Combined Ehlers-Danlos and Marfan's Syndromes

WITH A CASE REPORT


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SUMMARY

Although the Marfan's and Ehlers-Danlos syndromes are well documented, patients showing features of both disorders are rarely seen.

We describe a patient in whom features of both disorders were manifested, and review some of the aspects of these syndromes, especially as they may present to different disciplines.


The Ehlers-Danlos syndrome, first described by Ehlers' and Danlos, and Marfan's syndrome, which Marfan described in 1896, are both well-known clinical entities. A combination of the two is rare. We know of only four cases documented in the literature since 1951. In 1965, Goodman et al. described a 20-year-old mentally retarded Negro with hyperelastic skin, mobile joints, and 'cigarette paper' scars; he also had arachnodactyly, myopia and mitral incompetence. Family studies disclosed that some members had characteristic Marfan's syndrome, others, characteristic Ehlers-Danlos syndrome, and one had a mixture of the two.

Walker et al. coined the term 'Marfanoid hypermobility syndrome' suggesting that this combination of disorders was a separate genetic entity. However, the true genetic relationship of Marfan's syndrome and Ehlers-Danlos syndrome, two heritable disorders of connective tissue, remains speculative, since it is unknown whether the level of defect is in amino acid or connective tissue synthesis.

In this article the clinical findings in a patient who manifested features of both Ehlers-Danlos and Marfan's syndromes, are presented and the clinical features as well as the surgical implications of both conditions are discussed.

CASE REPORT

A 16-year-old Xhosa male from the Transkei arrived at a mission hospital complaining of a swelling in the region of the right axilla and shoulder. Two days previously, while he was running, he tripped and fell on his right side. This was followed by pain and swelling of the right shoulder and axilla. On examination, swelling of the shoulder region was noted, he was anaemic, and 3 units of blood were administered. Four days later the radial pulse on the side of the injury was absent, and on the 7th day after his injury he was transferred to a Provincial hospital. The shoulder swelling had increased.

In hospital, it was found that his right arm was pulseless but viable, and no neurological deficit could be elicited. His haemoglobin was 9 g/100 ml. After angiography which revealed a large false aneurysm arising from the subclavian artery, an exploration of the region was undertaken. The anatomy was distorted by oedema and haematoma, and because of uncontrollable arterial bleeding, the wound was packed with gauze and the skin sutured over it. During this operation 7 more units of blood were transfused. Over the next 48 hours, the patient's condition remained static and it was decided to transfer him to Groote Schuur Hospital where he arrived 10 days after his injury.

On admission he was found to be semiconscious, shocked and anaemic. He was mildly jaundiced and the right shoulder region was grossly distorted by a large axillary swelling about the size of a soccer ball. There was apparently no neurological deficit, but assessment was difficult. The patient was resuscitated and an arteriogram showed the subclavian artery to be avulsed immediately distal to its origin, with a large false aneurysm at the site of avulsion. The distal axillary artery was supplied via shoulder collaterals.

At operation, a median sternotomy was made, but recognition of anatomical structures was extremely difficult owing to a massive haematoma which extended into the mediastinum. The subclavian artery was isolated with difficulty and ligated, after which the large haematoma was evacuated. The skin in the region of the axilla and base of the neck appeared non-viable, no doubt due to the severe tension caused by the haematoma and gauze packs. This area subsequently sloughed and required split skin grafting (Fig. 1).

Postoperatively there was an obvious brachial palsy involving C7-T1. Electronmicrographic studies demonstrated degeneration of the affected muscles, and treatment consisted of active and passive physiotherapy and occupational therapy. The patient is fortunately left-handed and in other respects he made a good recovery. No family history was obtainable.

*Date received: 1 May 1973.
Clinical Features

The patient’s body habitus was that of a Marfan’s syndrome (Fig. 2). He was tall, thin, with long arms and legs, his arm span was greater than his height (185 cm: 180 cm), and his segment ratio, i.e. crown-pubis to pubis-heel length, was 0.89 (normal about 0.93).

Arachnodactyly was also a notable feature and the patient had positive ‘thumb’ and ‘wrist’ tests. Redundant folds of skin were present over the elbows and knees and the skin of the forearm could be pulled out, to fall back into its original position when released (Fig. 3). The shins were covered with scars closely resembling the ‘cigarette-paper’ scars found in the Ehlers-Danlos syndrome (Fig. 4), and the metacarpophalangeal joints could be hyperextended to a considerable degree. He was found to have left ventricular hypertrophy with a grade 3/6 regurgitant murmur at the apex; a diagnosis of mitral incompetence was confirmed by the cardiologists. There were no ocular abnormalities, but the patient had the typical high-arched palate associated with Marfan’s syndrome (Fig. 5).
Special Investigations

Apart from an initial mild haemolytic jaundice and raised muscle enzymes, his biochemistry was normal. Plasma electrophoresis demonstrated a reduced albumin (2.3 g/100 ml) with elevated alpha and gamma globulins (1.2 g/100 ml and 3.4 g/100 ml, respectively).

