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Main Article

Aspiration and development of subglottic stenosis in patients with Wegener's granulomatosis

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Abstract

Objective: In patients with Wegener's granulomatosis, subglottic stenosis can develop due to active disease; however, some patients develop subglottic stenosis with no clear evidence of airway inflammation. In some cases of idiopathic subglottic stenosis, an association with gastroesophageal reflux disease has been found. Our study assessed the potential role of gastroesophageal reflux as an aetiological factor in the development of subglottic stenosis in patients with Wegener's granulomatosis.

Design: We assessed evidence of active reflux disease, using 24-hour pH monitoring and assessment of bile salts in bronchoalveolar lavage fluid.

Subjects: Ten Wegener's granulomatosis patients with subglottic stenosis underwent 24-hour pH monitoring and bronchoscopy and lavage of the right middle lobe. A similar number of control patients were included.

Results: There was no statistically significant difference in the occurrence of bronchoalveolar bile salts in patients with subglottic stenosis ($n = 2$) versus control patients (zero) ($p = 0.457$). There was good correlation between the detection of reflux by 24-hour pH monitoring and the detection of bronchoalveolar bile salts ($\kappa = 0.769$).

Conclusion: In this small study of patients with Wegener's granulomatosis, there was no evidence of an association between the development of subglottic stenosis and gastroesophageal reflux.

Key words: Wegener's Granulomatosis; Subglottic Stenosis; Gastroesophageal Reflux

Introduction

Wegener's granulomatosis is a multisystem disorder characterised by necrotising, granulomatous vasculitis. This can lead to a myriad of manifestations, the most common and serious of which include necrotising glomerulonephritis, upper airway disease and pulmonary manifestations.[1] Indeed, some authors have suggested that 50–70 per cent of Wegener's granulomatosis patients will have some upper airway or endobronchial lesion.[2,3] Until recently, Wegener's granulomatosis had a very poor prognosis. However, with the introduction of steroids and other immunosuppressive therapies, medical treatment has dramatically improved patient survival.

Wegener's granulomatosis still has a chronically remitting and relapsing course, and medical therapy often needs to be lifelong. Despite intensive research, the aetiology is as yet unclear.

The ear, nose and throat are often involved as sites of initial onset of Wegener's granulomatosis. As a result, the otolaryngologist needs to be aware of this important condition. Indeed, as many as 25 per cent of Wegener's granulomatosis patients will at some point in their illness develop some form of airways disease. The disease's many clinical signs include sinusitis with nasal crusting and saddle nose deformity. The ear can be affected with an exudative otitis media.

Perhaps one of the most important manifestations of Wegener's granulomatosis to recognise, and the most difficult to treat, is subglottic stenosis. It is said to occur in 10–20 per cent of Wegener's granulomatosis patients, and can result in significant morbidity and mortality. Its exact aetiology is unclear, and some patients can develop stenosis without any evidence of active pulmonary vasculitis. Furthermore, such subglottic stenosis is often not responsive to systemic immunosuppression, and can persist despite adequate treatment. It has been postulated that gastroesophageal reflux disease contributes to the aetiology of endobronchial disease in cases of Wegener's granulomatosis.[4]

This process is very similar to the development of bronchiolitis obliterans with reflux in patients with lung transplants. Although the aetiology of bronchiolitis obliterans is unknown, for many years it has been thought that gastroesophageal reflux disease may play

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a major role in this process. Blondeau *et al.* demonstrated that the presence of bile salts in bronchoalveolar washings was associated with the development of bronchiolitis obliterans.[5] This is substantiated by the finding that performing an anti-reflux procedure can reverse the development of this condition. Hence, evidence exists that reflux may be associated with the development of significant lung pathology. Indeed, a recent review on the matter has suggested there is mounting evidence for an association between reflux (and aspiration) and the development of other chronic respiratory diseases.[6]

The bronchial tree should normally be clear of bile salts. Therefore, our study aimed to assess the presence of bile salts in bronchoalveolar lavage washings, as an indication of reflux disease, and to correlate the presence of bile salts with the development of significant airway stenosis.

Methods

In order to investigate their condition, patients with Wegener's granulomatosis and major airway stenosis underwent laryngoscopy and bronchoscopy. Our prospective study was performed at a tertiary referral centre to which patients with significant airway problems were referred.

Ten sequential patients referred with airway obstruction secondary to active Wegener's granulomatosis underwent endobronchial dilatation and concurrent bronchoalveolar lavage. This was performed by wedging the bronchoscope into the middle lobe subsegmental bronchus, instilling two 30-ml aliquots of Physiological saline and then recovering the fluid by gentle aspiration. Fluid samples were collected from the middle lobe in all cases. The aspirate was then analysed for bile salts.

The control group consisted of 10 patients undergoing bronchoscopy for investigation of pulmonary symptoms such as chronic cough, or for routine surveillance following lung transplantation. In all these patients, bronchoalveolar lavage and analysis of bile salts was performed routinely, and was clinically indicated. These control patients had no history of gastroesophageal reflux or Wegener's granulomatosis.

Aspirated fluid was analysed via spectrophotometric testing for bile salts, using a modular spectrophotometer (Roche, diagnostics, Burgess Hill, UK) measuring changes in absorption at 405 nm. In theory, there should be no bile salts present in the lungs; however, as in a previous study, we used an arbitrary level of 8 μmol/l as the upper limit of normal.[7]

Patients who consented underwent 24-hour pH monitoring and oesophageal motility studies. No control patients underwent these investigations. Eight out of 10 Wegener's granulomatosis patients completed their pH studies.

