Section of Dermatology

President M Feiwel FRCP

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Cases

Ehlers-Danlos Syndrome

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The patient, Mrs V W, was born prematurely by breech delivery on 21 April 1937. At birth it was noticed that she had talipes equinovalgus deformity of both feet. During infancy there was a marked delay in motor milestones and generalized hypotonia. The hypotonia persisted through childhood, but intellectual development seemed normal. Frequent bruising and purpura of the skin and a tendency to laceration of the skin on minor trauma with poor healing were noted.

An increased range of joint movements was noticed and she underwent various orthopædic procedures including bilateral rotation osteotomies of tibia and femur to improve her gait. On account of poor circulation of her legs, lumbar ganglionectomy was performed in 1951.

Symptoms in more recent years include slowly progressive 'weakness' and at present she can walk approximately fifty yards with the aid of calipers and crutches.

Examination

The patient is a tall woman of 5 ft 11 in (2 m) with an arm span measurement less than her height. She shows the following features: bilateral epicanthic folds, blue sclerae, tissue paper scarring over both knees, hyperextensible joints, velvety skin, criss-cross lines on palms and soles and a high arched palate. She also has indurated areas on both lower legs with an ulcer above the left lateral malleolus. Cardiovascular system: left parasternal heave with a pansystolic murmur maximal at the left sternal edge and apex. Central nervous system: myopathic facial appearance though no weakness was demonstrable and she could whistle without difficulty. She has bilateral dropped shoulders and atrophic sternomastoid muscles. Diffuse hypotonia with weakness of neck and limb muscles was noted. Sensory system and reflexes were normal. No lens subluxation.

Investigations: Muscle biopsy (left quadriceps), no evidence of myopathic or neurogenic disease seen; EMG November 1976 (right biceps, right vastus, right sternomastoid), no evidence of myopathy; ECG, left ventricular hypertrophy, 24 hour tape – no significant abnormality; echocardiogram, slight enlargement of left ventricle, no mitral valve prolapse, no rheumatic change.

The following tests were within normal limits or negative: FBC, ESR, sequential multiple analysis biochemical screen, serum thyroxine, serum folate and B_{12}, WR and VDRL, coagulation studies including platelet function tests, antinuclear factor, chest X-ray, creatine phosphokinase.

Comment

This patient shows features of the Ehlers-Danlos syndrome (EDS), namely joint hypermobility, tissue paper scars at sites of trauma and velvety, hyperelastic skin. Blue sclerae and bilateral epicanthic folds were also seen. The Ehlers-Danlos syndrome has been classified into seven types based on clinical, genetic and biochemical criteria. Biochemical investigation has demonstrated collagen defects in four of the seven types namely IV, V, VI, VII. No specific defect has been reported in types I, II and III. We think this patient falls into the first or gravis type (Table 1) (McKusick 1974, Uitto & Lichtenstein 1976).

In addition to these features she has a pansystolic murmur suggestive of mitral regurgitation. Mitral regurgitation has been reported in patients with EDS and is thought to be due to a floppy mitral valve (Brandt *et al.* 1975, Madison *et al.* 1963, McKusick 1972). We were unable to demonstrate this by echocardiography. Cardiac abnormalities seen in EDS are shown in Table 2.

The patient also complains of generalized pro-

Table 1
Features of the seven types of Ehlers-Danlos syndrome

	Type I	*Type II*	*Type III*	*Type IV*	*Type V*	*Type VI*	*Type VII*
Other names	Gravis	Mitis	Benign hypermobile	Ecchymotic arterial or Sack-Barabas type	—	Ocular	Arthrochalasis multiplex congenita
Defect	Unknown	Unknown	Unknown	In synthesis of type III collagen	Lysyl oxidase deficiency	Defficiency of procollagen lysyl hydroxylase	Deficiency of procollagen protease (or peptidase)
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal dominant	?	X-linked	Autosomal recessive	Autosomal recessive
Clinical features							
Skin	Severe hyperextensibility fragility bruisability	Mild	Minimal	Thin pale skin with prominent venous network, severe bruisability	Marked stretchability, variable fragility and bruisability	Moderate skin features	Moderate bruisability and stretchability
Joints	Severe and generalized hypermobility	Mild, may be limited to hands and feet	Generalized marked hypermobility	Minimal laxity limited to the digits	Minimal hypermobility	Moderate	Severe laxity
Other features	Premature rupture of membranes of affected foetus		Barlow syndrome (floppy mitral valve syndrome)	Rupture of bowel. Rupture of great vessels. Elastosis perforans serpiginosa		Severe scoliosis ocular fragility (rupture of sclera or cornea and/or retinal detachment after minor trauma)	Short stature congenital dislocations

Table 2
Cardiac lesions in Ehlers-Danlos syndrome (Beighton 1969)

Atrial septal defect
Tetralogy of Fallot
Mitral regurgitation
Tricuspid regurgitation
Aortic regurgitation
Bicuspid right atrioventricular valve
Pulmonary artery stenosis
Aortic stenosis
Aneurysm sinus of Valsalva
Partial persistence of A-V canal
Aortic arch anomalies

gressive weakness associated with wasting of some muscles especially the sternomastoids. Muscle enzymes and EMG done recently, and muscle biopsy taken two years ago, were all normal. It is probable that her weakness and hypotonia is secondary to the hypermobility and instability of her joints.

