

Abnormalities of the lungs and thoracic cage in the Ehlers-Danlos syndrome

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ABSTRACT Twenty patients with the Ehlers-Danlos syndrome, (10 type I, six type II, and four type IV) were studied to assess the frequency of respiratory abnormalities in this condition. Five patients (25%) had had at least one episode of haemoptysis, but none had any defect of coagulation. There was a high frequency of recurrent sinusitis, notably in those with the type I syndrome. Two patients had bullous lung disease, one of whom (type IV) had had three pneumothoraces and subsequent pleurodesis; he also had tracheomegaly (the Mounier-Kuhn abnormality). Minor skeletal abnormalities such as pectus excavatum were common, particularly in patients with type IV disease. Three patients had the straight back syndrome. There were no consistent spirometric or lung volume abnormalities, but eight patients (40%) had a raised gas transfer coefficient (Kco), possibly due to an increased intrapulmonary vascular volume. Two other patients had very low values of Kco that were unexplained.

The Ehlers-Danlos syndrome is an inherited defect of connective tissue characterised by soft and hyperextensible thin skin, hypermobile joints, and a particular tendency to bruising and bleeding. Other associated abnormalities include hernias, varicose veins, large arterial rupture, mitral valve prolapse, various ophthalmic complications, and obstetric problems such as premature rupture of the membranes and perineal tears.¹ Eight or more clinical types are currently recognised² and specific biochemical abnormalities of collagen are known in Ehlers-Danlos syndrome types II, III, V, VI, and VII (table 1).³ There is no evidence to suggest abnormalities of elastin or other connective tissue components, although an abnormality of fibronectin has been described in type VIII.⁴

No systematic study of pulmonary abnormalities in this group of disorders has been reported, although there have been several individual case reports describing pneumothoraces or bullae^{1,5-12} and haemoptysis^{8,9,13-18}.

We have undertaken a study of the clinical features and lung function of a group of patients with Ehlers-Danlos syndrome types I, II, and IV.

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Accepted 10 December 1984

Patients and methods

Twenty five patients with type I, II, or IV Ehlers-Danlos syndrome attending outpatients at Northwick Park Hospital, Harrow, were contacted by letter asking if they would be prepared to take part in the study. Eighteen agreed, the remaining two patients in the study having been diagnosed at Guy's Hospital. Age, sex, and Ehlers-Danlos syndrome type are shown in table 2. Eleven were male (aged 11-45 years) and nine female (aged 15-45 years). Patients 2 and 3 are the children of patient 1, patient 18 the daughter of patient 17, and patient 8 the son of patient 7.

Each patient gave a full medical history, answered a modified Medical Research Council respiratory questionnaire, and underwent clinical examination. Measurements were made of FEV₁, forced vital capacity (FVC), and peak expiratory flow rate (PEFR) by standard methods before and after inhalation of bronchodilator. Total lung capacity (TLC) and residual volume (RV) were measured in a body plethysmograph.²⁰ Transfer factor for carbon monoxide, both total (TLco) and corrected for lung volume (Kco), were measured by the single breath method and alveolar volume by helium dilution. Maximal expiratory and inspiratory flow-volume curves were obtained by using an Ohio spirometer

Table 1 Clinical, genetic, and biochemical classification of the various types of the Ehlers-Danlos syndrome

Type	Inheritance	Major manifestations	Biochemical defect	
I	Gravis	Autosomal dominant	Marked joint hypermobility and bruising, fragility, hyperextensibility of skin	Unknown
II	Mitis	Autosomal dominant	Moderate joint mobility and hyperextensible skin	Unknown
III	Benign	Autosomal dominant	Marked joint hypermobility, minimal cutaneous manifestations	Unknown
IV	Ecchymotic	Autosomal recessive	Hypermobility limited to digits, marked skin fragility and bruising, arterial and gastrointestinal rupture	Deficiency type III collagen
V	X linked	X linked recessive	Minimal joint mobility, marked hyperextensibility of skin with moderate bruising, skeletal disorders	Lysyl oxidase deficiency
VI	Ocular	Autosomal recessive	Appreciable joint hypermobility, very hyperextensible skin with little bruising, scleral and corneal fragility	Lysyl hydroxylase deficiency
VII	Arthrocalasis multiplex congenita	Autosomal recessive	Appreciable joint hypermobility, moderate skin fragility with hyperextensibility and bruising, short stature, multiple dislocations	Defective conversion of pro-collagen to collagen
VIII	Periodontitic	Autosomal dominant	Moderate joint mobility and skin fragility but minimal hyperextensibility, advanced periodontitis	Unknown

