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Immotile cilia syndrome: Nasal mucociliary function and nasal ciliary abnormalities*†

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SUMMARY

We present 17 patients with a typical symptomatology of immotile cilia syndrome, seven of them with complete situs inversus. Firstly, a study of the nasal mucociliary transport was made by means of the radioisotopic technique with serum albumin-Tc99m. In all cases there was absence of transport. Secondly, we studied the ultrastructure of the nasal cilia. Defects in the dynein arms were frequently found (65%). In two cases (11%) there were no cilia; in two other cases the cilia were normal, and in another two cases alterations of the central pair of microtubules were seen. Ciliary complexes were detected in all cases. We conclude that in patients with chronic or recurrent infections of the airways without known cause we must initiate a study of the nasal mucociliary transport. If this is absent or decreased, study of ciliary ultrastructure should be carried out. If mucociliary transport is normal, immotile cilia syndrome is ruled out and ultrastructural study of the cilia is not required.

Key words: immotile cilia syndrome, nasal mucociliary transport, nasal ciliary ultrastructure

INTRODUCTION

The association of situs inversus, sinusitis and bronchiectasis was first described by Siewert (1904), and later Kartagener (1933) described it in more detail.

The entity is currently known as Kartagener's syndrome. The precise nature of this disease was not established until Camner et al. (1975) suggested that ciliary immotility is the underlying cause of the syndrome. Since situs inversus and the ciliary defects are not always different, Eliasson et al. (1977) proposed the term "immotile cilia syndrome" for all congenital ciliary alterations that lead to poor ciliary function with defective clearance.

The aim of the present work was to determine the different changes in the ciliary axoneme that are responsible for absence of transport in our 17 patients. We also discuss the diagnostic strategy for the diagnosis of the syndrome. According to our experience, it is relevant to study nasal mucociliary transport with a radioisotopic technique.

MATERIAL AND METHODS

We studied 17 patients (10 males; 7 females), aged 5-50 years (mean age: 25 years; Table 1). All patients were born along the Spanish mediterranean coast.

Clinical study included the evaluation of family history, the existence of repetitive respiratory infections, the amount of sputum and nasal mucus produced daily, otitis, onset of clinical manifestations, infertility (defined as two years of infertility after two years of active sexual activity without contraceptive measures) and presence of situs inversus.

Bronchiectasis and sinusitis were studied by computerized axial tomography using high-resolution techniques. Alpha-1-antitrypsin and immunoglobulins were assayed in all cases, and the sweat test was performed to determine the possible presence of associated disease.

The 17 patients were subjected to an evaluation of nasal mucociliary transport using ^{99m}Tc-labelled albumin according to the method commonly used by us (Armengot et al., 1989). The albumin macro-aggregates utilized were 10-60 μm in diameter, 0.01 ml (<100 μg) of the tracer being applied in each case. The droplet surface radioactivity was 25 μCi. The measurements were made at room temperature with a relative humidity of 62%.

Biopsies of the nasal mucosa were performed by curettage of the inferior turbinate under microscopical guidance and applying 2% lidocaine as anaesthetic. The samples were always obtained at least six weeks after the last outbreak, and medication, tobacco and alcohol were avoided 24 h before the study.

RESULTS

All patients met the clinical diagnostic criteria of primary ciliary dyskinesia as defined by Afzelius (1981). Three of them present-

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Table 1. Clinical characteristics of the patients with immotile cilia syndrome (S: sinusitis; B: bronchiectasis; SI: situs inversus).

case	age	sex	family history	S	B	SI	fertility
1	16	m	-	+	+	-	infertile
2	22	m	-	+	+	-	infertile
3	32	f	-	+	+	-	fertile
4	30	f	+	+	+	+	fertile
5	50	f	+	+	+	+	fertile
6	30	m	-	+	+	-	fertile
7	26	f	-	+	+	-	fertile
8	29	m	-	+	+	+	infertile
9	26	m	-	+	+	-	fertile
10	15	f	-	+	+	-	not known
11	24	m	-	+	+	+	infertile
12	5	m	+	-	-	+	not known
13	12	m	-	+	+	-	not known
14	7	f	-	-	+	-	not known
15	25	f	-	+	+	+	fertile
16	40	m	-	+	+	+	infertile
17	45	m	-	+	+	-	infertile

ed a family history of interest. Two adult males were fertile (25%) and six were infertile (75%), with a lack of sperm motility. The adult females were fertile. Bronchiectasis and sinusitis were present in all adult patients (Table 1). Alpha-1-antitrypsin, immunoglobulin and sweat test results were normal.