She was reported, at the age of 20, as a case of combined Marfan's and Ehlers-Danlos syndromes (Dubowitz 1969). We think it is unlikely that she has Marfan's syndrome as she has a normal height/arm span ratio and normal lenses.

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DISCUSSION

Dr F M Pope (*Clinical Research Centre, Division of Cell Pathology, Watford Road, Harrow*): Ehlers-Danlos syndrome (EDS) is extremely heterogeneous, presently comprising several variants. Biochemical defects have been identified in four of them: types IV–VII (Pope *et al.* 1975, Di Ferrante *et al.* 1975, Pinnell *et al.* 1972, Lichtenstein *et al.* 1973). Types I–III are inherited as autosomal dominant traits, type V as a sex-linked recessive character and the other three as autosomal recessives (Beighton 1970, McKusick 1972). The Marfan syndrome is similarly heterogeneous. Initially homocystinuria was separated completely from this group, and then a loose-jointed (Marfanoid) (Walker *et al.* 1969) and latterly a heavy variant have been recognized (McKusick 1975). Collagenous abnormalities are likely in these disorders and await biochemical identification.

The patient under discussion undoubtedly has the Ehlers-Danlos syndrome. The loose-jointedness, blue sclerae, hypermobile joints and paper tissue scars are diagnostic of EDS type I. Aortic and mitral incompetence have been observed previously in this variety especially and can also occur in types II, III and IV (Silvermann, Pope, Fortuin & McKusick unpublished). Her orthopædic deformities are less common, but do occur in the disease. Commonly, as in her case, these patients are thought to have a myopathy. Some myopathic processes, such as Nemaline myopathy, can closely mimic inherited connective tissue diseases. Because of her tall stature and tall maternal grandfather the possibility of the Marfan syndrome was suggested. Her normal span and lenses are evidence against this. It is probable that the coincidence of two such fundamental biochemical collagen defects (EDS + Marfan) would be fatal clinically.

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Dr R A J Eady: How specific are the known biochemical disorders? For example, does a deficiency of procollagen peptidase affect the biosynthesis of all four main types of collagen, or is the lesion limited to only one substrate? I believe that we should have this information if the pathogenesis of some varieties of Ehlers-Danlos syndrome (e.g. type VII or dermatosporaxis) is to be explained in biochemical terms.

Dr F M Pope: Procollagen is a precursor form of collagen which has both carboxyl and amino-terminal extensions, whose function is to align collagen chains for crosslinkage (Martin *et al.* 1974, Byers *et al.* 1975). An enzyme procollagen peptidase cleaves off the extra piece and its absence is followed by the formation of abnormal collagen fibres in cows and sheep with dermatosporaxis (Lenaers *et al.* 1971, Helle & Nesse 1972, Becker *et al.* 1976). Humans show a much milder disorder, with lax joints and short stature predominantly (Lichtenstein *et al.* 1973) compared with the fatal animal disorder. Since there are four types of collagen, and thus eight extension peptides, there may be several (perhaps four and possibly eight) different peptidases. Different clinical syndromes would then be expected for each variety of enzyme defect. This could explain the reason for the difference between the catastrophic animal disease and the relatively benign human disorder. Some types of Ehlers-Danlos syndrome or other inherited connective tissue disorders may be explained on this basis too.

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Professor M W Greaves: Dr Pope has laid considerable emphasis on the biochemical changes in collàgen in this disorder. I should like to know whether distinctive changes can be identified in skin fibroblast cultures, and their ability to synthesize collagen. Also have changes in mucopolysaccharide ground substance been sought in Ehlers-Danlos syndrome?

Dr F M Pope: Three of the seven clinical varieties of EDS have identified biochemical abnormalities. Thus EDS IV (ecchymotic variety, or acrogeria) shows a total inability to produce type III collagen (Pope *et al.* 1975, 1977). This often results in fatal premature arterial rupture. The disease is analogous to the thalassemias in which certain hæmoglobin chains are missing. If the analogy is complete, we may expect a spectrum of separate diseases in which the quantity of type III collagen production ranges from zero (as in EDS IV) to small amounts. I would expect that the particular clinical features would vary accordingly.

Type V EDS is the sex-linked type and Di Ferrante *et al.* (1975) have shown a deficiency of the crosslinking enzyme, lysyl oxidase, from cultured fibroblasts of one affected individual. Type VI EDS, which combines retinal detachment and kyphoscoliosis with otherwise typical EDS, is due to under-hydroxylation of lysyl residues in various collagen chains. First shown in tissue studies by Pinnell *et al.* (1972), it was later confirmed in cultured fibroblasts (Sussman *et al.* 1974). Type VII EDS combines short stature and spectacularly hypermobile joints and is due to a deficiency of procollagen peptidase, as mentioned earlier.

