Cardiovascular Aspects of the Ehlers-Danlos Syndrome

Report of a Case with Pulmonary Artery Bifidity and Aortic Arch Anomaly

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THE connective-tissue disorder known as the Ehlers-Danlos syndrome encompasses the following features: cutaneous hyperelasticity, fragility of the skin and blood vessels, and loose-jointedness; other secondary findings may be present.

The association with cardiovascular anomalies has been reported only rarely and the occurrence of the angiographic findings described below seems never to have been observed so far.

Case History

Y.J., a 10-year-old boy of Italian extraction was admitted to the Centre de Cardiologie for cardiovascular evaluation. The child, born after an uneventful pregnancy, had been found at an early age to suffer from a connective-tissue disorder characterized by hyperextensibility of the joints and hyperelasticity of the skin; no other family members were known to be affected by this disease.

There was no history of rheumatic fever, diphtheria, or scarlet fever. Cyanosis was never observed.

In 1961, an unusual aortic shadow was disclosed by a routine roentgen examination at school. Dysphagia and dyspnea were absent; a barium swallow was normal. In 1962, an operation was performed for repair of bilateral inguinal hernia, with subsequent normal healing of the wounds. However, recurrent hernia on the right side required a second operation 1 year later. No marked tendency to easy bruises or hemorrhages was reported. The mental development was within normal limits.

Physical examination showed the boy to be 4 feet 11 inches high and his weight to be 86 pounds. Cyanosis and clubbing were absent. Blood pressure was 100/80 mm. Hg, and all arteries were palpable.

The skin had a velvety appearance and feel and was hyperelastic: it could be pulled easily for 2 or 3 inches over the forehead, elbows (fig. 1A), sternum (fig. 1B), and knees, but immediately resumed its position afterwards.

From the Centre de Cardiologie (Director: Dr. P. W. Duchosal), and the Department of Radiology (Director: Dr. P. Wettstein), University Hospital, Geneva, Switzerland.

Figure 1

Hyperelasticity of the skin. A, left: elbows; B, right: sternum.
without leaving any wrinkles. The joints of the wrists, fingers, and toes were hyperextensible (fig. 2).

Other findings included exaggerated width of the nose-bridge, moderate bilateral epicanthus of the eyelids, normal color of the scleras, bilateral cornea degeneration,—i.e., a slight bilateral megalocone with a diameter of ca 12.5 mm. Both corneas were found to be very thin. Their thickness did not exceed 0.35 mm. Alterations of a congenital type and of a rather rare configuration were present at the posterior surface of cornea on both sides. Vision of the right eye was 0.3 and 0.4 to 0.5 for the left eye—arched palate. There was no arachnodactyly. A moderate degree of pes planus was present. Scars of inguinal hernia operations and one scar on the left knee were noted.

No hematomas were visible and no subcutaneous nodules could be palpated.

Cardiac examination revealed no thrill and no heave. The heart sounds were normal; there was a grade I/VI protosystolic murmur over the aortic area and a grade II/VI protomesosystolic murmur over the right carotid artery. No diastolic murmur was audible. These findings were confirmed by a phonocardiogram.

The electrocardiogram (fig. 3) was within normal limits. The roentgen examination demonstrated a normal cardiac shadow and a somewhat prominent aortic knob (fig. 4).

A carotid sphygmogram showed an abnormal pattern with a sharp and unique peak, and a reduced dicrotic notch (fig. 5).

Examination of the other systems was not contributory. Laboratory findings were as follows: Hemoglobin 88 per cent, hematocrit level 41 per cent, red blood cells 4,300,000, white blood cells 7,500, platelet count 384,000. Urinalysis was normal. The bleeding time and coagulation time were normal. The clot retraction time was delayed. A Rumpel-Leede test was negative after 3 minutes. Permission for skin biopsy was not given.

Right heart catheterization performed under moderate sedation, revealed normal pressures (RA, 3 mm. Hg; RV, 26/3; PA 24/8, mean 10) and normal oximetry values (SVC, 73 per cent and 13.1 vol. per cent; RA, 72 and 12.9; RV, 73 and 13.1; PA, 76 and 13.7). The hydrogen tests confirmed the absence of any significant left-to-right shunt. It was not possible to advance the catheter into a wedge position. Femoral artery saturation was normal (97 per cent and 17.5 vol. per cent). The cardiac output was not

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**Figure 2**

Hyperextensibility of the joints.

**Figure 3**

Electrocardiogram.
measured. Considering the possible risks, trans-septal left heart catheterization was not attempted.

The angiocardiography obtained by injecting the contrast material into the right ventricle, demonstrated an unusual division of the main pulmonary artery at the bifurcation, conveying the impression of a duplicate pulmonary artery.

**Figure 4**

Chest x-ray showing prominent aortic knob.

**Figure 5**

Sphygmogram: top, right carotid; bottom, left carotid.

**Figure 6**


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EHLLERS–DANLOS SYNDROME

Figure 7


(fig. 6, A and B); the right and left branches had a similar and normal caliber, and no dilatation was to be seen. Smaller branches of the pulmonary arteries seemed normal as far as caliber and distribution were concerned.

The later films showed no dilatation of the ascending aorta; however, the course of this vessel was abnormal, the arch forming a loop directed from right to left and backwards. A marked tortuosity of the efferent vessels, in particular of the right brachiocephalic artery was also visible (fig. 7, A and B). Narrowing of an artery, however, was nowhere to be seen.