linked to an X-Y recorder. Normal ranges were defined as the mean ± 2 standard deviations from the mean¹⁹ and values outside these ranges were taken to indicate a significant functional abnormality. Reduced values for FEV₁ and FVC with a normal forced expiratory ratio (FEV₁/FVC% (FER)) were regarded as indicating a restrictive ventilatory defect and reduced values of FEV₁ with a reduced

FER as indicating an obstructive defect. Quasistatic pressure-volume curves of the lungs were obtained for two patients.²¹ Skinprick tests for six common allergens were performed on each patient. A posteroanterior and lateral chest radiograph was obtained in 18 cases. From the lateral radiograph, the distance from the middle of the anterior border of T8 to a vertical line connecting T4 and T12 (the

Table 2 Abnormalities of respiratory history, pulmonary function, and radiology in 20 patients with Ehlers-Danlos syndrome

Patient No	Sex	Age (y)	Smoking	Skin Tests	Respiratory history	MRC grade of dyspnoea	KCO (mmol/min/kPa/l)		Radiological abnormalities
							Value	Predicted	
<i>Type I</i>									
1	F	36	No	HD/HDM	Pneumonia (x2); Rec "wheezy bronchitis"	1	2.2	1.6-2.0	Pectus excavatum
2	F	16	No	-ve	Rec sinusitis; rec "wheezy bronchitis"	1	2.2	1.7-2.1	Hypoplastic sternum; corrected ductus arteriosus
3	M	13	No	-ve	Recurrent sinusitis	1	3.0	1.7-2.2	No radiograph
4	F	45	Yes	-ve	Chronic bronchitis; pleurisy (xl); Rec sinusitis; Haemoptysis	3	1.8	1.5-1.9	Bilateral upper zone fibrosis
5	M	32	Yes	Mult	Pneumonia (xl); Rec "wheezy bronchitis"	2	1.9	1.5-2.0	Pectus excavatum; right sided aorta
6	F	33	Yes	-ve	Pneumonia (xl)	1	2.0	1.6-2.0	—
7	M	34	Yes	-ve	—	1	1.7	1.4-2.0	—
8	M	14	No	-ve	—	1	2.0	1.7-2.2	—
9	M	11	No	-ve	—	1	2.0	1.7-2.2	—
10	F	39	Yes	HDM Grass	—	1	1.6	1.5-1.9	—
<i>Type II</i>									
11	M	25	Yes	-ve	Haemoptysis (xl)	1	0.95	1.5-2.1	No radiograph
12	F	28	No	Cat	Sinusitis (xl); Haemoptysis (xl)	1	2.1	1.6-2.0	Pectus excavatum; scoliosis
13	M	15	No	HDM	—	1	2.1	1.6-2.1	Right apical bulla
14	F	45	Yes	-ve	Rec sinusitis; pleurisy (xl)	1	0.96	1.5-1.9	Pectus excavatum
15	F	39	Yes	-ve	Rec haemoptysis; Rec sinusitis; asthma	Variable†	2.3	1.5-1.9	—
16	F	19	Yes	-ve	—	1	2.1	1.2-2.1	Pectus excavatum; scoliosis; MDV = 1.1
<i>Type IV</i>									
17	M	45	No	Mult	Pneumonia (xl); Pleurisy (xl); Pneumothorax (x3)	2	2.0	1.3-1.8	Pectus excavatum; thin ribs; scoliosis; pleural thickening
18	F	12	No	Grass	—	2	2.5	1.7-2.2	Hypoplastic sternum; thin ribs; scoliosis
19	M	31	No	-ve	Hamoptysis (xl)	3	2.5	1.5-2.0	Dilated aorta; thin ribs; MDV = 1.2
20	F	15	No	Mult	—	1	2.6	1.7-2.2	MDV = 0.7

HD—house dust; HDM—house dust mite, multiple positive skin test responses; KCO—gas transfer coefficient; MDV—mid dorsal value; Rec—recurrent; "wheezy bronchitis": attacks of cough with wheezing. Normal values from Cotes.¹⁹ The range is calculated from the mean and 1 standard deviation. *Probably asthma.