Nasal mucociliary transport was totally absent in all patients. In normal persons nasal mucocillary transport velocity, as determined by the ^{99m}Tc-albumin technique, is 2–11 mm/min (Armengot et al., 1990).

The ciliary alterations as demonstrated by ultrastructural investigation included:

(1) absence of dynein arms (11 patients; 65%; cf. Figure 1); in eight cases this loss was complete, whereas in the remaining three cases loss was partial. In three cases the absence of dynein arms was associated with alterations in the number of peripheral microtubules (Figure 2). In six cases there was situs inversus.

(2) supernumerary central microtubules (two cases; 12%; cf. Figure 3).

(3) normal cilia were seen in two cases (12%), one of them demonstrating situs inversus (Figure 4).

(4) absence of cilia was seen in two cases (12%).

(5) compound cilia were observed in 15 cases (88%).

These alterations were all seen in >60% of the cilia examined.

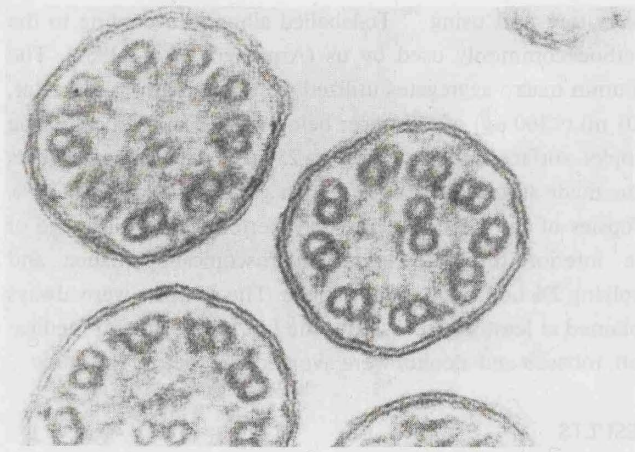

Figure 1. Cross section of nasal cilia. Note the absence of dynein arms as compared with normal cilia in Figure 4 (x200,000).

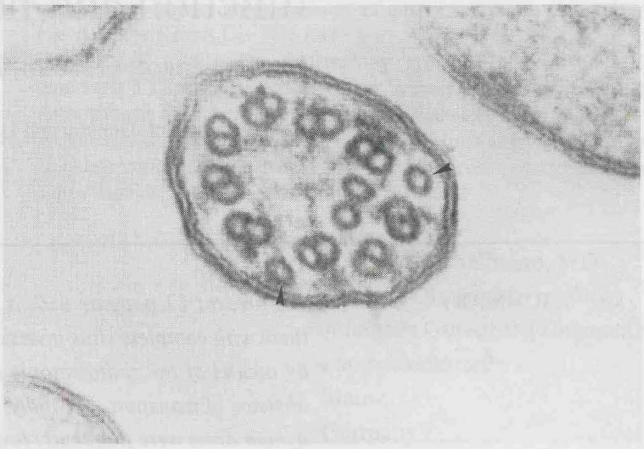

Figure 2. Cross section of nasal cilia. Note the absence of dynein arms in association with numerical alterations of peripheral microtubules (arrow; x200,000).