Discussion

The Ehlers-Danlos syndrome is a dominant, autosomal, heritable disorder of connective tissue. Individuals of European extraction would seem to be affected more often, but one case has been observed in India, and Negroes may also be involved.

Opinions are conflicting in regard to the basic defect; it has often been ascribed to an architectural anomaly of the collagen fibers, the so-called "defective wicker-work" of Jansen; the subject is still controversial, however, and it would appear from the biopsy studies by Wechsler and Fisher that the defect lies rather in a diminished number of collagen fibers with relatively increased elastic fibers; according to these authors, both types of fibers are qualitatively normal under electron microscopic examination.

The clinical manifestations include hyperextensibility of the joints, hyperelasticity of the skin, which is fragile and often heals with difficulty following traumas, leaving shiny "cigarette-paper" scars; subcutaneous nodules with frequent calcifications have been described. The tendency to bruises and hematomas, occasionally fatal, seems to be related to capillary fragility rather than to a defective clotting mechanism. Tests of coagulation are generally normal, but the Rumpel-Leede test may be positive; abnormal clot retraction tests and deficiency of the plasma thromboplastin component have been noted.

McKusick and others have described additional lesions of the musculoskeletal system, of the eye, and of internal organs, in particular of the digestive and respiratory tracts. There have been few well-documented observations of cardiovascular involvement (table 1): four reports of probable or definite congenital cardiac defects, two reports of rheumatic heart lesions, and one of aortic disease. McKusick described three cases of fatal dissecting aneurysm in patients with a possible Ehlers-Danlos syndrome. He
Table 1

Previously Reported Cases of the Ehlers-Danlos Syndrome with Cardiovascular Involvement

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Age, sex</th>
<th>Clinical diagnosis (or findings)</th>
<th>Cathet. angiocard.</th>
<th>Operation</th>
<th>Death † (A: autopsy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margarot (1933)</td>
<td>9 ♀</td>
<td>Loud syst. murmur over pulmonary area; loud P₂</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Freeman (1950)</td>
<td>13 ♂</td>
<td>Atrial septal defect</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Wallach (1950)</td>
<td>26 ♂</td>
<td>Fallot's tetralogy</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fantl (1961)</td>
<td>11 ♀</td>
<td>Low ASD with mitral and tricuspid clefts</td>
<td>+</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>McKusick (1960)</td>
<td>40 ♂</td>
<td>Aortic stenosis, mitral insufficiency</td>
<td>—</td>
<td>—</td>
<td>†</td>
</tr>
<tr>
<td>Madison (1963)</td>
<td>17 ♂</td>
<td>Mitral and tricuspid insufficiency</td>
<td>+</td>
<td>—</td>
<td>† A</td>
</tr>
<tr>
<td>Tucker (1963)</td>
<td>42 ♀</td>
<td>Aortic insufficiency + sinus of Valsalva aneurysm</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>McKusick (1960)</td>
<td>14 ♂</td>
<td>E-D syndrome possible. Dissecting aneurysm</td>
<td>—</td>
<td>—</td>
<td>† A</td>
</tr>
<tr>
<td></td>
<td>15 ♂</td>
<td>—</td>
<td>—</td>
<td>† A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 ♂</td>
<td>—</td>
<td>Laparotomy</td>
<td>† A</td>
<td></td>
</tr>
<tr>
<td>McKusick (1960)</td>
<td>17 ♂</td>
<td>Syst. and diast. murmur? Friction rub? (Enlargement of rt. heart cavities)</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Further observed one 17-year-old girl with cardiac murmurs and angiocardiographic signs of right heart enlargement, and one asymptomatic case with incomplete right bundle-branch block.

Relative difficulty in recognizing the disease may account for the scarcity of reports available; this is especially true when one or more features of the syndrome are absent or only discrete. Cases presenting loose-jointlessness or skin hyperextensibility alone have been labeled as “formes frustes.”

Our patient had definite hyperextensibility of the joints, hyperelasticity of the skin, and he would seem to fulfill the criteria of the Ehlers-Danlos syndrome, notwithstanding the absence of definite skin fragility or bruise tendency. Moreover, his history of bilateral hernia and the above-mentioned findings (exaggerated width of nose-bridge, eye involvement, arched palate, flat feet), were also suggestive of the syndrome.

Anomalies of division of the pulmonary artery are uncommon. Our survey of the literature yielded only one comparable case: in their series of 22 observations of pulmonary artery anomalies, Coelho et al. reported one instance of abnormal bifurcation of the pulmonary artery with identical caliber of the two main branches. It may be of interest to point out that in another case of the same series, a patient with the Marfan syndrome, anomalies of ramification of the pulmonary artery were present, forming a “weeping-willow” pattern of distribution. This might suggest that anomalies of the pulmonary artery may occasionally exist in disorders of connective tissue; it might perhaps also provide an additional common feature between the Marfan and the Ehlers-Danlos syndromes. Otherwise, apparently none of these cases was combined with congenital aortic defects. The association of the above-mentioned anomalies of the pulmonary artery and of the aortic arch must be
very rare indeed. Discussion of the embryologic development is however beyond the scope of this paper.

It is to be hoped that in the future, a systematic search for similar anomalies may help clarify the problem.

Summary

The case of a 10-year-old boy is reported because of the association of the Ehlers-Danlos syndrome with bifidity of the pulmonary artery and anomaly of the aortic arch.

The cardiovascular aspects of this connective-tissue disorder are reviewed, and the possibility of another common feature with the Marfan syndrome is briefly discussed.

Acknowledgment

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References

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