†Because of asthma.

Table 3 Measured values of tracheal diameter (mm) at a film focus distance (FFD) of 100 cm,²³ estimated values for FFD of 150 cm, and suggested upper limit of the normal tracheal diameter for adults at an FFD of 150 cm

Tracheal diameter	Film focus distance	
	100 cm	150 cm
Smallest diameter	13.0	12.2
Largest diameter	25.0	23.5
Mean (SD) diameter	20.2 (3.4)	19.0 (3.2)
Suggested normal upper limit of tracheal diameter (ie mean and 2 SDs)	27.0	25.4

mid dorsal value, MDV) was used as a measure of the straight back syndrome²²; satisfactory measurements were obtained in 15 patients.

The minimum and maximum anteroposterior and lateral diameters of the trachea and, where possible, the right and left main bronchus were measured. In a review of tracheobronchiomegaly (the Mounier-Kuhn abnormality), Katz *et al*²³ established normal ranges for minimum and maximum diameters of the major airways. They, however, used a film focus distance (FFD) of 100 cm (40 in) for their posteroanterior chest radiographs, compared with 150 cm (60 in) in this study. The respective estimated magnifications would be 1.18 for an FFD of 100 cm and 1.11 for 150 cm. The normal range of Katz *et al* and the corrected range for the larger FFD are shown in table 3.

Results

RESPIRATORY HISTORY

The abnormalities of the 20 patients are shown in table 2. Eight (40%) of the patients were current smokers. Five patients (20%) claimed to be unduly breathless, two of whom (Nos 4 and 19) had a restrictive defect as shown by spirometry. One patient, a heavy smoker, had chronic bronchitis. Three patients (Nos 1, 15, and 17) gave a history of attacks of wheezing and patient 15 was shown subsequently to have asthma. Five patients (25%) reported at least one episode of haemoptysis, usually associated with a respiratory tract infection, although two patients coughed up blood over prolonged periods of time. One of these latter patients had polycythaemia rubra vera.

Five patients, all with type I Ehlers-Danlos syndrome, gave a history of recurrent attacks of cough and wheezing. Three were smokers and two non-smokers. Five patients had recurrent attacks of sinusitis and four had had pneumonia. One patient

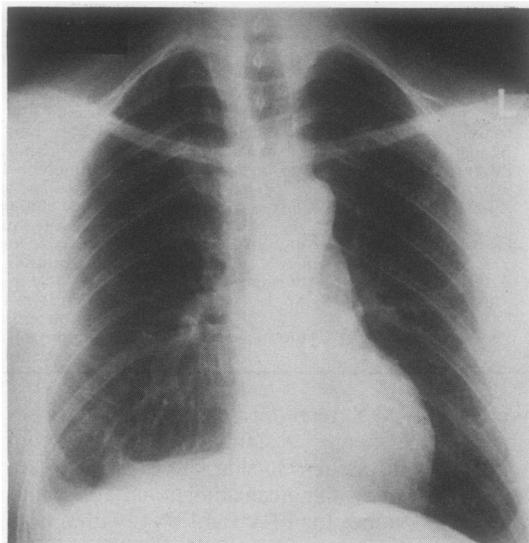


Fig 1 Posteroanterior Chest radiograph of patient 17 showing thin, tapering ribs and the Mounier-Kuhn abnormality (tracheomegaly), with a minimum tracheal diameter of 27 mm. The pleural changes at the right base are the result of a pleurodesis.

(No 17) had suffered three pneumothoraces and had undergone pleurodesis.

RADIOLOGY

Eight patients had normal chest radiographs and



Fig 2 Lateral chest radiograph of patient 20 showing the straight back syndrome (mid dorsal value 0.7 cm).