No defect is yet identified in EDS types I–III. All are inherited as autosomal dominant traits and collagen synthetic studies, especially in cultured fibroblasts, may be crucial. It is probable that the present clinical classification of EDS into seven types will prove biochemically inadequate. Thus, for example, EDS types I, IV and VII may all contain several distinct varieties of disease. No changes in mucopolysaccharide components have yet been identified in either EDS or any of the related disorders.

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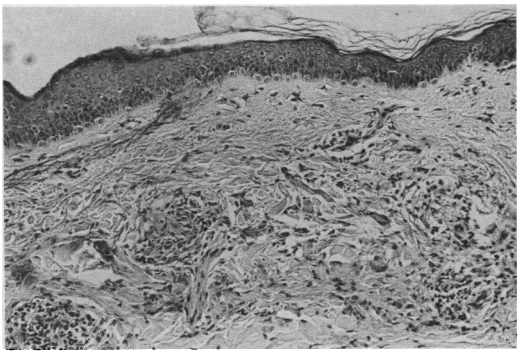

Fig 2 *Skin histology showing diffuse granulomata with slight necrobiosis*

Cutaneous Granulomata with Primary Biliary Cirrhosis

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For two years Mrs E S, aged 74, had a generalized pruritus which was associated for the last year with a widespread sheeted papular eruption on the trunk and limbs. On examination there was slight generalized hyperpigmentation and a sheeted glistening flesh-coloured papular eruption affecting the upper chest, back and arms (Fig 1). Liver palpable 6 cm and spleen 3 cm below the costal margin; no clinical jaundice or xanthelasma.

Investigations: HB, 10.2 g/dl; WBC, 3000 cells/μl; platelets, 143 000/μl; ESR, 90 mm/hr; partial thromboplastin time 16 s (control 13 s); bilirubin, 14 μmol/l; alkaline phosphatase, 850 iu/l (normal 30–85 iu/l); aspartate aminotransferase, 157 iu/l (normal 50 iu/l); IgM, 6.0 g/l (normal 0.5–1.7 g/l); IgG, 29.4 g/l (normal 5–16 g/l); IgA, 1.7 g/l (normal 1.4–4.2 g/l); Kveim test, negative; Mantoux test, negative; antimitochondrial antibodies 1:320. Barium swallow showed no œsophageal varices; Schirmer's test abnormal, suggesting keratoconjunctivitis sicca. Technetium scan showed hepatomegaly with a patchy uptake and increased splenic uptake. Chest X-ray was normal with no evidence of hilar lymphadenopathy or fibrosis. Skin biopsy (Fig 2), taken from the back, revealed granulomata in the dermis consisting of monuclear cells, epithelioid cells and Langhan's type giant cells. Liver biopsy (Dr B Portmann, Fig 3) showed changes consistent with primary biliary cirrhosis (PBC), namely enlargement of portal tracts with ill-defined granulomata; focal collections of lymphocytes and plasma cells around small bile ducts, the epithelial cells of which were swollen and abnormal; piecemeal necrosis; and extensive fibrosis.

Treatment
One sachet of cholestyramine every day for pruritis; methyl cellulose eye drops and monthly injections of vitamins A, D and K.

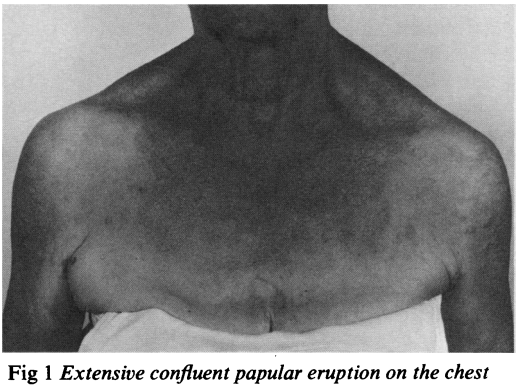

Fig 1 *Extensive confluent papular eruption on the chest*

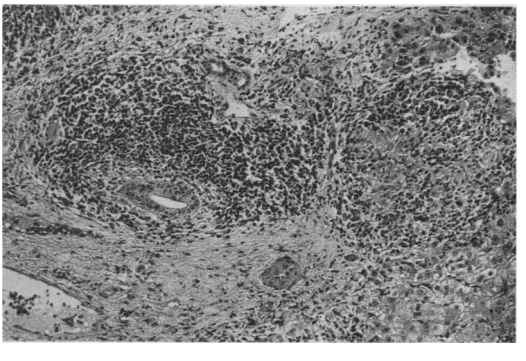

Fig 3 *Liver biopsy showing granulomata chronic inflammatory reaction around the bile ducts, piecemeal necrosis and portal tract fibrosis*