

Short reports

Ciliary disorientation: a possible variant of primary ciliary dyskinesia

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Abstract

Random ciliary orientation has recently been proposed as a variant of primary ciliary dyskinesia. We report a 12 year old boy with all the features of primary ciliary dyskinesia and absent nasal mucociliary clearance in whom repeated biopsies of the nasal epithelium showed normal ciliary beat frequency. The only abnormality discovered was disorientation of the central microtubules of his cilia.

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In 1933 Kartagener¹ described a syndrome characterised by the following triad: situs inversus, bronchiectasis, and chronic sinusitis. It was not until 15 years ago, however, that Afzelius² and Pedersen and Mygind³ proposed that abnormal ciliary movement was the cause.⁴ A number of apparently inherited abnormalities of the ciliary axoneme have been noted in patients with primary ciliary dyskinesia, most commonly absence of dynein arms.^{2,3}

Very recently a possible variant of primary ciliary dyskinesia has been described in which the ciliary beat frequency was slower than the normal range, but the main abnormal finding was random ciliary orientation.⁵ The authors proposed that cilia can be structurally normal by electron microscopy and have a nearly normal beat frequency, but at the same time lack efficacy because the direction of their beating is random.

Case report

A 12 year old boy who had coughed and been wheezy and snuffly from the age of two weeks was referred to our unit for ciliary studies. Pregnancy and birth had been normal. He had required repeated antibiotic courses from a young age and at eight months a chest radiograph showed dextrocardia. A provisional diagnosis of primary ciliary dyskinesia was made. He now coughed up sputum on a daily basis, had impaired hearing, a persistently blocked nose and post nasal drip, and became

wheezy and short of breath with exercise. There was no family history of respiratory disease and he was the fourth of four children who were all otherwise well. There was no relevant past medical history apart from tonsillectomy and adenoidectomy at the age of three.

On examination there were bilateral wheezes and crackles in the chest, dextrocardia, and transposition of the abdominal organs. The following relevant investigations were normal or negative: pulmonary function tests, full blood count and differential white cell count, biochemistry, serum immunoglobulins, IgG subclasses, α_1 antitrypsin, rheumatoid factor, auto antibodies, *Aspergillus* precipitins, sputum culture. Peak flow recordings showed some variability, suggesting asthma. Chest radiography showed dextrocardia and patchy shadowing in both lower zones medially; radiographs of the sinuses were normal and the frontal sinuses were present. A high resolution computed tomographic scan showed widespread bronchiectasis of all lobes with the lingula and medial segment of the right middle lobe being worst affected. Nasal mucociliary clearance as assessed by the saccharin test was abnormal with no taste after 60 minutes, although the patient could taste saccharin normally when it was placed on the tongue. Brush biopsy of the nasal epithelium was performed on two occasions five months apart. On both occasions there were many fully ciliated strips of epithelium, the ciliary beat frequency was normal (13 Hz and 15 Hz), and the ciliary beat pattern was considered normal. Ultrastructural studies of the cilia by transmission electron microscopy were performed as previously described⁶; 234 cilia were examined for the presence of dynein arms and seven abnormalities were discovered; 600 cilia were examined for microtubular arrangement and 14 defects were found (two compounds, nine extra tubules, and three outer doublets disarranged). These results are well within the expected frequency of abnormalities in normal subjects.

Ciliary orientation was examined with an Improvision (Image Processing and Vision Company Ltd, Coventry, UK) image analysis system running on an Apple Macintosh II-fx computer. Areas were chosen with a minimum of 10 cross sections of cilia in which the central pairs of tubules could clearly be seen and which originated from a single cell. On each image a line was electronically drawn through the central pair of tubules of each cross section from left tubule to right and the angle of the line was measured by the computer, the top being 0°, right being 90°, and so on. Eighteen cells (201 cilia) selected from the sample of the patient were examined. For comparison cilia were examined in 82 cells