Statistical analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences version 15 software program. Data were summarised using frequencies and proportions. The association between Wegener's granulomatosis and the presence of bronchoalveolar bile salts, and between reflux symptoms and bile acid and pH test results, were assessed using Fisher's exact test. Agreement between the results of bile salt and pH tests was assessed using the κ statistic. A significance level of 0.05 or less was taken to indicate statistical significance.

Results

Of the 10 Wegener's granulomatosis patients, the incidence of subglottic stenosis was seven out of 10 (70 per cent) and the incidence of main bronchial stenosis four out of 10 (40 per cent). Of the entire cohort, four patients reported symptoms of reflux disease. The mean age of the Wegener's granulomatosis patients was 35 years (range 18–53); that of the controls was 62 years (range 57–73).

Only two Wegener's granulomatosis patients were found to have bile salts in their bronchial aspirate, compared with none of the control group ($p = 0.474$). All Wegener's granulomatosis patients consented to pH studies; however, because of active nasal disease, only eight of these patients completed their pH studies. The pH study was positive in three patients. No patients had any evidence of oesophageal dysmotility.

We assessed the usefulness of detection of reflux by 24-hour pH monitoring, and of detection of bronchoalveolar bile salts, in determining the presence of reflux disease. Using the κ statistic, we found a good correlation between detection of reflux by 24-hour pH monitoring and detection of bronchoalveolar bile salts ($\kappa = 0.769$).

Furthermore, there was a good correlation between the presence of reflux symptoms and the presence of bronchoalveolar bile salts (100 *vs* 11 per cent; $p = 0.032$), and also between the presence of reflux symptoms and positive pH studies (100 *vs* 7 per cent; $p = 0.005$) (Table I).

Discussion

As far as we are aware, this is the first prospective study to specifically assess the relationship between

TABLE I

ASSOCIATION BETWEEN REFLUX SYMPTOMS, BRONCHOALVEOLAR BILE SALTS AND 24-HOUR PH MONITORING RESULTS

Reflux symptoms	Bile salts		*p*	pH monitoring		*p*
	Yes*	No†		+ve‡	−ve**	
Present (*n* (%))	2 (100)	2 (11)	0.032	3 (100)	1 (7)	0.005

*n=2; †n = 18; ‡n = 3; **n = 15. +ve = 24-hour pH monitoring positive for gastroesophageal reflux; −ve = 24-hour pH monitoring negative for gastroesophageal reflux

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aspiration and development of subglottic stenosis in patients with Wegener's granulomatosis.

In our small sample, we found no evidence for an association between gastroesophageal reflux and active endobronchial Wegener's granulomatosis, either from pH studies or from assessment of bile salts obtained at bronchoalveolar lavage.

Limitations of the study include the facts that control patients declined 24-hour pH monitoring, and that not all the patients with Wegener's granulomatosis underwent these tests, mainly due to access limitations as a result of nasal disease.

Maronian *et al.* hypothesised that subclinical reflux disease acted as a synergistic factor in patients with Wegener's granulomatosis, precipitating the granulomatous disease process and resulting in stricture formation.[4] However, their cohort included only three patients with Wegener's granulomatosis.

Reflux symptoms are not always present in Wegener's granulomatosis patients with subglottic stenosis. In one study assessing six patients with Wegener's granulomatosis and subglottic stenosis, no symptoms of reflux were recorded.[8] However, another study found reflux symptoms in up to 25 per cent.[9] Our study findings suggest that, when symptoms are present, further investigation for gastroesophageal reflux disease should be undertaken.

- **The development of subglottic stenosis in Wegener's granulomatosis patients can occur during active disease or in times of remission**
- **The exact aetiology is unclear, but in cases of idiopathic subglottic stenosis it has been suggested that aspiration may be important**
- **This study assessed the potential role of aspiration in the development of subglottic stenosis in Wegener's granulomatosis patients, by assessing bile salts in bronchoalveolar lavage fluid and undertaking 24-hour pH monitoring**
- **Results suggest that aspiration is not important in the development of subglottic stenosis in these patients**

Although there is currently no 'gold standard' test for gastroesophageal reflux disease, we found that positive results for both bronchoalveolar bile salt assessment and 24-hour pH monitoring were significantly associated with the presence of reflux symptoms; furthermore, there was good agreement between these two tests. It is clear from other studies that symptoms on their own are poor indicators of the existence of reflux. Our findings suggest that a combination of reflux symptoms and positive results for bronchoalveolar bile salt and 24-hour pH monitoring may constitute a better guide. However, the measurement of bile salts in bronchoalveolar lavage fluid may underestimate the prevalence of aspiration; some studies detected bile salts in only 75–86 per cent of patients with documented reflux.[10] Even proximal oesophageal pH studies have been shown to have a low sensitivity and specificity for detection of reflux.[11]

The treatment of subglottic stenosis in patients with Wegener's granulomatosis can be very difficult. Bronchoscopy, intralesional steroid injections, dilatation and even stenting have all been tried, with varying degrees of success.[12] However, more recent evidence has suggested that steroid injections, endoluminal laser therapy or balloon dilatation should constitute standard treatment, and that airway stenting and tracheostomy are rarely required, if ever, in this group of patients.[13] Despite this, many patients are still left with significant airway problems. Therefore, prevention is undoubtedly the ultimate goal.

This study found no evidence to suggest an association between significant airway stenosis and gastroesophageal reflux in patients with Wegener's granulomatosis. However, due to our small sample size, we cannot rule out the possibility that there may be an association that we were unable to detect.

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