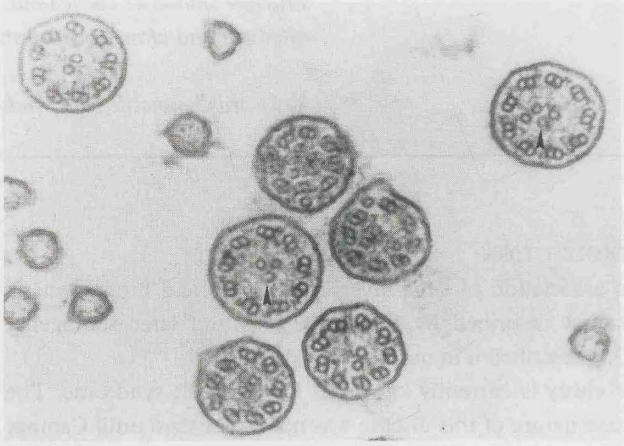

Figure 3. Cross section of nasal cilia. Note supernumerary central microtubules (arrows; x45,000).

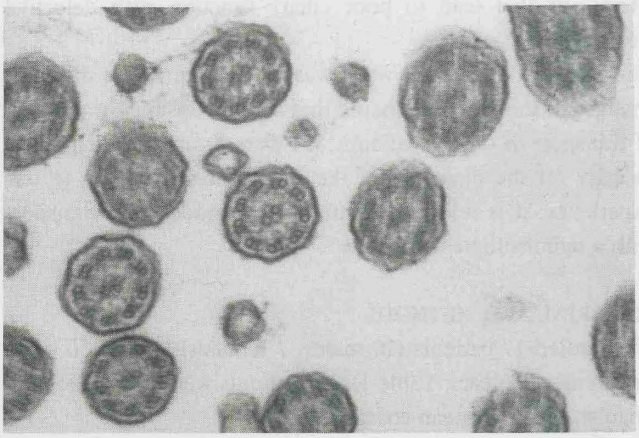

Figure 4. Cross section of nasal cilia. Normal cilia in a Kartagener's syndrome patient (x45,000).

DISCUSSION

Immotile cilia syndrome should be considered in the differential diagnosis of patients suffering from chronic or recurrent infections in the upper and lower airways, from early childhood on. This symptomatic profile may be accompanied by other symptoms or characteristic signs, such as situs inversus of the patient or a relative, headache, corneal abnormalities, hyposmia, and sterility in males (Afzelius, 1981).

The 41% incidence of situs inversus in our series was near the 50% reported in the literature (Afzelius, 1981). Although Kartagener's syndrome has always been associated with dynein arms defects (Vevaina et al., 1986), no such relation was apparent in our study, especially since one of the patients with Kartagener's syndrome showed normal ciliary ultrastructure, while others presented dynein arm defects but no situs inversus.

Although male sterility is considered a sign of primary ciliary dyskinesia, in our series 25% of the patients were fertile. According to the literature 20% of the affected males remain fertile (Afzelius, 1986). Ciliary and sperm axonematal ultrastructure are identical, but their polypeptide composition is different (Link, 1973).

The study of ciliary ultrastructure is difficult (Escudier et al., 1989), and although the minimum number of cilia that should be counted is not clear, most authors recommend to evaluate 50 or even 100 cilia (Vevaina et al., 1986). Of those examined, at least 40% must exhibit alterations to establish the diagnosis of primary ciliary dyskinesia (Holmes et al., 1968). In our series we examined at least 50 cilia per biopsy (mean: 60 cilia), and over 60% exhibited such alterations. The most frequently observed ultrastructural alterations in our series were total or partial loss of dynein arms (65%), followed by absence of cilia (12%) and alteration of the central microtubules (12%). Normal cilia were also present in two cases (12%): in these cases the lesion would be located at the molecular level and would not be detectable with currently used techniques. Compound cilia are regarded as being acquired and have been related to tobacco smoking and, in particular, viral infections (Rubin, 1988).

According to our experience, primary ciliary dyskinesia should be subjected to a stepwise study, i.e. following clinico-radiological examination, nasal mucociliary transport should be appraised by radio-isotopic techniques. If transport is abolished and the patient presents a characteristic and complete symptomatology, diagnosis may be considered definitive. If mucociliary transport is normal, immotile cilia syndrome is excluded, i.e. ultrastructural study of the cilia is not required.

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