EXTENDED REPORT

Asthma and airways collapse in two heritable disorders of connective tissue

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Objectives: This study investigated the clinical impression that there was an increased prevalence of respiratory disorders in both the Hypermobility Syndrome (HMS)/Benign Joint Hypermobility Syndrome (BJHS) and Ehlers–Danlos Syndrome (EDS), compared with the normal population.

Methods: A questionnaire was distributed to 509 subjects (221 healthy controls, 126 HMS, 162 EDS) who documented respiratory symptoms and previously diagnosed respiratory and atopic disorders. A subgroup of 157 responders underwent full clinical and serological assessments, and 57 subjects were assessed physiologically.

Results: A significant increase in the frequency of a wide range of respiratory symptoms and reduced exercise tolerance was observed in subjects with both HMS and EDS compared with controls. In particular, there was an increased prevalence of asthmatic symptoms (HMS: OR 2.4, 95% CI 1.4–4.1, $p=0.002$; EDS: OR 3.1, 95% CI 1.8–5.2, $p<0.001$) and atopy (HMS: OR 2.7, 95% CI 1.6–4.5, $p<0.001$; EDS: OR 2.6, 95% CI 1.6–4.4, $p<0.001$), which was subsequently confirmed by clinical assessment. Pulmonary physiological studies revealed increased lung volumes, impaired gas exchange and an increased tendency of both the lower and upper airways to collapse.

Conclusions: We have demonstrated, for the first time, that individuals with HMS/BJHS and EDS have respiratory symptoms in association with various pulmonary physiological abnormalities. The increased prevalence of asthma may be due to linkage disequilibrium between the genes causing these conditions or a function of the connective tissue defect itself. In the non-asthmatic population, changes in the mechanical properties of the bronchial airways and lung parenchyma may underlie the observed increased tendency of the airways to collapse.

Ehlers–Danlos Syndrome (EDS) is an inherited disorder of connective tissue that exhibits considerable clinical and genetic heterogeneity. It affects multiple organ systems and is characterised by a classical triad of joint hypermobility, dermal extensibility and cutaneous scarring. Complications are usually a manifestation of increased connective-tissue extensibility and fragility.[1] The classification system has been simplified into six clinical syndromes, which attempt to encompass the molecular basis of each form.[2] The Hypermobility Syndrome (HMS) was defined as the occurrence of musculoskeletal symptoms in hypermobile subjects in the absence of demonstrable systemic rheumatic disease, and specifically excludes EDS.[3] Generalised hypermobility may be present in up to 5% of the general population[4] with up to 30% of adults displaying some hypermobile joints.[5] Joint mobility is also affected by age, gender, ethnicity and regular training.[6] There is significant overlap between the clinical phenotype of HMS and both EDS and Marfan's syndrome, with both of the latter having a recognised genetic component.[1 5 7] Although HMS is generally believed to be a benign disorder that predominantly affects the joints, perhaps in association with a proprioceptive defect,[8] it may share some of the systemic features seen in other hereditary connective tissue disorders, albeit to a lesser degree. In an attempt to define the full phenotype of HMS, and to aid distinction from other related conditions, the term Benign Joint Hypermobility Syndrome (BJHS) was proposed and a validated set of criteria developed.[9]

In the clinic, we observed that a significant proportion of patients with EDS and HMS/BJHS exhibited respiratory symptoms. A previous uncontrolled study in EDS suggested there was a high prevalence of respiratory symptoms in 20 subjects, although no consistent pulmonary function changes were noted. Skeletal deformities including pectus excavatum, thoracic scoliosis, kyphoscoliosis and Straight Back Syndrome have been documented to cause a restrictive defect in pulmonary function in 5% of subjects with EDS.[10] Eight cases of pneumothoraces have also been reported, three of whom almost certainly had the vascular type of EDS,[10] an uncommon but lethal variant.[1] No studies have previously systematically investigated the respiratory manifestations of BJHS.

