

Cardiac Abnormalities in the Ehlers-Danlos Syndrome

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There have been several reports of cardiac abnormalities in patients with the Ehlers-Danlos syndrome, but it is not certain whether these anomalies are part of the syndrome or whether they represent chance concomitants (McKusick, 1966).

In an investigation in Southern England, 100 patients with this syndrome have been examined. The results of this survey, from the cardiac point of view, are presented in this paper, and the features that were encountered are discussed with reference to previous reports.

DESCRIPTION OF SYNDROME

Affected patients have hyperextensible skin, which can usually be stretched for several centimetres (Fig. 1). On release it springs back to take up its former position. The skin also tends to split on minor trauma and the bony prominences are frequently covered with wide, thin scars (Fig. 2).

Joint hypermobility is often a prominent feature of the condition, but in some patients it may be present only in the digits (Fig. 3).

Molluscoid pseudotumours and calcified subcutaneous spheroids are found, and patients may also have musculoskeletal deformity. A bleeding diathesis is a common concomitant, and visceral, dental, and ocular abnormalities occur.

The Ehlers-Danlos syndrome is a familial condition and is usually inherited as an autosomal dominant trait, though an X-linked form of the syndrome has recently been described (Beighton, 1968a).

PRESENT INVESTIGATION

The 100 patients in the survey were fully examined, and an unselected group of 29 of them had electrocardiographic and radiological investigations. The relevant cardiological findings, together with

the results of these investigations, are presented in Table I.

A systolic murmur was heard in 10 of the patients who had been fully investigated, and in 7 of them this finding was associated with a thoracic deformity, while one had electrocardiographic evidence of complete heart block. Fourteen other patients had systolic murmurs which were not thought to be significant, and 4 of these patients also had abnormalities of the chest wall.

One patient in the series had the clinical signs of mitral incompetence, with the appropriate changes in the chest *x*-ray and the electrocardiogram, while an elderly man had aortic stenosis and incompetence. A fit middle-aged man had a loud systolic murmur in the pulmonary area, and though no diagnosis had been made in his case, it was of interest that his deceased sister had both an atrial septal defect and Ehlers-Danlos syndrome.

A right-sided aortic arch was a chance radiographic finding in one patient, an 18-year-old youth, and 4 others had abnormal cardiac shadows which were probably the result of displacement of the heart by a deformed chest wall. One middle-aged man had widening of the aorta which was consistent with atherosclerosis.

Three patients had a degree of right bundle-branch block: 2 of them had pectus excavatum, and the third was the boy with the right-sided aortic arch, who also had a wandering pacemaker and borderline right axis deviation. One 21-year-old woman had complete heart block which was associated with a loud systolic murmur, but her cardiologist did not consider that this murmur was indicative of any structural cardiac abnormality. Four other patients had minor abnormalities of the electrocardiographic vector, which were probably caused by an abnormal chest wall in 2 of them.

A 29-year-old man had experienced severe chest pains when the airliner in which he was flying at 35,000 feet over Africa had suddenly lost its pressurization. He was admitted to a local hospital in a

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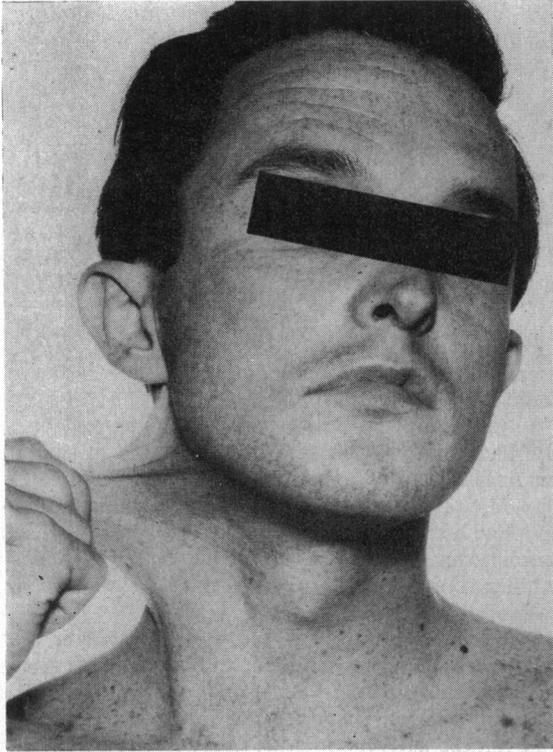


FIG. 1.—Hyperextensible skin.



