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Ultrastructural abnormalities of bronchial cilia in children with recurrent airway infections and bronchiectasis

L CORBEEL, F CORNILLIE, J LAUWERYNS, M BOEL, AND G VAN DEN BERGHE

Departments of Paediatrics and Pathology, University of Leuven, Belgium

SUMMARY Anomalies of the bronchial cilia were studied in 5 children with recurrent pulmonary infections. Case 1 had Kartagener’s syndrome and an absence of the inner and outer dynein arms in most cilia, although a few shortened and even some normal arms could be seen. Cases 2 and 3 had unilateral bronchiectasis without family history of Kartagener’s syndrome. Serial studies of the bronchial epithelium at times showed a bilateral lack of the inner dynein arms and a partial lack of outer arms. These abnormalities persisted in these 2 children after they had recovered from the acute pulmonary infection but disappeared after 6–8 months of antibiotic treatment. Cases 4 and 5 had recurrent pulmonary infections without bronchiectasis and many shortened outer dynein arms could be seen, but these anomalies disappeared after recovery. In all 5 children such architectural ciliary anomalies were present as megacilia, fused cilia, naked cilia, and completely disorganised axonomas. These architectural defects were particularly numerous in the children without bronchiectasis. Our observations suggest that anomalies of the bronchial ciliary microtubular system may not only be congenital but may also be acquired; this might well help to explain some cases of repeated respiratory tract infection and bronchiectasis.

Microtubules are straight, hollow, intracellular structures present in many living cells; they control directed movements—such as the migration of chromosomes during mitosis. They play an important role in chemotaxis and phagocytosis of the granulocytes and in the degranulation process of exocrine and endocrine glandular cells. The motility of the cilia, flagella, and sperm tails depends on a special assembly of microtubules with a similar ultrastructure forming a so-called axonema.

Fig. 1 shows a cross-section of a normal cillum. From 2 central microtubules, radial spokes radiate to 9 peripheral pairs of microtubules joined by a nexin link, the whole structure forming an axonema. Each pair comprises a microtubule B and a microtubule A with two side arms arranged clockwise. The side arms are made up of a protein, dynein, demonstrating ATPase activity; this explains their contractile properties, and allows each microtubule A to grasp the microtubule B of its neighbouring pair. The result is a bending movement of the entire ciliary structure. A congenital ciliary abnormality, the lack of dynein arms, has been described by Eliasson et al. as an aetiological factor in chronic airways infections and male sterility, and was referred to as the immotile-cilia syndrome.

This lack of dynein arms is associated with an appreciably delayed mucociliary transport in the airways; it is present in patients with Kartagener’s syndrome who have a special manifestation of the hereditary immotile cilia syndrome. Situs inversus is found in half of such patients because the change in position of the heart to the left, and of the gut to the right, during fetal development seems also to depend on the same tubulin-dynein microtubular system. This defect was present in the middle-ear cilia of a boy with Kartagener’s syndrome and in the nasal mucosa as well. Recently Sturgess et al. described a similar delay of mucociliary clearance in 3 siblings with defective ciliary radial spokes.

The heterogeneity of the immotile cilia syndrome has been confirmed by Afzelius and Eliasson who described 5 flagellar mutants, and by the finding of a normal nasal ultrastructure in a 32-month-old child with Kartagener’s syndrome.

We studied the ultrastructural anomalies of the bronchial ciliary microtubular system in 5 patients
Thin (1 μm) and ultrathin (50–70 nm) sections were cut with a Sorvall ultramicrotome. The thin sections were stained with toluidine blue and used to indicate areas of bronchial epithelium chosen for ultrathin sectioning. The ultrathin sections were stained with uranyl acetate and lead citrate. All sections were studied with a Philips EM 300 at an operating voltage of 60 kV.

Patients

Case 1. A 14-year-old girl with Kartagener's syndrome, complete situs inversus, and bronchiectasis had been treated with doxycycline 4 mg/kg per day continuously since she was 10 years old. A lobectomy of the lingula had been performed at age 11 years. Exploration of the cellular and humoral immunity showed a lack of IgA in blood and secretions. The random mobility, chemiluminescence of the granulocytes, phagocytosis, and opsonisation were normal. A bilateral bronchial biopsy was performed when she was aged 13 years.

Case 2. This girl had suffered from recurrent airways infections since she was aged 2 years. On admission, at age 6/12 years, she had purulent sputum of the right and consolidation or collapse of the lower lobe, with a foreign body in the right bronchial tree; there was also clubbing of the fingernails. A tooth was expectorated spontaneously after a first bronchoscopy but the pneumonia took 2 months of antibiotic treatment and several chest aspirations to clear. Severe bronchiectasis was demonstrated confined to the right lower lobe; the left bronchial tree was normal. Consecutive biopsies of the bronchial

Methods

Bronchial biopsies were taken during bronchoscopic examination in 5 children. One had Kartagener's syndrome, 2 had repeated pneumonia and unilateral bronchiectasis, and 2 others had repeated pneumonia without bronchiectasis.

Small fragments of bronchial mucosa were immediately fixed by immersion in 2.5% glutaraldehyde in phosphate buffer at pH 7.2 and 4°C. After primary fixation, tissue fragments were centrifuged at 3000 rev/min for 5 minutes. The pellets so obtained were postfixed with 1% OsO₄ in phosphate buffer at pH 7.2 and finally embedded in epoxy resin.
mucosa were performed, first on the left side at age 6 years 4 months, later on the right side, and finally on both sides at age 7 6/12. She was treated continuously with amoxycillin 50 mg/kg per day orally and remained free of symptoms.

