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Changes in the bronchial epithelia in patients with immotile cilia syndromes

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Immotile cilia syndromes is a cause of recurrent infection of the airways and recurrent bronchopneumonias. Among the ciliary abnormalities are found changes in the structure of the microtubules, unco-ordinated ciliary movements caused by the absence of inner or outer or both dynein arms, and abnormalities of the kinetosomes and/or rete ridges. In patients with ciliary dyskinaesia bronchitis occurs early in life (during infancy) and usually has a recurrent tendency, so that bronchial biopsy is frequently undergone for diagnostic purposes. In this study we include 127 bronchial biopsies from patients (from 2 months to 49 years) unsuccessfully treated for recurrent respiratory tract infections. When performing regular diagnostic procedures on the light and electron microscopic level, we have looked for cilia abnormalities and also focused on changes within the mucosa and submucosa. The most common abnormality recorded was absence of the inner dynein arms, but in 40 cases neither of the dynein arms were present. Only a few patients had classical Kartagener's syndrome. Special attention is drawn to biopsies from elderly patients, in whom long-standing infections were followed by extensive damage to the bronchial epithelium, including even a total absence of ciliated cells. In some cases enhanced regenerative processes and some foci of squamous metaplasia were found. In two cases even foci of low-grade dysplasia were diagnosed.

key words: immotile cilia syndrome, electron-microscopy

INTRODUCTION

Unspecific clinical symptoms such as productive infections, sinusitis, and otitis media, especially in a chronic and recurrent form, could be one of the most common indications for performing a bronchial or nasal biopsy for the study of the ciliary apparatus. In some cases immotile cilia syndromes may be suggested by male infertility [2, 4]. Although primary ciliary dyskinesis was for many years identified as Kartagener's (or Sievert) syndrome, a wide range of different abnormalities that give rise to functional ciliary abnormalities have now been reported. Among these are irregularities of axoneme structure, which are recognised under transmission electron microscopy. In this group we identified abnormality of or absence of the dynein arms, changes within the radial spokes, abnormalities of the central tubules and abnormalities in the number and localisation of the microtubules (for review see [2]). From an epidemiological point of view and according to

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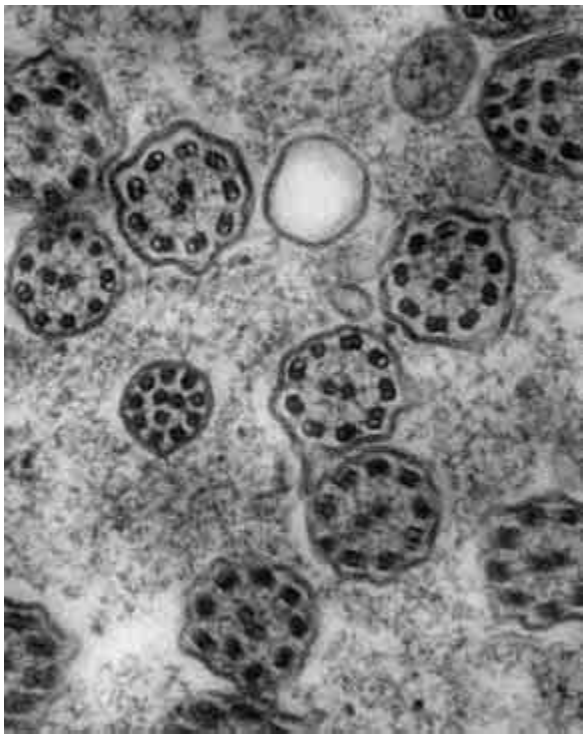

Figure 1. Transverse sections of cilia which lack both dynein arms. One cilia in its apical section contains three central microtubules. Another cilia contains an additional peripheral doublet of microtubules. Electron micrograph, primary magnification 50,000 ×.

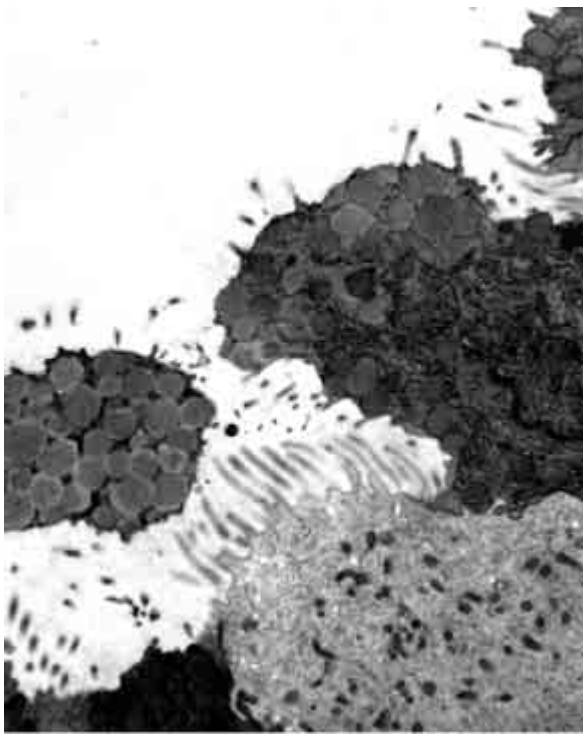

Figure 2. Surface of epithelium with more than the usual number of goblet cells. One cell has only microvilli on its free surface. Electron micrograph, primary magnification 3,000 ×.

restricted diagnostic criteria, the immotile cilia syndrome could be diagnosed in 1/8.000 to 1/120.000 of the population and, according to Rott [3], it could be even more prevalent. For clinical therapy strategy in patients with expected immotile cilia syndrome an ultrastructural diagnosis is a key step. The focus of this study is on the most common abnormalities in patients with suspected immotile cilia syndrome and the occurrence of additional bronchial lesions.