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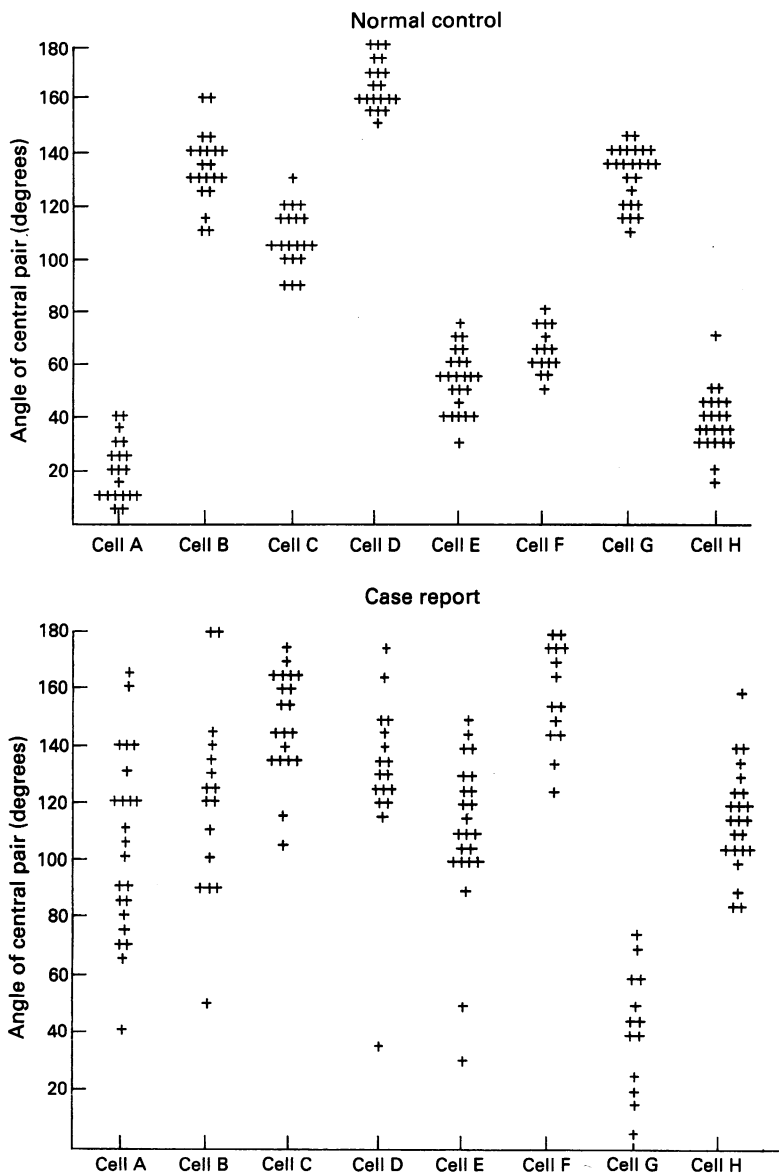
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(total 1621 cilia) taken from 10 asymptomatic non-smoking subjects with no history of recent respiratory infection. Statistical analyses were carried out with SAS software.

The angles of ciliary orientations within each cell were approximately normally distributed for all subjects. In the 10 normal subjects the angles of orientation within each cell were less widely dispersed than in the patient (fig); the mean standard deviation of the angles in the 82 normal cells was 10.44° (95% confidence interval 9.99 to 10.89) whereas that in the 18 cells of the patient was 22.27° (18.64 to 25.90). A nested analysis of variance confirmed that most (92%) of the variation in angles in the normal subjects was attributable to different cells, whereas most (77%) of that in the patient was explained by variation in angles within cells.



Distribution of angles of central pairs of microtubules of cilia from eight cells from normal controls and the patient in this case report.

Discussion

Ciliary disorientation has been described previously in some but not all patients with cilia ultrastructural defects,^{7,8} but orientation was normal in patients with bronchiectasis.⁷ The observations of Rutland and De Iongh⁵ are very important in that ciliary disorientation may be a further variant of primary ciliary dyskinesia. Our case differs from that described by Rutland and De Iongh in one important feature; the ciliary beat frequency of the samples taken on two separate occasions was completely normal, as was the beat pattern of the cilia as far as could be ascertained by light microscopy. Although a clear difference in orientation of cilia has been shown between the patient and controls, we cannot be certain that this is responsible for the clinical presentation nor the abnormal nasal mucociliary clearance. Good ciliation of the biopsy specimens on two separate occasions five months apart made secondary changes to the epithelial surface resulting from viral or bacterial infection less likely, as infection usually leads to loss of cilia and a poorly ciliated epithelium.⁹ It is likely, however, that the mucosa was inflamed because of the patient's continual nasal symptoms.

Acquired abnormalities do occur to both the respiratory epithelium and ciliary ultrastructure.⁹ The possibility that disorientation is a secondary phenomenon, perhaps caused by exposure to viruses, bacteria or air pollutants, has not been excluded.⁹ There are no published data to document the time course for the reversal of ciliary alterations resulting from longstanding inflammation of the airways. The case for a primary defect would be strengthened if inheritance of disorientated cilia could be shown, but in the previously reported case and in the case presented here no family history of respiratory illness was present. It would also help to be able to demonstrate the abnormality at two sites in the respiratory tract, but biopsies from the lower respiratory tract are not easy to obtain in paediatric patients. For the time being ciliary disorientation must be tentatively ascribed as a variant of primary ciliary dyskinesia.

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