FIG. 2.—Typical wide, thin scars over the knees.

coma, and when his wife, a trained nurse, reached him three days later, she noticed that he was jaundiced. He gradually recovered and when he was seen in England several months later he was apparently well. However, a chest x-ray revealed a widening of the ascending aorta, which had not been present on a film taken one year previously. On the evidence available, a tentative diagnosis of dissection of the aorta was made.

One patient differed from the majority of the other patients in the series in that her main clinical stigmata were widespread, thin, darkly pigmented scars, associated with a prominent bleeding diathesis. Her brother, sister, and father, all of whom had been similarly affected, had all died sudden deaths from cardiovascular catastrophes or intestinal acci-

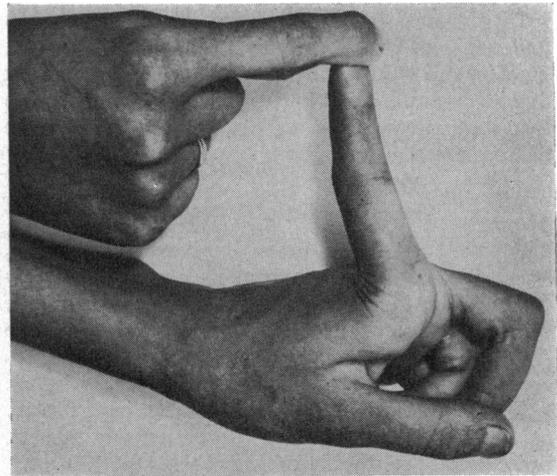


FIG. 3.—Hypermobility of the fingers.

dents. Several years previously she had been unconscious for five days after a caesarean section and had awakened with a left-sided hemiplegia. It had been thought at that time that she had some kind of cerebrovascular accident. However, her eventual recovery was complete.

DISCUSSION

About 300 other cases of Ehlers-Danlos syndrome have been reported, and those with cardiac abnormalities are shown in Table II.

A substantial proportion of the patients, particularly those more severely affected, have abnormalities of the thoracic wall, which are usually secondary to abnormal spinal curvature. It is likely

TABLE I
RESULTS OF ELECTROCARDIOGRAPHIC AND X-RAY INVESTIGATIONS IN 29 PATIENTS WITH
THE EHLERS-DANLOS SYNDROME

Case No.	Age (yr.), and sex	Cardiac features	Chest x-ray heart shadow	Thoracic deformity	ECG findings
1	29 M	Dissected aorta?	Prominent ascending aorta	—	—
2	28 F	Pulmonary ejection systolic murmur	—	+	Abnormal T wave vector in horizontal plane
3	48 F	Mitral incompetence	Enlargement consistent with mitral incompetence	—	—
4	49 M	—	—	+	—
5	30 F	Pulmonary ejection murmur	—	+	—
6	31 M	Apical ejection systolic murmur	—	—	—
7	31 F	Pulmonary ejection murmur	Prominent pulmonary conus	+	Incomplete right bundle-branch block (grade 1)
8	18 F	Apical systolic murmur	—	+	—
9	20 M	—	Right cardiac border prominent and raised	—	—
10	7 F	—	—	—	—
11	26 M	—	—	—	Sinus bradycardia
12	28 M	—	Cardiac shadow displaced to left	+	—
13	21 F	Loud apical systolic murmur	—	—	Complete heart block
14	50 F	—	Cardiac shadow displaced to left	+	Abnormal T wave vector in horizontal plane
15	24 M	—	—	—	—
16	20 F	—	—	—	—
17	51 F	—	—	—	Low voltage; flat T waves (myxoedema)
18	15 M	—	—	—	—
19	52 M	—	Widened ascending aorta consistent with atherosclerosis	—	—
20	13 M	Apical systolic murmur	—	+	—
21	44 F	Apical systolic murmur	—	+	—
22	18 M	—	Right-sided aortic arch	—	Wandering pacemaker; incomplete right bundle-branch block (grade 1); QRS: +90°
23	21 M	—	—	—	—
24	31 F	Pulmonary ejection murmur	Cardiac shadow displaced to left	+	Incomplete right bundle-branch block (grade 2); left axis deviation; QRS: 20°
25	14 M	Apical systolic murmur	—	—	—
26	19 M	—	—	—	QRS: +100°
27	18 M	—	—	—	—
28	11 M	—	—	—	Dominant R in V1
29	22 M	—	—	—	Atrial ectopics

that the majority of the systolic murmurs heard in the patients in the series were either due to the influence of the abnormal shape of the chest or were of no pathological significance.

