Pulmonary disease in patients with Marfan syndrome

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ABSTRACT Hospital case notes and chest radiographs of 100 patients with Marfan syndrome were investigated for evidence of pulmonary disease. The criteria for inclusion of details of a given patient in the study were the occurrence of Marfan abnormalities in at least two separate body systems (skeletal, cardiovascular, ocular) or in one body system where there was a family history of a classically affected first degree relative. Selection of cases was biased towards those with cardiorespiratory problems by virtue of the hospitals from which the patients were drawn. Forty eight patients underwent cardiac surgery. Eleven patients had a history of spontaneous pneumothorax, which had been recurrent in 10 cases and bilateral in six. Eight had had pneumonia or excessively frequent respiratory infections and two had bronchiectasis. Chest radiographs showed emphysematous bullae in five, upper lobe fibrosis in four, and aspergilloma in two. The cases reviewed together with other published evidence suggest that spontaneous pneumothorax and bullae are causally related to Marfan syndrome. The presence of idiopathic upper lobe fibrosis in four Marfan patients is interesting but provides insufficient evidence to assess possible causality.

Marfan syndrome is a disorder of connective tissue, inherited as an autosomal dominant of variable expression, and in its classical form comprises abnormalities in the skeleton, cardiovascular system, and eye.[1] Disorders of the respiratory system have been noted in some patients with the syndrome in published reports. No previous study, however, has investigated the nature of pulmonary disease in patients with Marfan syndrome. We have conducted a retrospective survey of the hospital case notes and chest radiographs of 100 patients with Marfan syndrome to review the pattern of pulmonary disease in this group of patients.

Methods

Since there is no diagnostic test for the connective tissue abnormality which results in the abnormalities in Marfan syndrome the diagnosis rests on clinical features alone. To exclude doubtful atypical or "forme fruste" cases we used the following inclusion criteria: the presence of abnormalities compatible with Marfan syndrome in at least two body systems (skeletal, cardiovascular, ocular) or in one sys-

tem together with a family history of Marfan syndrome.

Only the following features were used as criteria in confirmation of the diagnosis, although other Marfan features were often also present. *Skeletal:* Arachnodactyly (where available a metacarpal index exceeding 8·4), arm span greater than height, high arched palate, pectus excavatum deformity, kyphoscoliosis, hyperextensible joints; a minimum of two of these features was required to document skeletal abnormality. *Cardiovascular:* Aortic root enlargement, aortic regurgitation, mitral valve prolapse, increase in aortic compliance (determined by a continuous wave Doppler ultrasound technique[2]). *Ocular:* Ectopia lentis. *Family history:* For this to be regarded as positive a classically affected first degree relative was required.

Patients diagnosed as having Marfan syndrome were obtained from the disease indexes of 12 London teaching hospitals by searching through hospital notes indexed according to the World Health Organisation International Classification of Disease as 759·8 (congenital malformation syndromes affecting multiple systems). We examined the records of each patient and identified those who according to the above criteria had Marfan syndrome. One hundred patients were identified. This included 34 from the Brompton Hospital and 28 from Guy's Hospital,

Table 1 *Age and sex distribution of 100 patients with Marfan syndrome*

	Age (y)							Total
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	
Male	2	9	20	16	7	5	4	63
Female	5	5	16	7	2	1	1	37

obtained by a systematic search of all available records. Eleven further cases were obtained from the National Heart Hospital and 27 from the other hospitals by a non-comprehensive search. The hospitals providing cases include specialised referral centres for cardiac investigation, cardiothoracic surgery, and at Guy's Hospital a regional genetics centre. We excluded a considerable number of cases labelled as Marfan syndrome because they did not meet the criteria or because there was insufficient information, including absence of chest radiographs.

The records of each patient were reviewed for evidence of pulmonary disease and the chest radiographs were examined by one of us (KMC).

Results

Of the 100 patients from 99 separate families 63 were male and 37 female, giving a male to female ratio of 1·7:1. The mean (SD) age for male patients was 32 (14) years and for female 26 (12) years, with an age distribution as shown in table 1. Cardiac surgery had been performed in 48 patients, including aortic (40) and mitral valve (4) replacement, resection of aortic root with reimplantation of coronary arteries (10), repair of coarctation (2), and closure of ventriculoseptal defect (1). Twenty patients had died (10 male and 10 female). The

mean age at death for males was 36 (10) years and for females 22 (9) years. Only two patients died from respiratory causes, one due to respiratory failure secondary to severe scoliosis and one after surgery for removal of aspergilloma. Seventeen died from cardiac causes and one from a road traffic accident.