PATIENTS AND METHODS

Questionnaire

Following approval from the Local Research Ethics Committee, all subjects from a local register of patients with hereditary connective tissue disorders (HMS and EDS) and members of the UK EDS support group were sent a respiratory questionnaire. This register was initiated and the questionnaire circulated prior to the publication of the most recent classification criteria for BJHS[9] and the revised nosology for EDS,[2] and the previously accepted criteria were used. The current survey utilised previously validated symptoms and activity components of the St. Georges Respiratory Symptoms Questionnaire, which was originally designed to detect symptoms in patients with both asthma and chronic bronchitis.[11] The reporting of wheeze several days per week and/or early morning wheeze was used to define the presence of ''asthma symptoms'', whereas ''bronchitis symptoms'' were considered present if any two of the following were reported, cough or sputum production on

Abbreviations: BJHS, Benign Joint Hypermobility Syndrome; CI, confidence interval; EDS, Ehlers–Danlos Syndrome; FEV, forced expiratory volume; FVC, forced vital capacity; HMS, Hypermobility Syndrome; MMEF, maximum mid-expiratory flow; OR, odds ratio; RV, residual volume

most days of the week and early morning wheeze. Questions documenting smoking history and previously diagnosed atopic disorders were included. Non-responders were sent up to three mailings of the questionnaire. All questionnaires were circulated in spring of the same year. All major EDS subtypes were represented in the survey. Control subjects were recruited from patients attending the local dental hospital and staff (porters, domestic, catering, nursing and secretarial) of a local hospital.

Clinical assessment

A subgroup of 157 subjects (55 controls, 59 HMS, 43 EDS) was selected from the respondents of the questionnaire, without reference to their respiratory status. Recruitment was based predominantly on geographical location and ability to attend for assessment. An attempt was made to recruit a control population of comparable age and sex to both patient groups. All were subjected to a structured interview and clinical examination to confirm previous diagnoses. EDS was diagnosed clinically and subclassified into one of six subgroups according to the revised nosology.[2] A considerable overlap between the hypermobility type of EDS and the BJHS is well recognised, and some rheumatologists believe that they may be the same condition. For the purposes of this study, patients who developed EDS by an experienced consultant physician with a special interest in the hereditory connective tissue disorders and who fulfilled the revised nosology, Villefranche, 1997[2] were classified as hypermobility type EDS. All patients with a previous consultant diagnosis of HMS were evaluated further, and BJHS was diagnosed in 51/59 HMS individuals who fulfilled the Revised (Brighton 1998) Criteria for the Diagnosis of BJHS.[9] Eight patients had hypermobility and musculoskeletal symptoms, but either had only two documented soft-tissue lesions or had recurrent episodes of pain that lasted for less than 3 months and therefore did not fulfil the Brighton criteria. The median age of those with HMS who did not fulfil the criteria was 22, whereas the median age of those who did fulfil the Brighton criteria was 41. Only one of these eight individuals had asthma. For clarity, we have only presented the clinical data on the BJHS subgroup in this manuscript, although the results were comparable with the HMS group as a whole.

Asthma was diagnosed if there was a history of episodic cough and wheeze, especially nocturnal symptoms, with documented variable airflow obstruction (see below), in the absence of cardiovascular disease. Atopy was defined as two out of three of asthma, eczema and hayfever. Chronic bronchitis was considered present if there was a history of chronic cough and sputum production on most days for a minimum of 3 months a year, for at least two successive years. Cardiovascular disease was excluded, and electrocardiograms, chest x rays and echocardiograms were requested, where clinically indicated.

Peak expiratory flow-rate monitoring

Diurnal peak expiratory flow-rate (PEFR) readings were recorded in all subjects using a Wright peak flow meter. Written instructions were supplied with the instrument, and the patient documented the highest of three readings in the early morning and evening for 14 days. The recordings from the first 3 days were excluded from the analysis, as they have previously been shown to exert a bias towards under-recording, despite careful training.[12]

Pulmonary physiology

We sought to further define the extent and nature of the physiological changes in these disorders by undertaking pulmonary function tests on a cohort of 57 individuals (30 BJHS, 27 EDS). Patient selection was random and based on the availability of equipment on the day of assessment and not on the presence of respiratory symptoms. All assessments were performed on the same apparatus by the same blinded observer according to the recommendations of the European Coal and Steel Community.[13]

The results were corrected for age, sex, height and weight, and expressed as both absolute values and a percentage of predicted values using the reference range above.[14] Values of forced vital capacity (FVC), vital capacity [maximum] (VC [max]), total lung capacity (TLC) (box), residual volume (RV) and RV/TLC greater than 120% predicted and values of the forced expiratory volume in 1 min (FEV_1)/FVC, carbon monoxide transfer per unit lung volume (TLCO/VA) and maximum mid-expiratory flow (MMEF) 75/25 less than 80% predicted were considered abnormal. A FEV_1/PEFR ratio of 10 or more was additionally used as an indication of upper-airways collapse.[14]

Total serum IgE levels

Serum was collected and stored at −70°C from all subjects with BJHS or EDS, and all samples were analysed in a single batch using Pharmacia CAP System fluorescent enzyme immunoassay. The upper limit of the adult normal range is 125 kU/l.