Case 3. This boy had suffered from recurrent lower respiratory infections with fever since he was aged 3 years. He was first seen by us at age 6 years 10 months because of bilateral pneumonia which resolved after 1 month of antibiotic treatment. Recurrence of the lung infiltrates on both sides after interruption of the antibiotic treatment prompted bronchial biopsy and bronchography. Bronchiectasis was apparent in the lower and middle right lobe but not on the left side; antibiotics were given for 16 months. Bronchial biopsy was repeated.

Case 4. A 5-year-old girl was admitted because of right lower lobe pneumonia which resolved after 3 weeks of treatment with erythromycin. One week after stopping this treatment the girl developed bilateral pneumonia. Titres of antibodies against Mycoplasma pneumoniae rose from nil on the first attack to 1/32 1 month later. There was no bronchiectasis. Bronchial biopsies were performed at that stage and 3 months later.

Case 5. This child had a first attack of bronchiolitis at age 6 months and was admitted at 15 months with a severe bronchopneumonia and pleural effusion on the left side which was treated with antibiotics. As the radiological lesions had not cleared after 3

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Fig. 3 Ciliary cross-sections (left side) in a patient with unilateral bronchiectases. Note normal dynein arms (arrow heads) and outer microtubule membrane bridge (arrow). Inner dynein arms are absent at many tubules (asterisks) while the outer ones are shortened. × 71 820; inset × 134 064.

Fig. 4 Two types of megacilia. (Left) a single axonema is embedded in an excess of cytoplasmic matrix, (right) five axonemas constitute a compound cilium; × 94 905.
months of antibiotic treatment, a bronchoscopy and bronchial biopsy were performed; there was no bronchiectasis. Exploration of both humoral and cellular immunity was normal. Four months later, when the patient was well, further biopsy was performed on the left bronchus.

Results

Two types of ultrastructural anomalies were observed: (1) anomalies of the microtubular dynein arms, and (2) architectural ciliary anomalies.

A lack of both dynein arms in most cilia was found in Case 1 who had Kartagener’s syndrome, although a few shortened and even some normal arms were present (Fig. 2).

Cases 2 and 3, who had unilateral bronchiectasis without family history of Kartagener’s syndrome, showed a bilateral lack of the inner dynein arms and a partial lack of the outer arms in many cilia (Fig. 3). In some cilia outer microtubule membrane bridges could be seen connecting the microtubule A to the ciliary membrane. Striking architectural ciliary anomalies were found in Cases 2, 3, 4, and 5, but these were less pronounced in Case 1 who had Kartagener’s syndrome. Such architectural anomalies are best described as megacilia or compound cilia, naked cilia, or completely disorganised axonemas.

Typically an excess of cytoplasmic matrix was found in some megacilia (Fig. 4). In some cilia, 3 central single microtubules or an excess of peripheral pairs could be seen. In compound cilia several ‘9+2’ axonemas were surrounded by the same ciliary membrane while naked cilia had no membrane. In Case 5, who had severe bronchopneumonia of long duration with pleural effusion on the left side but in whom bronchiectasis was absent, disorganisation of axonemas was nearly complete with random orientation of microtubular pairs in a single cytoplasmic extension (Fig. 5). All these anomalies gradually regressed and had disappeared after about 6 to 8 months of antibiotic treatment.

Discussion

The ciliary ultrastructural anomalies were associated with recurrent or long-lasting airways infections in these 5 children. The link between the dynein anomalies and the recurrent infections in Kartagener’s syndrome has already been reported. Kartagener’s syndrome is a special manifestation of a hereditary disease and is now referred to as immotile cilia syndrome. Defective mucociliary clearance was demonstrated by the transport of aerosols containing albumin microspheres labelled with technetium—m 99.\(^1\)

The abnormal ciliary movements in the nasal mucosa have been studied recently with a phase contrast microscope\(^4\) and the average number of beats was analysed with videotape.\(^5\)

No functional studies could be performed in our patients. Nevertheless striking ultrastructural anomalies—such as compound cilia, cilia with disorganised axonemal microtubular structures, and naked axonemas—suggest a malfunctioning ciliary apparatus.

The fact that the anomalies regressed in Cases 2, 3, 4, and 5 suggests that they may have been acquired. The ciliary anomalies could explain why some
infections result in bronchiectasis. Unilateral bronchiectasis as in Cases 2 and 3 could have been due to differences in the severity, or the type, of the ciliary anomalies. Recently, similar ultrastructural defects were observed in nasal and bronchial cilia of a 12-year-old boy with repeated upper and lower respiratory tract infections.10

The less pronounced architectural anomalies in Case 1 with Kartagener's syndrome could have been due to the 3-year course of antibiotic therapy before the biopsy. Similar architectural anomalies were seen by Katz et al.11 in other patients with immotile cilia syndrome. They have also been observed in patients with neoplastic diseases, in those who smoke, and in the nasal mucosa of adults with chronic sinusitis.12,13

Cases 4 and 5 did not have bronchiectasis but displayed recurrences of radiological and clinical pneumonia. In Case 4 the titre of antibodies against Mycoplasma pneumoniae increased significantly. A prolonged pneumonia may occur after infections with Mycoplasma pneumoniae.14 The ultrastructural ciliary anomalies offer an explanation for the chronic and repeated character of these disorders. A defect in mucociliary clearance resulting in bacterial infection suggests that prolonged antibiotic treatment may be helpful.

References


Correspondence to Professor L Corbeel, Department of Paediatrics, University of Leuven, Children's Hospital, Herestraat 49, 3000 Leuven, Belgium.

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L Corbeel, F Cornillie, J Lauweryns, M Boel and G van den Berghe

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