SPONTANEOUS PNEUMOTHORAX
Eleven patients had had spontaneous pneumothorax. Only three of these had entered the study hospitals for this reason, one of them having been referred for specialist management. The mean (SD) age of the 11 patients at the time of the first pneumothorax was 22 (5) years. Nine were male. Height was known for eight patients, six of whom were 1·83 m (6 ft) or more in height. Eight of the 11 patients had pectus deformity, kyphoscoliosis, or both. All but one patient had sustained at least two episodes of pneumothorax and in six patients both sides of the chest had been affected. Pulmonary disease was present in six patients: two had apical bullae and four apical fibrosis (table 2).

BULLAE
Five patients had bullae and all were male (table 2). Three of these were in their early twenties when bullae were first documented.

BRONCHIECTASIS AND PULMONARY INFECTION
Bronchiectasis was present in two patients. Pneumonia had occurred in another five patients. A history of excessively frequent lower respiratory tract infection was given by three patients. Pulmonary tuberculosis had been diagnosed in three patients.

Table 2 *Characteristics of patients with pulmonary disease*

Sex	Age (y)	Height (cm)	Span (cm)	Thoracic deformity		Marfan features				Pulmonary abnormality				
				Pectus	Kypho	Skel	CVS	Eye	FH	PN	Bull	Asp	Fib	Br
F	33	170		E		+			+	+				
M	19	188				+		+		+				
M	21	188		A		+	+		+	+	+			
M	26	175	188	A	+	+	+			+			+	
M	25	191		E		+		+		+	+			
M	41	193	196	A		+	+			+			+	
M	23	185		E	+	+	+	+		+				
M	25					+	+	+		+				
F	26	183		E		+	+			+				
M	30				+	+	+			+			+	
M	56				+	+	+			+			+	
M	44	193	198			+	+				+			
M	40	196	206	E		+	+				+	+		
M	46	183	191	E		+	+					+	+	+
F	31				+	+	+						+	+
M	64	193				+	+				+			

E—pectus excavatum; A—chest wall asymmetry; Kypho—kyphoscoliosis; Skel—skeletal; CVS—cardiovascular; FH—family history; PN—previous pneumothorax; Bull—bullae; Asp—aspergilloma; Fib—fibrosis; Br—bronchiectasis.

Table 3 Coexistence of pulmonary fibrosis and Marfan syndrome

Sex Age (y)	Features of Marfan syndrome		History of pulmonary disease	Chest radiographs	Histology	Pulmonary function tests	
	Skeletal	Cardiovascular				Test	% predicted
M 41	High arch palate, upper thoracic kyphosis, mid thoracic scoliosis	Mitral valve prolapse, aortic root dilatation, increased aortic wall compliance (187%)	Pneumothorax, bilateral empyemas treated by decortication	Bilateral upper lobe fibrosis		FEV$_1$ FVC^1 VC TLC TLco	43 40 39 66 49
M 30	Archnodactyly, high arch palate, upper thoracic scoliosis	Floppy mitral valve, increased aortic wall compliance (134%)	Recurrent pneumothorax	Bilateral upper lobe fibrosis	Severe fibrosis with non-specific inflammatory cell infiltration	FEV$_1$ FVC^1 VC TLC TLco	65 56 53 70 77
M 56	High arch palate, kyphoscoliosis	Mitral valve prolapse, increased aortic wall compliance (134%)	Pneumothorax	Bilateral upper lobe fibrosis		FEV$_1$ FVC^1 VC TLC TLco	69 84 76 93 69
M 46	High arch palate, arachnodactyly, severe pectus excavatum	Aortic regurgitation	Recurrent chest infections	Bilateral upper lobe fibrosis, bronchiectasis on bronchogram, aspergilloma in left upper lobe		FEV$_1$ FVC^1 VC TLC	39 38 36 59

FVC—forced vital capacity; VC—vital capacity; TLC—total lung capacity; TLco—transfer factor.

PULMONARY FIBROSIS OF OBSCURE ORIGIN
Four patients had bilateral upper lobe fibrosis of obscure cause. Details of these are shown in table 3. Causes of upper lobe fibrosis, including pneumoconiosis, tuberculosis, sarcoidosis, ankylosing spondylitis, extrinsic alveolitis, and other conditions, had been sought and not found. Another patient had pulmonary fibrosis that was attributed to treatment with carmustine for a fourth ventricular ependymoma.

PULMONARY ASPERGILLOMA
Aspergillomas were found in two patients.

Discussion

Marfan syndrome is a genetically determined disorder characterised by a defect of connective tissue that reduces its tensile strength, and results in abnormalities in the skeleton, cardiovascular system, and eye. As no confirmatory biochemical test yet exists, the diagnosis must be made on the clinical features alone. Some of the clinical features are not specific to Marfan syndrome and are found in other clinical entities—for example, Ehlers-Danlos syndrome. To exclude these other conditions and minor or "forme fruste" cases of Marfan syndrome we rejected cases which did not fulfil strict selection criteria and cases for which insufficent evidence was available to confirm the diagnosis.