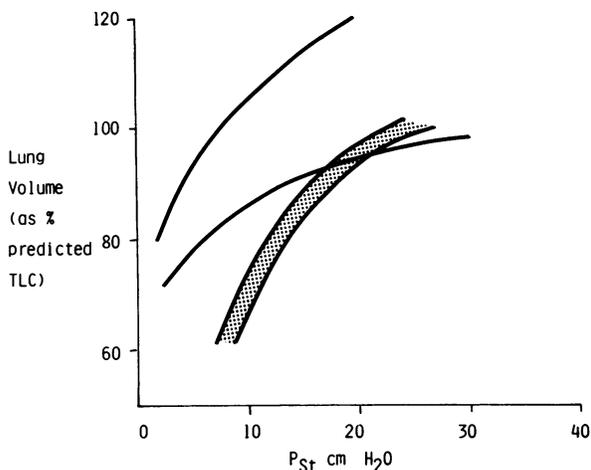


Fig 3 Pressure volume curves of the lungs in 2 patients (Patient no 12—upper curve; patient no 6—lower curve). The curves shown are best fit curves for values of lung recoil pressure (P_{st}) at volume intervals of 10% predicted TLC, averaged from several quasistatic deflation manoeuvres. Shaded area represents normal range for young women.²¹

two patients did not have radiographs taken. The others showed various abnormalities.

Skeletal abnormalities Six patients had mild pectus excavatum and three had very thin ribs with a characteristically increased downward slope (fig 1). A mild scoliosis was seen in four patients. Three with mid dorsal values of 1.1, 1.2, and 0.7 cm fitted the criteria for the straight back syndrome (fig 2). The mean MDV for the 15 patients in whom accurate measurement was possible was 1.66 cm (range 0.7–3.1 cm). Two patients, both young girls, had appreciably hypoplastic sternums.

Pulmonary disease One patient had bilateral upper lobe fibrosis and one had a single right apical bulla measuring 5 × 3.5 cm. Patient no. 17 had bilateral multiple bullae which had resulted in three spontaneous pneumothoraces. He also had tracheomegaly with a maximum tracheal diameter of 27 mm (fig 1).

Cardiac abnormalities Patient no 5 had a right sided aortic arch and in patient 19 the aorta appeared unfolded for his age. Patient 2, who had had a ductus arteriosus ligated, had a normal cardiac contour.

RESPIRATORY FUNCTION TESTS

The results are summarised below and in table 2; a full table of pulmonary function measurements is available on request.

Spirometry and flow volume curves One patient (No 3) showed a restrictive defect on spirometry and two (nos 15 and 19) had a mixed obstructive and

restrictive defect. Patient 15, who smoked and had asthma, showed an increase in FEV_1 of more than 15% on inhaling 2.5 mg of nebulised salbutamol. Patient 19 had never smoked and showed no improvement in FEV_1 with 2.5 mg nebulised salbutamol. Seven patients showed a slight "scoop" on the expiratory limb of the flow-volume curves, suggesting mild airflow obstruction.

Lung volumes TLC was reduced in six patients (nos 3, 4, 13, 15, 17, and 19). One of these (no 4) had radiographic evidence of bilateral apical fibrosis and one (no 17) had had a pleurodesis for recurrent pneumothoraces.

Gas transfer Eight patients (40%) had a KCO value of more than 1 SD above the mean predicted value (Nos 1, 2, 3, 12, 15, 17, 19, 20). Four of these (Nos 3, 15, 17, and 19) had a reduced alveolar volume and TLC. One further patient (No 18) had a high KCO; both the TLCO and TLC were normal, but VA was unexpectedly low and the apparently high KCO is assumed to result from a technical error. Two patients (Nos 11 and 14) had reduced values of KCO and TLCO with normal lung volumes.

Pressure-volume curves Pressure-volume curves were obtained in two patients (Nos 6 and 12) and are shown in figure 3. The curve for patient 12 is shifted upwards and to the left, but her spirometric values were normal, and this apparent shift is likely to be simply a reflection of her above average TLC, which was nevertheless within the normal range.

Skin tests Eight patients had one or more positive skinprick test reactions.

Discussion

A range of abnormalities was observed in our patients, but there was no particular correlation with the clinical classifications of the disease.