A chest X-ray film confirmed left ventricular hypertrophy. X-ray studies of the hands showed a positive metacarpal index. The sum of the length of the 4 main metacarpals when divided by the sum of the width of these metacarpals was more than the accepted figure of 7.8.

A phonocardiogram confirmed the presence of a pansystolic regurgitant murmur of mitral incompetence.

Histology of the skin removed at surgery showed 'patchy loss of collagen with irregular arrangement of elastic fibrils-increased in some areas and diminished in others.'

THE EHLERS-DANLOS SYNDROME

Van Makeeren’s ‘india-rubber man’ attracted attention to his cutaneous contortions 3 centuries ago, but it remained for Ehlers (1901) and Danlos (1908), who described features of the disease, to have their names attached to the syndrome.

Postulates as to the basic defect in this condition are as many and varied as its clinical features. The defect remains unknown, but different authors have at various times claimed that it is a defect either of collagen or of elastic fibres in the dermis. Those who propound the latter are uncertain whether there is an increase or a decrease of elastic tissue. Still others hold that the mucopolysaccharide ground-substance, and not elastin or collagen, is the cause.¹³

Jensen, quoted by McKusick,¹⁰ stated that the basic abnormality was a defect in the side-to-side anastomoses which exist between collagen fibrils (the ‘defective wicker-work’ theory), suggesting a disorder in the organization of the collagen fibres into a network of bundles—so that supportive connective tissue readily splits under stress.

More recently evidence based on biochemical investigation of connective tissue has been described.¹¹ An amino-oxidase, essential for the oxidative de-amination of lysins required for the cross-linking of polypeptide chains, is deficient. This leads to a defect in the synthesis of elastic arterial tissue, suggesting a ‘hereditary enzymopenia’.

The pathogenesis of the vascular abnormalities of the Ehlers-Danlos syndrome, viz. subcutaneous ecchymoses (due to capillary and small vessel rupture) and haemorrhage (due to large vessel rupture), has been more firmly postulated, the causes being defective vascular and peri-vascular tissue, failure of clot retraction, and abnormal platelet structure and function, i.e. a thrombocytopenia as described by Kashiwagi et al.¹² These factors may all contribute to the onset and persistence of bleeding episodes in the disease.

The Ehlers-Danlos syndrome is transmitted as an autosomal dominant with variable expressivity—thus giving rise to a wide variety of clinical types, each expressing some (or all) components of the syndrome. It is equally common in males and females and has been reported most often in Whites, but this may not be significant.

Clinical Features

The clinical features are predominantly cutaneous, musculoskeletal, ophthalmological, and visceral.

Cutaneous: The striking cutaneous features are the hyper-extensible skin and abnormal cutaneous response to trauma. The skin feels velvety, but is not lax, and after stretching it returns to its original position. Redundant folds of skin are present on the hands, soles, and over joints. The ears can be folded in like those of a premature infant (‘lap ears’). The skin splits very easily, but there is comparatively little bleeding and the edges gape, resulting in ‘fish-mouth’ wounds. Healing is slow and sutures hold poorly, tending to cut through, leaving thin ‘cigarette paper’ scars. The epithelium is atrophic, friable and easily broken. In the gravis and ecchymotic varieties, the scars are wide and pigmented, but in the latter type the pigmentation is much deeper (vide infra).

Usually the skin bruises with the slightest trauma, in fact widespread ecchymoses are characteristic of one lethal phenotype of the syndrome.

The molluscoid pseudotumours described by Danlos,¹ develop at points of pressure, especially over the knees and elbows. Some patients also develop spheroids, or pea-sized cysts containing fat, which later become calcified and slip about under the skin. They present a characteristic appearance on X-ray films.

Musculoskeletal: The joints demonstrate hyperextensibility and many are liable to recurrent dislocation. There is usually muscular hypotonicity, some of these infants presenting as ‘floppy babies’. Other abnormalities which may be associated with the syndrome are spinal deformities such
as kyphoscoliosis; pes planus; and talipes equinovarus. There is also a marked tendency to develop hernias. There is no characteristic body habitus as seen in Marfan's syndrome.