The only patients in the whole series with valvular abnormalities were an elderly man with aortic stenosis and incompetence, and a middle-aged woman with mitral incompetence. It is likely that the man's lesion was due to calcification of the valve, while the woman's abnormality was probably the result of her childhood rheumatic fever. There have been previous reports of mitral valvular disease in patients with Ehlers-Danlos syndrome (McKusick, 1966; Madison, Bradley, and Castillo, 1963), and it is possible that this patient had a lesion of this nature. Frieden, Hurwitt, and Leader (1962) discussed the Ehlers-Danlos syndrome when they reported their patient who died after an operation for aortic incompetence. At operation ruptured valve cusps were found, and he was thought to have some uncommon genetically determined disorder of con-

nective tissue which might have been related to the syndrome. McKusick (1966) described a woman who had systolic and diastolic murmurs and a dilated right side of the heart. An initial diagnosis of the Ehlers-Danlos syndrome was made, but later the diagnosis was changed to that of pseudo-Turner syndrome, which in some ways resembled the Ehlers-Danlos syndrome. Rossi and Angst (1951) also reported a murmur in a patient with Turner's syndrome, and it is important that these conditions are not confused with the Ehlers-Danlos syndrome. Aortic incompetence was present in a patient described by Goeminne and Van Hove (1965), but it is probable that this patient did not have the syndrome.

Atrial septal defect has been previously reported by Freeman (1950), Fantl, Morris, and Sawers (1961), and Sestak (1962), and it was possible that one patient, the brother of Sestak's case, also had an atrial septal defect. This anomaly had also initially been diagnosed in another patient, and she

TABLE II
CARDIAC ABNORMALITIES IN THE EHLERS-DANLOS SYNDROME

Case No.	Age (yr.), and sex	Family history	Condition	Other features	Author
1	13 F	-	Atrial septal defect	-	Freeman (1950)
2	43 F	+	Atrial septal defect with tricuspid incompetence	Right bundle-branch block	Sestak (1962)
3	11 F	+	Partial atrioventricular canal; left leaflets of mitral and tricuspid valves	Deficient Hageman factor; successful repair of ASD	Fantl <i>et al.</i> (1961)
4	26 F	-	Fallot's tetralogy	Right bundle-branch block	Wallach and Burkhart (1950)
5	2 F	+	"Congenital cardiac defect"	Mother had Ehlers-Danlos and died after operation on internal carotid aneurysm	Rubinstein and Cohen (1964)
6	10 M	-	Bifid pulmonary artery; abnormal aortic arch	-	Bopp <i>et al.</i> (1965)
7	28 M	-	Abnormal aortic arch	-	Robitaille (1964)
8	40 M	-	Aortic stenosis and mitral incompetence	Murmurs first heard shortly after birth; sudden death in 1957	McKusick (1966)
9	17 M	-	"Bicuspid" tricuspid valve	Death from spontaneous rupture of subclavian artery; friable cardiac muscle at necropsy	McFarland and Fuller (1964)
10	17 M	+	Mitral and tricuspid incompetence	Death in congestive cardiac failure	Madison <i>et al.</i> (1963)
11	42 F	-	Aneurysm of right sinus of Valsalva; aortic incompetence; pulmonary hypertension	-	Tucker <i>et al.</i> (1963)
12	9 M	+	Systolic murmurs	Murmurs due to thoracic deformity	Margarot, Deveze, and de Carrera (1933)
13	25 F	-	Systolic and diastolic murmurs; dilated right side of the heart	Probably a pseudo-Turner syndrome	McKusick (1966)

had a forceps delivery of her first child for this reason. The diagnosis was later revised when it was realized that her murmur was probably due to the very narrow antero-posterior diameter of her chest.