Statistical analysis

Statistical analyses were performed using the SPSS 11.0 for Windows statistical package (Chicago, Illinois, USA). The frequency of dichotomous variables and the median and interquartile range of continuous parameters are shown. Non-parametric analyses (Mann–Whitney U test for continuous variables and the Pearson chi-square test for dichotomous variables) were used to compare the two patient groups with the control population. When numbers were too small to provide an accurate chi-square result, that is if there was an expected count of less than 5 in any cell, Fisher's exact test was used. Two-sided p values below 0.05 were considered statistically significant throughout. As an approximation of the relative risk, odds ratios (ORs) and their 95% confidence intervals (CI) were calculated to quantify the magnitude of association between various respiratory symptoms and previously diagnosed asthma and atopy and in both patient groups compared with the control population. Forward stepwise maximum likelihood binary logistic regression was used to correct the ORs for age, gender and smoking status. Corrections for familywise type I error were made according to the Holm technique.[15] The critical p value for testing at the 5% significance level was set at $p = 0.017$ for the chi-squared tests and $p = 0.008$ for the logistic regression analyses. Binominal analyses were undertaken to generate CIs for the pulmonary function tests.

Post-hoc analyses were performed to determine whether there was any significant difference between HMS/BJHS and EDS. These secondary analyses should be viewed as exploratory, with $p<0.1$ suggesting potentially interesting results for future study. The significance levels from these secondary analyses were therefore not corrected for multiple comparisons.

RESULTS

Respiratory questionnaire

The questionnaire was completed by 509 subjects (221 controls, 126 HMS, 162 EDS), and the response rate was 92% after three mailings. There was no statistically significant difference in the age of responders between the groups (controls 39 (27–55), HMS 37 (25–49), EDS 37 (25–49) years). There was an increased number of females in both patient groups compared with the control population (controls 66%, HMS 91% ($p<0.0001$), EDS 78% ($p = 0.009$) female), as is well recognised

for these disorders.[6] No difference in the response rates was detected between males and females. The total number of cigarettes smoked was expressed in pack years, in which one pack year was equivalent to having smoked 20 cigarettes per day for one year. There was no significant difference in pack years (controls 0 (0–5), HMS 0 (0–6), EDS 0 (0–6) pack years), the number who currently smoked (controls 21%, HMS 21%, EDS 19%), or in the number of lifelong non-smokers between the three groups (controls 63%, HMS 55%, EDS 56%).

There was a statistically significant increase in the prevalence of asthma, atopy and a wide range of respiratory symptoms in both patient groups compared with normal controls (table 1). Prior diagnoses of asthma and atopy were both associated with age ($p<0.0001$), but not smoking (current and total pack years). Neither individual respiratory symptom nor limited exercise tolerance was associated with age or smoking history. Gender was significantly associated with all variables, which is consistent with the increased prevalence of joint hypermobility in females.[16] The ORs presented in table 1 were adjusted for age, gender and smoking status.

Asthmatic symptoms and a prior diagnosis of asthma, however, did not explain all reported symptoms. The prevalence of previously diagnosed chronic bronchitis was low (<1%), and a composite score for the presence of symptoms suggestive of chronic bronchitis was used as a surrogate marker. Additionally, subjects in both patient groups also demonstrated increased dyspnoea walking on the level and around the home (table 1). Post-hoc analyses revealed a significant increase in nocturnal cough or wheeze ($p = 0.02$) and dyspnoea around the home ($p = 0.02$) in subjects with EDS compared with HMS.

