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Ciliary dyskinesia with normal ultrastructure

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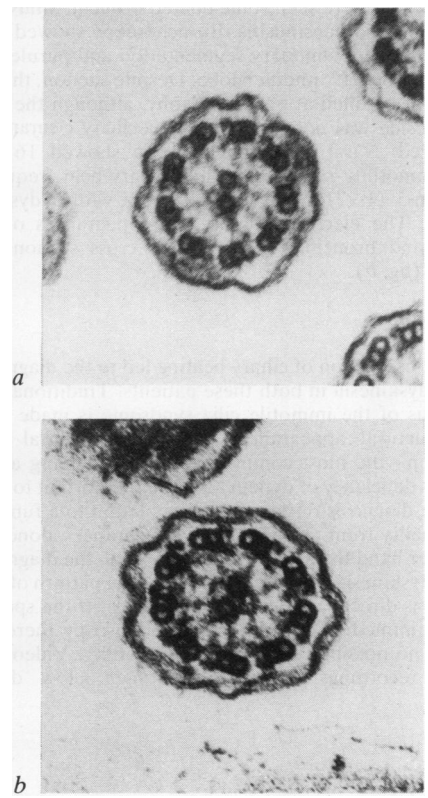
There is increasing awareness of the association between primary ciliary abnormalities and bronchiectasis. The most frequently recognised is that between dynein deficient cilia and Kartagener's syndrome.[1] Afzelius, however, predicted that without embryonic ciliary movement the rotation of the archenteron would be random and that in half of the cases of the "immotile cilia syndrome" there would be a normal cardiac situs.[2] In recent years other primary structural abnormalities of cilia have been described in association with lower respiratory tract infection—namely absence of radial spokes[3] and transposition of the microtubules.[4] The finding that some individuals with Kartagener's syndrome have normal ciliary ultrastructure[5,6] implies that either the association of the clinical syndrome with abnormal cilia does not always hold or that functional abnormalities of cilia may occur in the absence of ultrastructural defects. No observations of ciliary motility have been reported on patients with Kartagener's syndrome and normal ciliary ultrastructure. With Kartagener's syndrome the presence of ciliary dysfunction is readily suspected, but in patients with ciliary dyskinesia and normal situs (who also present with symptoms of sinusitis and bronchiectasis or recurrent chest infections) a functional abnormality may not be recognised unless tests of ciliary motility are performed. We report two cases of ciliary dyskinesia and associated clinical abnormalities but normal ciliary ultrastructure.

Methods

Nasal mucociliary clearance was assessed by the saccharin test,[7] in which a sweet taste is normally perceived within 20 minutes.[8] In patients who failed to taste within 60 minutes a non-invasive brushing technique[9] was used to sample cilia from the inferior nasal turbinate for determination of dyskinetic beat pattern, assessment of degree of ciliary immotility, and measurement of ciliary beat frequency by a photometric technique.[9] The degree of ciliary immotility was assessed in 50 squares of a graticule viewed by high power phase contrast microscopy. Only those squares in which all cilia were immotile were counted (that is, immotility was underestimated). Samples from 30 normal people or patients without primary ciliary dyskinesia showed less than 5% immotility. The pattern of beating was classified as normal or dyskinetic. Dyskinetic cilia move stiffly, often with reduced amplitude, and do not beat in synchrony with surrounding cilia; normal metachronal waves are not seen. The ciliary beat frequencies of 10 actively beating cilia was expressed in Hertz as the mean (standard deviation in parentheses). Nasal brushings were processed as previously described for ultrastructural studies.[10] All suitably orientated cross sections of cilia throughout the section were photographed and examined for the presence of dynein arms, radial spokes, and microtubular doublets.



Electron micrographs of cross sections of cilia showing outer and inner dynein arms, radial spokes, and normal arrangement of nine microtubular doublets: (a) case 1—nasal cilium; (b) case 2—bronchial cilium. (× 100 000.)

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Case reports

Case 1

A 28 year old woman had a life long history of cough, productive of purulent sputum, and sinusitis necessitating multiple sinus washouts and surgery. Examination showed finger clubbing, purulent nasal discharge, and bilateral basal crepitations. The chest radiograph showed normal cardiac situs and basal bronchial wall thickening suggestive of bronchiectasis. The nasal mucociliary clearance was grossly prolonged and nasal brushings showed 60% ciliary immotility with a dyskinetic beat pattern on two occasions. The ciliary beat frequency was 9·2 (1·3) Hz (normal range 12–16 Hz). The ultrastructural appearance of more than 50 cross sections of cilia was normal (fig, *a*).

Case 2

A 32 year old woman with productive cough and posterior rhinorrhoea since childhood had suffered recurrent left sided pleurisy in association with infective exacerbations over the previous six years. Examination showed dextrocardia and widespread inspiratory crepitations and rhonchi. The chest radiograph confirmed dextrocardia and showed a collapsed, consolidated left "middle" lobe, within which were seen some dilated bronchi. Sinus radiographs showed pansinusitis. Bronchoscopy showed mirror image bronchopulmonary segmentation and purulent secretions in the left "middle" lobe. Despite suction, the latter could not be filled at bronchography, although the rest of the left side was normal. Nasal mucociliary clearance was prolonged. Nasal and bronchial cilia showed 16% and 14% immotility respectively, and ciliary beat frequencies were 16·5 (1·97) and 14·25 (1·8) Hz with a dyskinetic pattern. The electron microscopic appearances of nasal (>30) and bronchial (>50) ciliary cross sections were normal (fig, *b*).

Discussion

Direct observation of ciliary beating led to the diagnosis of ciliary dyskinesia in both these patients. Traditionally, the diagnosis of the immotile cilia syndrome is made on the ultrastructural appearances of cilia in a nasal biopsy specimen—the most common abnormality being absence or gross deficiency of dynein arms. It is important to realise that the diagnosis represents extrapolation to a functional abnormality from morphological appearances alone. If on the other hand the ultrastucture is normal, the diagnosis of ciliary dyskinesia will be missed unless the pattern of ciliary beating is directly and carefully observed. If the specimen is fixed immediately for electron microscopy there is, of course, no possibility of examining motility. Video multiplanar recordings of ciliary beating[11] allow detailed analysis of the pattern of dyskinesia but are generally unnecessary to distinguish normal and abnormal beat patterns. Cursory microscopic examination of a specimen for the presence of ciliary beating is, however, clearly inadequate for diagnosis in some cases (including our case 2) because relatively fast beating cilia and a low degree of immotility may appear normal to the rapid, unquantitating glance. This case exemplifies the inappropriateness of the term "immotile cilia syndrome" as most of the cilia were beating actively without reduction in beat frequency

Case 1 illustrates the importance of considering the diagnosis of ciliary dyskinesia in all patients with recurrent or chronic respiratory tract infections, even those with laevocardia. Screening of such patients with the simple, inexpensive saccharin test[8] allows identification of a group of patients with grossly abnormal clearance in whom the diagnosis should be suspected more strongly and in whom ciliary function tests are indicated. Ciliary dyskinesia will be present in a small proportion of these patients.

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