Ophthalmological: These may be extra-ocular or intra-ocular. The former are common and include epicanthic folds, redundant skin on the upper eyelids, and strabismus. The latter group are rare and are possibly chance concomitants of the syndrome.

Visceral: Patients with these features are liable to spontaneous rupture of any part of the gastro-intestinal tract and this is a well-described cause of death. They also tend to develop diaphragmatic herniae and diverticula.

Respiratory complications are well documented. Emphysema, pneumothorax, and recurrent haemoptysis have all been described. Several cardiac abnormalities such as the tetralogy of Fallot, atrial septal defects, mitral and tricuspid incompetence, have been described, but the connection remains unproved. More frequently, associated complications are dissecting aneurysm of the aorta and spontaneous rupture of medium and large arteries, e.g. popliteal and subclavian. Premature delivery due to premature rupture of the membranes is also described.

Clinical Classification of the Ehlers-Danlos Syndrome

Two classifications of the phenotypes are presented because it is believed that an understanding and a recognition of the different entities are important in the practical approach to the condition.

Beighton's classification: Gravis (30%); mitis (45%); benign hypermobile (10%); ecchymotic (5%); X-linked recessive (10%).

These are determined according to the major clinical features as shown in Table I.

In Table I the last vertical column demonstrates how a knowledge of the different clinical types of the Ehlers-Danlos syndrome may give an indication of the surgical risk and complications liable in any particular case.

Barabas' classification: Classical, varicose, arterial. These again may be correlated with the major clinical features as shown in Table II.

Beighton's approach is widely accepted and seems to be the more practical one.

Surgical Implications

The practical value of the clinical subclassification of the Ehlers-Danlos syndrome is borne out when one considers the potential surgical complications attendant on this condition. A knowledge of the type would enable one to prognosticate, within limits, the nature and severity of the complications—thus, cases of Beighton's gravis or ecchymotic type would tend to have the worst prognosis.

Complications of the Ehlers-Danlos Syndrome Necessitating Surgical Intervention

Cutaneous. These patients are prone to spontaneous splitting of the skin or of the soft, thin scars, and poor sealing results in chronic ulceration.

Orthopaedic. Many orthopaedic conditions have been described, in association with the syndrome. Those most likely to result in surgical intervention are dislocations, joint effusions, foot deformities and enlarged bursae.

Gastro-intestinal. Bowel rupture, perforation, or gastro-intestinal haemorrhage, can occur, the latter being described as a cause of death. Diverticular formation also occurs.

Muscular. Herniae are common and the recurrence rate after repair is very high.

Clinical Classification of the Ehlers-Danlos Syndrome

<table>
<thead>
<tr>
<th>Clinical type</th>
<th>Extensible skin</th>
<th>Skin splitting</th>
<th>Bruising</th>
<th>Mobile joints</th>
<th>Surgical risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravis</td>
<td>++</td>
<td>++ (a)*</td>
<td>+</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Mitis</td>
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<td>±</td>
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<td>±</td>
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<tr>
<td>Ecchymotic</td>
<td>0</td>
<td>++ (b)*</td>
<td>++</td>
<td>±</td>
<td>±†</td>
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<tr>
<td>X-linked</td>
<td>++</td>
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(a) Wide, paler scars; (b) wide, very ecchymotic scars.
† In ecchymotic EDS joint hypermobility is confined largely to digits.

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Complications of the Ehlers-Danlos Syndrome Necessitating Surgical Intervention
Vascular. These complications are comparatively rare. Varicose veins and haematomas are usually not serious, but aneurysms, A-V fistulae, and arterial rupture after minor trauma, are potentially lethal.

Complications During Surgical Procedures

These may arise during treatment of incidental diseases or, more often, during the attempted management of the above. Sutures tend to tear out at wound edges, resulting in wound dehiscence. Even where the wound appears to heal initially although delayed, the scars widen and become weak, often resulting in incisional herniae. Owing to the increased fragility of large blood vessels, ties may cut through, and secondary haemorrhage is always a danger. Contiaial ooze from small vessels may result in intra- and postoperative haemorrhage, haematoma formation, and, as a result, wound dehiscence.

THE MARFAN SYNDROME

In 1896 Marfan used the term 'dolichostenomelia', literally, 'long thin limbs', to describe the condition known by his name today. Its synonym, 'arachnodactyly', coined by Achard in 1902, described one component of the syndrome only.