Clinical assessment

A total of 157 subjects (55 controls, eight HMS, 51 BJHS, 43 EDS (36 Classical, six hypermobility type and one Kyphoscoliosis type) were assessed clinically. The armspan/standing height ratio was normal in all patients, and no other features of Marfan's syndrome were present. Similarly, blue sclerae were noted in two of the EDS patients, but none of the BJHS or control population, which contrasts with the observed phenotype in the Chilean population.[17] There was no significant difference in the prevalence of previously diagnosed asthma, or specific respiratory symptoms between the subgroup selected for clinical examination and the original cohort that completed the questionnaire (data not shown). There was no significant difference in age (controls 36 (28–49), BJHS 41 (25–53), EDS 41 (32–50) years), gender (controls 76%, BJHS 88%, EDS 74% female) or number of current smokers (controls 14%, BJHS 20%, EDS 19%) between the groups. Chest-wall deformity secondary to thoracic scoliosis or pectus excavatum was seen in 8% BJHS and 9% EDS subjects, but not in any of the control subjects.

An increased prevalence of asthma was seen in both patient groups (controls 14%, BJHS 37%, EDS 23%), which was statistically significant for the BJHS group ($p = 0.011$). Only 1/6 of the patients with the hypermobility subtype of EDS had asthma, suggesting inclusion of this group had not significantly skewed the results for EDS. Although a trend towards an increase in atopy was seen in BJHS subjects (controls 19%, BJHS 31%, EDS 12%), this was not statistically significant ($p = 0.235$). Chronic bronchitis was diagnosed in two individuals (1 BJHS, 1 EDS), and no individuals had sustained a pneumothorax. Three individuals had valvular heart disease (one BJHS secondary to rheumatic fever, two EDS), and only one individual had stable angina. Thus, cardiac involvement did not account for the increase in asthma or other respiratory symptoms in these patient groups.

Pulmonary function tests

Some pulmonary physiological abnormalities were demonstrated in at least half of the BJHS and EDS (20 classical, four hypermobility type and one kyphoscoliosis type) patients (table 2). There were no significant differences between the two groups. The most striking abnormalities were the increase in lung volumes (TLC, VC, RV) and reduction in gas transfer (TLCO/VA), which may just be a reflection of the increased lung volumes.

Flow volume loops demonstrated an increased propensity of the lower airways to collapse during forced expiration, as shown by the reduction in MMEF 75/25 in approximately 60% individuals. The findings of increased static lung volumes, reduced MMEF 75/25 with relative preservation of FEV1/FVC ratios, are best explained by increased lung compliance. In addition, we identified a significant subgroup of patients who showed evidence of upper-airways collapse (BJHS 20% and EDS 16%).

Both individuals (one BJHS, one EDS (classical type)) with restrictive lung disease had coexistent chest-wall deformities. There was no association between lower- or upper-airways

Table 1 Frequency of asthma, atopy, respiratory symptoms and respiratory disability in the preceding year

	Prevalence of symptoms and clinical diagnoses (% subjects)					Adjusted Odds Ratios†	
	Control (n = 221)	HMS (n = 126)	HMS vs C (p value)*	EDS (n = 162)	EDS vs C (p value)*	HMS vs Control (OR, 95% CI, p value)	EDS vs Control (OR, 95% CI, p value)
Respiratory symptoms in last year							
Cough: several days per week	12	19	0.07	23	0.007	1.4 (0.76–2.6, 0.28)	2.0(1.2–3.6, 0.01)
Sputum: several days per week	4	17	<0.001	18	<0.001	4.9 (2.1–11.6, <0.001)	5.5 (2.5–12.6, <0.001)
Dyspnoea: several days per week	8	19	0.002	24	<0.001	2.1 (1.1–4.18, 0.03)	3.6 (1.9–6.9, <0.001)
Nocturnal cough or wheeze: occasionally	9	17	0.02	29	<0.001	1.7 (0.9–3.3, 0.14)	3.8 (2.1–6.8, <0.001)
"Asthmatic symptoms"‡	13	27	0.001	32	<0.001	2.4 (1.4–4.1, 0.002)	3.1 (1.8–5.2, <0.001)
"Bronchitis symptoms"§	7	13	0.05	19	0.001	1.9 (0.9–4.0, 0.11)	3.0 (1.5–5.7, 0.001)
Disability							
Dyspnoea: walking on the level	16	41	<0.001	50	<0.001	3.2 (1.9–5.4, <0.001)	6.1 (3.6–10.4, <0.001)
Dyspnoea: walking around the home	2	11	0.001	22	<0.001	6.3 (2.2–18.5, 0.001)	11.1 (4.2–29.2, <0.001)
Previous diagnoses							
Asthma	14	29	<0.001	27	0.001	1.9 (1.1–3.4, 0.02)	2.1 (1.3–3.7, 0.006)
Atopy	15	34	<0.001	32	<0.001	2.6 (1.6–4.5, <0.001)	2.6 (1.6–4.4, <0.001)