Our selection of cases was inevitably biased towards patients attending hospital, in particular those with cardiac or respiratory abnormalities since 45 of these were obtained from the Brompton Hospital or National Heart Hospital, whose interests are cardiorespiratory. These factors have undoubtedly contributed to the high mortality in this series, particularly as almost half of the patients had undergone cardiac surgery and one quarter of the deaths (five cases) had occurred at surgery. The mean age at death of 36 years for male and 22 for female patients is, however, similar to that of 33 and 29 years reported in a large American series.[3]

Spontaneous pneumothorax was the commonest respiratory abnormality detected in this series, being present at some time in 11%. Although this figure may have been influenced by our biased selection, most patients presented with the pneumothorax to local rather than specialist hospitals. A review of published reports up to 1969 revealed 15 cases of spontaneous pneumothorax among 300 cases of the syndrome.[4] The prevalence of a history of spontaneous pneumothorax in the general population has been estimated to be in the range of 5–35 per 100000.[5–7] A patient with Marfan syndrome is probably several hundred times more likely to sustain spontaneous pneumothorax than a normal individual.

In our 11 cases of pneumothorax all but one were recurrent, six were bilateral, and nine were in male patients. Combining our 11 patients with Marfan

syndrome and spontaneous pneumothorax with 40 we found in published reports (references supplied on request), we determined a male to female ratio of 3·9:1. A male to female ratio of 5–6:1 is found for spontaneous pneumothorax in otherwise healthy young adults, who are also likely to be tall, young, and male.[8] The possibility that Marfan syndrome may be common in patients presenting with spontaneous pneumothorax has been investigated in a study of patients presenting with this condition, in whom metacarpal index and height–arm span difference were determined and ophthalmological examinations performed.[9] Among 20 patients studied only two had spans which exceeded their heights and they were without other features to suggest the syndrome.

Spontaneous pneumothorax has been reported in association with other inherited disorders of connective tissue, including Ehlers-Danlos syndrome,[10] cutis laxa,[11] and the Marfanoid hypermobility syndrome,[12] which has features of both Marfan and Ehlers-Danlos syndromes.

Five of our patients had pulmonary bullae, which had been observed during the second decade of life in three cases. Our review of published reports has revealed an additional 45 cases of bullae, lung cysts, or emphysema, 22 of which were in patients under 20 years (references supplied on request). Of this total of 50 patients, 32 were male. Emphysema was reported in 27 and bullae with or without emphysema in 20. Although the total number of cases of Marfan syndrome "at risk" is not known, the age of the patients at least suggests a true association between the lung lesions and the Marfan syndrome.

Two of our patients had aspergillomas and these may well have formed within pre-existing bullous cavities since aspergillus is know to colonise abnormal air containing spaces in the lung.

Recurrent pneumothorax, bullae, and emphysema in Marfan syndrome are likely to be due to the generalised connective tissue defect to which cardiac valve abnormalities, aneurysms, ectopia lentis, and bone changes have been attributed. Several studies have documented abnormal elastic tissue in Marfan lungs.[13–16] Whether the changes in elastic tissue in the lung are secondary to a collagen defect or represent an additional abnormality remains to be determined. The suggestion that elastic fibre changes result from cyclical tissue stresses in tissue lacking adequate mechanical support owing to defective collagen seems reasonable.[17] Mechanical considerations suggest that stresses are maximal at the apices of the lungs in tall individuals with Marfan syndrome, and if pulmonary connective tissues were weak in these conditions this could account for the apical bullae.

Recent biochemical studies have provided further insight into the nature of a collagen defect. Analysis of tissue collagen from patients with Marfan syndrome has revealed defects in the biosynthesis of two polypeptide chains required for the formation of type I collagen.[17 18] Abnormalities in non-reducible crosslinks in collagen have been reported and these may explain the reduced tensile strength of Marfan connective tissue.[18 19]

Several reports suggest an increased susceptibility to pulmonary infection in patients with Marfan syndrome. It is possible that this may be related to bronchiectasis resulting from connective tissue weakness.

Of particular interest in the present series, there were four cases of pulmonary fibrosis whose origin was obscure. We were unable to relate these fibrotic changes to known causes of pulmonary fibrosis, including tuberculosis or other myocobacterial infection, sarcoidosis, ankylosing spondylitis, extrinsic alveolitis, allergic aspergilloma, pneumoconiosis, or drugs. Pulmonary fibrosis of obscure origin has been described previously in two patients with Marfan syndrome.[20 21] Examination of other case reports of idiopathic upper lobe fibrosis[22] has, however, revealed no diagnosis of or features to suggest Marfan syndrome.

If there is a causal relationship between upper lobe fibrosis and Marfan syndrome, it is tempting to speculate that the fibrosis might be due to healing of damage caused by stresses in the apical parts of the lungs of these tall people, the site where mechanical damage would be expected to be maximal. The cases described in our series and those from published reports are, however, too few to allow any definite conclusions to be drawn.

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