	18		
Ascending aorta	s.	104	Ascending aorta	96
	d.	65		
Femoral artery	s.	104	Femoral artery	95
	d.	65		
Flow			Resistance dynes·sec·cm. ⁻⁵	
Cardiac output	4,800 ml./min.		Pulmonary	67
Stroke volume	72 ml.		Systemic	1,094

Fig. 3A. Single frame of cineangiogram in 45 degree LAO projection showing the left ventricle in systole.

Fig. 3B. Single frame showing the left ventricle in diastole. Note the marked hypertrophy of the ventricular wall (arrows).

Fig. 4. Thoracic aortogram, LAO view. The ascending tract is normal. A single branch gives off the left carotid artery first, then the right subclavian and the right carotid arteries. The left subclavian artery seems to take origin as single vessel. In the distal part of the aortic arch the lumen of the vessel appears obviously reduced (arrows).

and normal configuration of their main branches as well as of the ascending aorta. The innominate artery gave off the left carotid artery first and then divided into the right subclavian and right carotid arteries. The left subclavian artery seemed to take origin as single vessel from the aortic arch. Immediately below the left subclavian artery, the width of the aorta appeared reduced more than one third, as compared to the ascending tract (Fig. 4). The possibility of shunts as well as of mitral and aortic regurgitation could be excluded by the oxygen measurements, the dye dilution curves and the cineangiograms.

DISCUSSION

This patient had hyperextensibility of the fingers' joints, hyperelasticity

and fragility of the skin: he would seem to fulfill the criteria of the Ehlers-Danlos disease.¹⁾ Moreover, his history of intestinal bleeding and bilateral hernia, as well as the findings of broad nasal bridge, molluscoid pseudotumor of the scrotum, calcified subcutaneous spheroids, microscopic alterations of the dermis and megacolon are also suggestive of the syndrome.¹⁾

The pattern of the branches of the aortic arch observed in this subject cannot be regarded as a peculiar finding being reported in 27% of the normal population.¹⁰⁾ On the contrary, the sudden and marked narrowing of the aortic lumen does not appear as a normal feature. Defects of the aortic arch and of its branches have been described in a case of Ehlers-Danlos syndrome by Bopp and collaborators⁵⁾ and interpreted as possibly related to the connective tissue disorders proper of this disease. The major cardiovascular aspect to be elucidated is, however, the striking concentric hypertrophy of the left ventricle. Pressure factors would not seem responsible for the latter both because the aortic pressure was normal and no systolic gradient existed across the aortic valve. Other hemodynamic causes of left ventricular load could be excluded on the basis of oxygen data, cineangiograms and flow measurements. The hypertrophy, therefore, would appear exclusively dependent upon a primary myocardial disorder.

A reasonable explanation of the elevated left ventricular end diastolic pressure might be a reduced compliance of the ventricle depending upon the high degree of concentric hypertrophy. The systolic ejection murmur heard over the precordium and radiated to the neck had probably vascular origin, due to the sudden narrowing of the aortic diameter. The latter, however, was not such as to induce pressure gradient between the proximal and the distal portion of the aortic arch.

Primary left ventricular hypertrophy of such degree as shown by this patient seems to have been unobserved thus far in the Ehlers-Danlos disease. Although it is tempting to incriminate the tissue anomalies proper of the syndrome as responsible for the cardiovascular findings here described, we certainly agree that, as Beighton²⁾ has pointed out, many of the reported cardiovascular abnormalities of this syndrome could merely be chance associations. This might be true also for the patient here described.

In order to give connective tissue disorders their appropriate position in the spectrum of cardiovascular disease, an effort is needed to recognize and record them. The present report is intended as a contribution to this effort.

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