* Critical p value for testing at the 5% significance level was p = 0.017; † forward stepwise maximum likelihood binary logistic regression was used to correct the ORs for age, gender and smoking status; critical p value for testing at the 5% significance level was p = 0.008; ‡ asthma symptoms: reporting of wheeze several days per week and/or early morning wheeze; § bronchitis symptoms: reporting of any two of the following, cough or sputum production on most days of the week and early morning wheeze.
OR: odds ratio; CI: confidence intervals.

Table 2 Frequency of abnormal pulmonary function test results in both patient groups

	BJHS% (95% CI)	EDS% (95% CI)
FVC>120% predicted	41 (40 to 43)	19 (18 to 20)
VC(max)>120% predicted	37 (36 to 38)	26 (25 to 27)
FEV_1/FVC<80%	10 (9 to 11)	12 (10 to 13)
TLC (Box)>120% predicted	30 (29 to 31)	38 (37 to 40)
TLC (He)>120% predicted	50 (49 to 51)	37 (36 to 38)
RV>120% predicted	37 (36 to 38)	52 (51 to 53)
RV/TLC>120%	11 (10 to 12)	19 (18 to 20)
TLCO/VA<80% predicted	75 (74 to 76)	52 (51 to 53)
MMEF 75/25<80% predicted	62 (60 to 63)	56 (55 to 57)
FEV_1/PEFR>10*	20 (19 to 21)	15 (14 to 16)

* An FEV_1/PEFR ratio of 10 or more was used as an indication of upper-airways collapse.[15]

collapse with age, sex, smoking (current or total amount), degree of hyperlaxity or presence of asthma and atopy.

Total serum IgE levels

Total serum IgE was increased above the upper limit of normal in 19% BJHS and 27% EDS subjects. In addition, 35% of BJHS asthmatics and 29% EDS asthmatics had elevated IgE levels.

DISCUSSION

We have demonstrated, for the first time, an increased frequency of respiratory symptoms and reduced exercise tolerance in subjects with HMS, BJHS and EDS compared with controls (table 1). In particular, there was an increased prevalence of asthmatic symptoms and atopy, which was confirmed following the clinical assessment of a subgroup of responders. In addition, many individuals appeared to have alterations in the mechanical properties of their lungs, resulting in both increased distensibility and an increased tendency of the airways to collapse (table 2).

The questionnaire response rate was excellent, and a non-response bias was thus unlikely to have affected our results. The frequency of cough, wheeze, dyspnoea, sputum production and hayfever in our control group was also comparable with reported community prevalence rates in both the UK[18] and Sweden.[19] Asthma did not explain all of the symptoms, suggesting the possibility of additional, and previously undiagnosed, respiratory pathologies. The prevalence of chronic bronchitis was low, despite the presence of ''bronchitis symptoms''. This may suggest that the symptoms were mild and not reported to the general practitioner. The high frequency of atopic disorders was compatible with the increased prevalence of asthma seen in both patient groups. The lack of association between any respiratory diagnosis or symptom with smoking is interesting, as it may suggest that the defect does not worsen with smoking and that the high level of wheezing seen in this study was not the result of bronchial reactivity to cigarette smoke.[19]

We confirmed the association between asthma and HMS, using the more stringent BJHS criteria, in the subgroup assessed clinically, and a similar trend was also seen in EDS. Approximately one-third of asthmatics had raised total serum IgE levels, which is comparable with the general asthmatic population.[20] A second atopic disorder was seen more commonly in association with asthma in BJHS compared with EDS (85% and 30% respectively, $p = 0.01$), which may be a reflection of the different genetic backgrounds. All patients with asthma clinically responded to conventional doses of inhaled corticosteroid and bronchodilator therapy, and there was no clinical indication to suggest that their asthma was dissimilar to that seen in the general population.