MATERIAL AND METHODS

We studied 127 airways biopsies taken for diagnostic purposes from patients with chronic and recurrent bronchial and pulmonary infections. The group studied consisted of 62 women and 65 men, aged from 2 months to 49 years. The patients were studied in the following age groups: below 1 year — 16 cases, from 1 to 16 years — 102 cases and over 16 years — 9 cases. In all cases tissue samples were taken from upper airways during fibroscopy under anaesthesia. Tissue samples were placed in Karnowsky fixative and later, following the standardised procedure, mounted in durcupan or epon blocks. Semi-thin sections were evaluated under a light microscope and ultra-thin sections were studied in the TEM column.

RESULTS AND DISCUSSION

25 biopsies were excluded from the ultrastructural studies, as in these cases there were no epithelia in the biopsy samples (non-diagnostic material). Of the patients selected for further studies, 61 cases were recorded as lacking the inner dynein arms and 40 patients lacked both arms (Fig. 1, 3). In 15 cases both the aforementioned changes occurred in neighbouring cilia. In all cases with dynein abnormalities we also observed "large" lesions of axoneme. Lesions such as kinetosome abnormalities and/or lack of rete ridges were also found. In several cases there were only single ciliated cells. In some cases the cell surface was mostly occupied by microvilli (Fig. 2) and only in some were single cilia observed. We also observed fusion of numerous axonemes with the formation of megacilia. Moreover, in 8 patients squamous metaplasia was observed. The patients in this group ranged in age from to 5 to 49 years. In the 2 oldest patients (38 and 49 years) foci of low-grade dysplasia were recorded in the metaplastic epithelium.

Defects in muco-ciliary clearance lead to accumulations of mucus in the airways. This serves as a background for bacterial and viral infections, which subsequently cause damage to the ciliary epitheli-

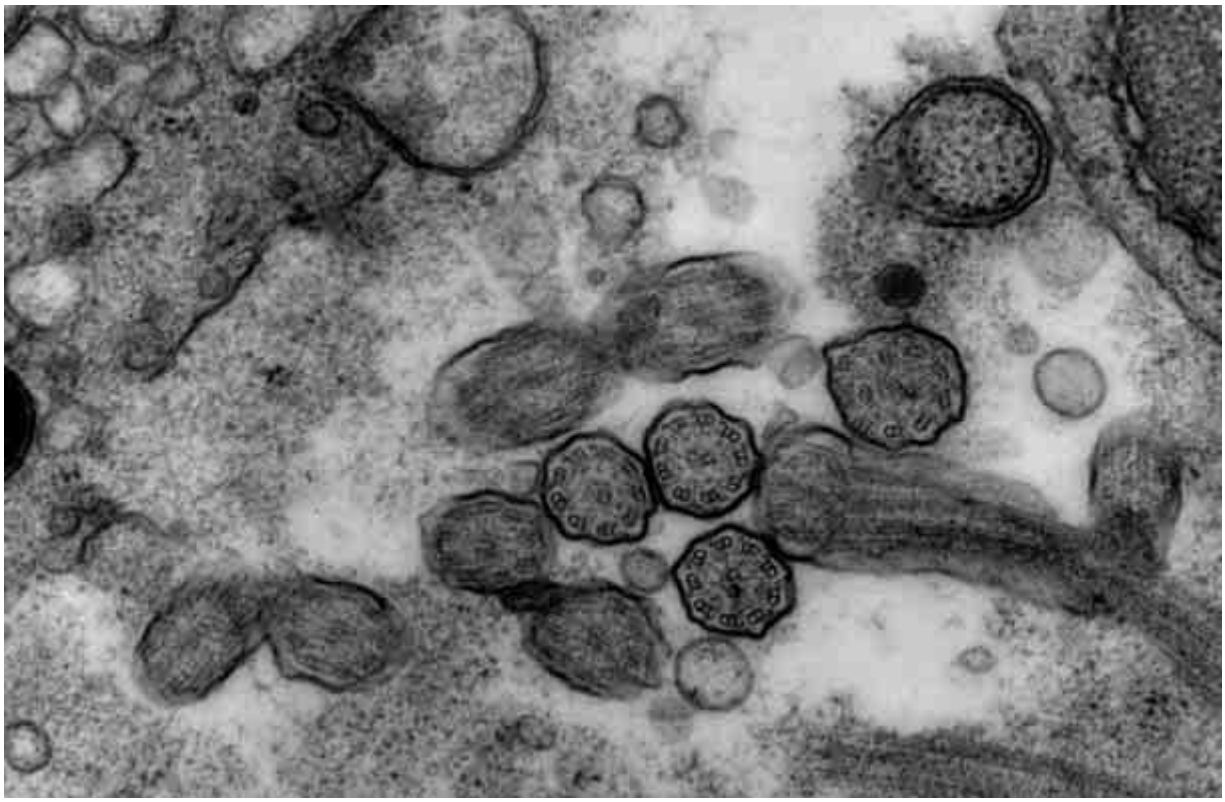

Figure 3. Cilia are present which lack the inner dynein arms. Electron micrograph, primary magnification 20,000 ×.

um of the airways. During clinical withdrawal to normal clearance successive regeneration occurs. Unfortunately the restoration of the function is slower than the regeneration, so the newly-formed epithelium faces repeated infection [1]. Repeated infection in such patients may even lead to bronchiectasis, usually in the second or third decade, when the incidence stands at almost 30% [5]. Recurrent pulmonary infections are described as one of the leading causes of early mortality in patients with this syndrome [2]. The results of the present study indicate that abnormalities in the regenerating epithelium should be taken into account.

There is still no successive genetic therapy for these patients. The only real hope in such cases is good symptomatic therapy and prevention, including a total prohibition on tobacco smoking.

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