The right-sided aortic arch found in one patient has not been previously described in the Ehlers-Danlos syndrome. Bopp, Hatam, and Bussat (1965) carried out angiographic studies on a boy with an "abnormal aortic arch" and showed a bifid pulmonary artery, while Robitaille (1964) investigated a man with an abnormal aortic arch in the same way. It is impossible to say whether these abnormalities have any direct relation with the Ehlers-Danlos syndrome.

Three patients in the series had a right bundle-branch block, and two of them also had abnormal chest walls, while the third was the patient with a right-sided aortic arch. A right bundle-branch block was present in the patient with the atrial septal defect described by Sestak (1962), and he also found an incomplete right bundle-branch block in a patient with cutis laxa. McKusick (1966) also reported an incomplete right bundle-branch block in a man who had no other demonstrable cardiac lesion.

This conduction defect is common in normal people, and there is nothing to suggest that it was anything more than either a chance finding or an abnormality related to the other structural features in the patients described. The complete heart block and the vector abnormalities were probably also chance findings.

It seems likely that Case 1 (Table I) survived a genuine dissection of the aorta. Similar events have been reported in three young men by McKusick (1966), and Lynch *et al.* (1965) reported a further case. Pemberton, Freeman, and Schepens (1966) mentioned the successful surgical repair of a dissection of the aorta in a man of 39; however, he died suddenly one month later, presumably from another dissection.

The patient with the family history of arterial rupture probably has a clinically distinct variety of the Ehlers-Danlos syndrome. Barabas (1967) suggested the existence of this entity, and described two patients with similar stigmata who had spontaneous arterial bleeding. There have been several other reports of arterial rupture in Ehlers-Danlos syndrome, including those of Mories (1960), McFarland and Fuller (1964), and McKusick (1966). This patient's cerebrovascular episode could have been due to an intracranial vascular malformation resembling those described by Schoolman and Kepes (1967), Graf (1965), and Rubinstein and Cohen (1964), which seem to occur in patients with this type of the syndrome.

However, arterial bleeding has occurred in patients with the usual manifestations of the Ehlers-Danlos syndrome, and such patients are at some risk from this complication (Beighton, 1968b).

Among the other cardiac abnormalities that have been previously reported in patients with this syndrome are Fallot's tetralogy (Wallach and Burkhart, 1950), a "congenital cardiac defect" (Rubinstein and Cohen, 1964) which caused the death of the

patient at the age of 2 years, and an aneurysm of the right sinus of Valsalva, which was associated with aortic incompetence and pulmonary hypertension (Tucker, Miller, and Jacoby, 1963). The necropsy on the patient reported by McFarland and Fuller (1964) revealed that the tricuspid valve had only two leaflets. This abnormality probably accounted for the systolic murmur which had first been noticed in this patient some years previously.

Excluding the present series, about 300 patients with Ehlers-Danlos syndrome have been reported. Of these, the 13 listed in Table II had cardiac abnormalities. As there must be many more undiagnosed or unreported patients with this syndrome, it is probable that the incidence of these anomalies is not high. Furthermore, there does not seem to be any consistent pattern of cardiac abnormality among these patients. Apart from the arterial episodes and arteriovenous malformations that have already been discussed, it would probably be correct, therefore, to regard structural cardiac lesions as chance or very rare concomitants of the syndrome.

SUMMARY

One hundred patients with the Ehlers-Danlos syndrome have been examined, and 29 of them had electrocardiographic and radiological investigations.

Though 24 patients had systolic murmurs, it was considered that these sounds were either due to the thoracic deformity which was present in several of the patients or were benign murmurs of no pathological significance. No consistent valvular or structural cardiac defect was encountered.

Three patients had a partial right bundle-branch block which was associated with thoracic deformity in 2 and a right-sided aortic arch in the third. One young patient had a complete heart block.

One patient made a full recovery from an episode of chest pain which probably represented a dissection of the aorta. Several members of another kindred had cardiovascular catastrophes or intestinal perforations, and it was possible that these patients had a clinically distinct form of the syndrome.

More than 300 patients with the Ehlers-Danlos syndrome have been reported. Thirteen of them had structural cardiac anomalies but these did not fit into any consistent pattern. On the basis of these reports and the results of the present investigation, it appears that these cardiac abnormalities must be either chance associations or very infrequent true concomitants of the Ehlers-Danlos syndrome.

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