In addition to asthma, the pulmonary physiological studies revealed increased lung volumes, impaired gas transfer, increased lung compliance and an increased tendency of the airways to collapse. We believe that this is most likely to be secondary to the pulmonary parenchyma providing inadequate connective tissue support to the small airways. An alternative explanation is that this may be secondary to gas trapping and emphysema. High-resolution computerised tomography scans performed on five subjects with the most marked physiological changes were essentially normal with no evidence of emphysema. In addition, abnormal FEV_1/FVC and RV/TLC ratios were observed in only a small proportion of subjects with increased residual volumes and lower-airways collapse. The presence of upper-airways collapse and coexistence of multiple defects in many individuals lend further support to our conclusion that the underlying connective tissue defects in BJHS and EDS alter the mechanical properties of the lungs, thus resulting in increased airway distensibility with an increased tendency to collapse.

There are several possible explanations for the association between asthma and the heritable connective tissue disorders. First, the genes contributing to asthma and either BJHS or EDS may be in linkage disequilibrium and thus tend to be co-inherited, which does not imply any similarities in the disease processes. Asthma displays clinical heterogeneity and is a complex, polygenic disorder that is influenced by environmental factors.[21] EDS is genetically heterogeneous with clinically distinct subtypes resulting from monogenic defects that modulate connective tissue biosynthesis.[1 2 22] A substantial heritable component to joint hypermobility was observed in participants of the UK national twin registry, confirming the importance of genetic factors.[5] The precise genetic defects in BJHS are largely unknown but are likely to involve the same pathways as EDS.[1 7 23] Indeed, there is a body of opinion that these are two overlapping conditions and that the hypermobility variant of EDS may be synonymous with BJHS, albeit a more extreme phenotype. We do not believe the finer points of the classification of 6/43 EDS patients detracts from the main body of this manuscript, and further studies will be required to investigate this further. None of the known asthma loci contain types I, III or V collagen, which have been implicated in some variants of EDS and BJHS and are constituents of the lung parenchyma. Of the genes identified in murine disease models of EDS (reviewed in Nuytinck *et al*[24] and Mao and Bristow[25]), those encoding tenascin-X (6p21.3) and lumican (12q21.3–22) are located within two of the asthma loci, and decorin (12q13.2) lies just outside. Tenascin-X deficiency has been shown to cause a clinically distinct and autosomal recessive form of EDS[26], and haploinsufficiency of Tenascin-X is associated with generalised joint hypermobility in females, perhaps implicating an additional contribution from hormonal factors.[27]

Alternatively, one of the genes contributing to BJHS and/or EDS may play a direct role in asthma pathogenesis. Here, subtle modifications of matrix proteins may alter tissue biomechanics, repair and remodelling responses following epithelial damage, or in the binding of growth factors that may influence cellular functions and cytokine biological activities.[28–30] This hypothesis is supported by the finding that mutations in fibrillin-1, a component of extracellular microfibrils, in Marfan's syndrome result in dysregulation growth factor β (TGFβ) activity.[31] This may contribute directly to the disease phenotype, in particular the observation of distal airspace enlargement in fibrillin-1 deficient mice,[31] which may contribute to the apical blebs and spontaneous pneumothoraces observed in Marfan's syndrome.[32]

In conclusion, we have demonstrated that individuals with two heritable disorders of connective tissue have increased

respiratory symptoms, particularly asthma. We recommend that all physicians involved in the care of these patients undertake a respiratory history and perform peak expiratory flow rate monitoring, where applicable, to make a definitive diagnosis of asthma, which is treatable with conventional inhaled therapy. Asthma is a polygenic disease, and some of the aetiological genes may overlap with those responsible for the heritable connective tissue disorders. Asthma and BJHS or EDS may therefore be different manifestations of the same genetic defect, with the ultimate phenotype being modified by other genetic, epigenetic and environmental factors. Alternatively, the increased prevalence of asthma and atopy may be secondary to the presence of linkage disequilibrium between the genes that cause asthma and those that result in EDS or BJHS. In addition, there was physiological evidence of increased lung distensibility and an increased tendency of the upper and lower airways to collapse. We believe that this is most likely to be secondary to the pulmonary parenchyma providing inadequate connective tissue support to the airways. However, further evaluation of these findings will be necessary before routine pulmonary function testing can be recommended in these disorders. Further investigation may lead to new clues in the pathogenesis of both asthma and the heritable connective tissue disorders.

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