Although there is far less controversy over the basic defect in the Marfan syndrome, it is by no means finally settled. Most authors agree that there is a defect in elastin fibre, but others suggest the fault lies in the synthesis of ground substance.

The pathogenesis of the arterial lesions is well documented. The term 'cystic medial necrosis' has been used, but neither cysts nor necrosis are a feature of the pathology. Instead, 'medial mucoid change' more accurately described the degeneration of the muscular-elastic wall of large arteries to an amorphous, basophilic ground substance, rich in mucopolysaccharides. This results in weakness, dilatation, and ultimately dissection or rupture of the vessel wall.

In the aorta, this process leads to the formation of a dissecting aneurysm; at the mitral valve, to mitral incompetence.

Incidence

Like the Ehlers-Danlos syndrome, Marfan's syndrome is transmitted as an autosomal dominant. However, penetrance is much stronger and the phenotypical expressivity, therefore, less variable. Unlike the Ehlers-Danlos syndrome there is no significant sexual or racial preponderance.

Clinical Features

Musculoskeletal: The body habitus is essentially that of dolichostenomelia. There is an abnormal vertex-pubes/pubis-sole ratio. The normal vertex-pubes ratio to total height is 0.93, whereas in Marfan's syndrome it is less than 0.85, making the pubis-sole length significantly longer than the vertex-pubes length.

The arm span is greater than the patient's height and the hand-to-height and foot-to-height ratios are in excess of 11% and 15%, respectively. Some cases show excessive length of the infrapatellar ligament, but this is not always so.

The fingers show arachnodactyly. The third metacarpal in the adult is in excess of 7 cm, and the third finger in excess of 10 cm. The finger-wrist test was described by Walker and Murdoch. Here the fifth finger and thumb overlap when opposed around the opposite wrist. The thumb sign is seen when an X-ray film is taken of the hand with the thumb adducted across the palm. If positive, the distal phalanx of the thumb projects beyond the bony skeleton of the hand.

Bones show excessive longitudinal growth (responsible for the habitus described above), and pectus excavatum, a high-arched (gothic) palate, and dolichocephaly are usually present.

The patients may also show a weakness of supporting tissues (viz. capsules, ligaments, tendons, fascia) resulting in hypotonia, kyphoscoliosis, hyper-extensible joints, pes planus, hernia, and sparse subcutaneous fat.

Ocular: Here ocular manifestations are common. Ectopia lentis occurs, due to defective suspensory ligaments, and is clinically apparent by detecting iridodinesis. Defective sclerae may present as blue sclerotics or with myopia. Retinal detachment is a known complication.

Vascular and cardiac: The vascular abnormalities have been well described by Padarnannou. Aortic aneurysms are common, almost always affecting the thoracic aorta. The aorta may also be the site of dissection and ectasia may in turn result in aortic incompetence followed by angina pectoris.

Mitral incompetence is due to fibromyxomatous degeneration of the valve ring or lengthening and redundancy of the chordae tendineae. It has in fact been shown that in all cases with murmurs suggestive of mitral incompetence, aneurysmal dilatation of the aortic sinuses is present.

The ECG may show prolongation of the P-R interval and bundle-branch block.

There is also an increased tendency to varicose veins.

Miscellaneous: Spontaneous pneumothorax is a recognized complication of Marfan's syndrome and may result in sudden collapse and death.

Finally, these patients may develop subcutaneous cysts (Miescher's elastoma) which are filled with an elastic-like material and which present as nodules or papules, mainly on the neck.

CONCLUSION

This case is presented as an example of an inherited disorder of connective tissue. It raises at least 3 points of interest:

1. In its presentation and evolution it encompasses several disciplines of medicine — arterial and plastic sur-
surgery are foremost, but also orthopaedics, dermatology, general medicine, and psychiatry. The patient passed through the hands of the ophthalmologists and cardiologists as well.

It is thus important to take cognizance of the multifaceted character of this condition so that, especially in the case of a highly compartmentalized hospital service, we may be aware that such a patient could present to any of the above-mentioned specialities.

2. The pathogenesis of the arterial rupture in this case is still not fully explained. The relative roles of extrinsic trauma and of the underlying disease process will remain conjectural. In the light of several reports of 'spontaneous' rupture of large arteries in connective tissue disorders, we may use this case to draw attention to the existence of this complication.

3. The major point of interest is most certainly that this case exhibits an almost certain combination of the features of both the Marfan and the Ehlers-Danlos syndromes. It may, therefore, throw some light on the pathogenesis and interrelationships of these different types of inherited connective tissue disorders.

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REFERENCES