Seven cases of pneumothorax in Ehlers-Danlos syndrome have been reported^{1, 5, 7, 8, 11, 12, 24} and three of these patients certainly had type IV disease.^{5, 7, 8} The patient described by Clark *et al*⁷ had bullae and type III collagen deficiency. Bullae were also reported in three other cases.^{1, 9, 11} The patient reported by Baumer and Hankey⁶ probably had a pneumatocele, the diagnosis of Ehlers-Danlos syndrome being coincidental. Pneumothorax appears to be less commonly seen in Ehlers-Danlos syndrome than in Marfan's syndrome.²⁵

Twenty five per cent of our patients had had at least one haemoptysis. This has previously been described in Ehlers-Danlos syndrome,^{8, 9, 13, 18} and in one patient¹⁸ it may have been due to bronchiectasis. The interesting patient of Grant and Adler's¹⁶ had diffuse intrapulmonary haemorrhage of obscure cause. Although minor abnormalities of clotting

have been documented in Ehlers-Danlos syndrome²⁶ there was no correlation between such abnormalities and a history of haemoptysis in our patients.

A history of recurrent sinusitis and pneumonia was relatively common in our patients, notably in patients with type I disease.

Tracheobronchiomegaly was first described by Mounier-Kuhn and Meyer in 1949,²⁷ and the clinical and radiological features have since been well described by Katz *et al*²³ and Himalstein and Gallagher.²⁸ There has been one previous report²⁹ of a patient with Ehlers-Danlos syndrome and the Mounier-Kuhn abnormality, and Wanderer *et al*³⁰ described the association of tracheomegaly with acquired cutis laxa. One further patient, with emphysema and untyped Ehlers-Danlos syndrome, was reported as having tracheobronchiomegaly; but no measurements were given.³¹

The major abnormality of lung function was a raised gas transfer coefficient in eight patients. This finding may be due to increased pulmonary blood volume or intrapulmonary haemorrhage but various other causes are known.³² One possibility is that the various collagen defects responsible for the different types of Ehlers-Danlos syndrome may alter the permeability or distensibility of blood vessel walls. Subtle abnormalities of type I, III, or basement membrane collagen could be implicated here. The total carbon monoxide transfer factor in these patients was not, however, increased. An alternative explanation is that the raised KCO in some patients resulted from extrapulmonary volume restriction due to thoracic cage abnormalities, although the abnormalities that we detected were relatively minor. There is no obvious explanation for the low KCO observed in patients 11 and 14. Pressure-volume curves were not obtained in these two patients, but emphysema is unlikely as flow-volume curves and lung volumes were normal.

The pressure-volume curves obtained in patients 6 and 12 are inconclusive but they show no evidence of generalised emphysema and the available histological evidence⁷ suggests that when bullae are present they are not usually associated with generalised emphysema. One patient (possibly having a new subtype of Ehlers-Danlos syndrome) has, however, been reported with severe panacinar emphysema³³ but this appears to be rare in Ehlers-Danlos syndrome, in contrast with the severe, early onset emphysema seen in cutis laxa, a condition characterised by abnormal elastic fibres.³⁴

Finally, various minor skeletal abnormalities were detected. These included thin, sloping ribs in three of the four patients with type IV disease, as has previously been described.³⁵ Our patients had only

minor degrees of scoliosis, as is usual in these particular types of Ehlers-Danlos syndrome. Severely deforming scoliosis is well known to be associated with lysyl hydroxylase deficiency (type VI Ehlers-Danlos syndrome),^{1,36} although it has been described in other types.³⁷ By radiological criteria 20% of our patients had the straight back syndrome.^{22,38}

Our findings suggest a variety of thoracic abnormalities in Ehlers-Danlos syndrome. Bullae and pneumothoraces are not uncommon, especially in type IV disease, in which type III collagen deficiency also leads to thin skin and arterial rupture.^{1,39} No consistent abnormality of lung function was detected but nearly half of our patients had an increased gas transfer coefficient. Ehlers-Danlos syndrome should be considered as a diagnosis in the presence of premature bullous disease, recurrent pneumothorax, or unexplained haemoptysis.

We are very grateful for the advice of Dr MK Davies, the secretarial assistance of Mrs P Jackson, and the technical help of Martin King and the staff of the respiratory function unit at Guy's Hospital.

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