Otological manifestations of primary ciliary dyskinesia

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Accepted for publication 16 August 1996

EL-SAYED Y., AL-SARHANI A. & AL-ESSA A.-R.
(1997) *Clin. Otolaryngol.* **22,** 266–270

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Primary ciliary dyskinesia is a hereditary defect in the ultrastructure of cilia, leading to poor ciliary motility. The sinonasal and the bronchial manifestations of the disease are well documented; whereas its otological aspects have received less attention. In this report, we describe the clinical profile of 16 patients with primary ciliary dyskinesia laying particular emphasis on the otological manifestations. All children (11 patients) had bilateral otitis media with effusion. Of the five adults, three had tympanosclerosis; one had bilateral cholesteatoma; and one patient had bilateral keratosis obturans in combination with tympanosclerosis. Hearing improvement and a dry ear was achieved in all the children treated by tympanostomy tube insertion. The study suggests that otitis media is a prominent feature of this disorder. Most subjects suffer from protracted bilateral otitis media with effusion throughout childhood.

Keywords *ciliary dyskinesia* *immotile ciliary syndrome* *Kartagener's syndrome* *keratosis obturans* *otitis media with effusion* *tympanosclerosis*

Introduction

Primary ciliary dyskinesia is of particular interest to the otolaryngologist; as many of its manifestations fall into his field. The disease is a hereditary defect in the ultrastructure of the cilia that renders them incapable of beating normally. Cilia are normally remarkably constant in their structure. They are present in several sites in the body including the sinonasal tract, Eustachian tube, middle ear mucosa, tracheobronchial tree, oviduct, ductuli efferents between the testes and the epididymis, and in the ependymal lining of the brain and the spinal cord.[1,2]

The cardinal features of the disorder are chronic sinusitis, bronchiectasis, and, in some patients dextrocardia. The dextrocardia is thought to be due to an inability of the embryonic cilia to rotate the heart to the left side with the situs laterality becoming a random process.[1] This implies that only 50% of patients with primary ciliary dyskinesia will be recognizable by dextrocardia (Kartagener's syndrome).

Other features of the condition include absent frontal sinuses, nasal polyposis, otitis media, and male sterility. Nasal polyps are present in approximately 20% of children with this disorder.[3] Male sterility is caused by immotile or sluggish spermatozoa since the sperm tails are modified cilia and their ultrastructure is also affected.[4] On the other hand, women exhibit fertility problems that may be associated with dysfunctional oviductal cilia.[5]

The prevalence of otitis media in patients with primary ciliary dyskinesia has been reported by a number of authors.[1,4,6] However, only few reports have specifically focused on its pathogenesis and management.[7–9] The purpose of this paper is to present the otological features of 16 patients with this condition and to discuss the principles of management of the disease.

Methods

Sixteen patients that have been identified by electron microscopy as having primary ciliary dyskinesia were included in the study. All patients had nasal mucosal biopsies obtained from the inferior turbinates; and four patients in addition had bronchial biopsies. At least 200 properly oriented sections of cilia were examined at a high resolution by electron microscopy and recorded on photographs. The diagnosis was based on the identification of consistent specific ciliary ultrastructural defects in the dynein arms, radial spoke linkage, or in the microtubular transposition. Inconsistent changes like compound cilia, disorganized axonemes and tubule deletion were considered nonspecific lesions; and were not included.

All patients were seen over a 5 year period during the years' 1991–1995. Four patients were diagnosed in the chest clinic,

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and another four in the paediatric clinic. The remaining eight patients were diagnosed in the ENT clinic. Of these latter eight. four were referred by primary care physicians and two by paediatricians because of protracted otitis media and nasal sepsis. Two patients (a brother and a cousin of two patients) were recruited following inquiry about other family members.

Each patient had a complete history taken and a physical examination. Special emphasis was placed on the age n-hen the diagnosis was established: and on the otological symptoms and signs. Pure-tone audiometry n-as performed for co-operative individuals. Impedance tympanometry studies were performed using a Madsen Z073 electroacoustic impedance bridge with a testing tone of 220 Hz coupled to Hew lett Packard XY plotter. Plain radiographs {and in some patients a CT-scan) of the chest and paranasal sinuses were obtained.

Results

Sixteen patients (nine males and seven females). ranging in age from 2 to 46 years (mean age. 17.5 years) were investigated. The clinical profile of the study group is shown in Table I

The age of establishing the diagnosis of the disease varied considerably: and was mainly influenced by the presence or absence of situs inversus. Most patients with dextrocardia a-ere diagnosed early in childhood (the mean was 3.7 years with Z-G years range). On the other hand. the mean age of establishing the diagnosis in those without dextrocardia was 20.9 years (7–47 years range). All patients had a history of chronic or recurrent infections of the upper and lower respiratory tracts. Nasal polypi or a history of nasal polypectomy was present in four patients.

All subjects younger than 12 years of age (I 1 children) showed evidence of otitis media with effusion at the time they were seen. The diagnosis was suspected by otoscopic examination and tympanometry findings (flat B-curve); and n-as confirmed by paracentesis. In all these children the middle ear contained very tenacious fluid. The condition was treated by ventilation tube insertion in combination with adenoidectomy. Intermittent purulent otorrhoea occurred in two children: but dry ears; resulted after medical treatment. In no instance did persistent infection necessitate removal of the tube. Reinsertion of tubes n-as performed in six children during a 1–4.5 years' follow -up period. Extrusion or blockage of the tubs was invariably followed by recurrence of the effusion (Table 2).

The ears of the five adults showed four with tympanosclerosis (combined with bilateral keratosis obturans in one patient) and one with bilateral cholesteatoma. The latter patient had bilateral modified radical mastoidectomies.

Pure-tone audiometry was carried out on seven of the 11 children. It showed pre-operative bilateral conductive hearing impairment with a mean 23 dB air-bone gap (average at 500, 1000. 2000 and 4000 Hz). Post-tube-insertion hearing was invariably normal. Audiograms of the adult patients were normal except for the patient with cholesteatoma who had a preoperative 35 dB bilateral conductive hearing- loss that showed no significant change following surgery.

Radiographs showed opacities or mucosal thickening of the

Table 1. Clinical data on 16 patients with primary ciliary dyskinesia

No	Sex–Age (years)	Age at diagnosis (years)	Dextrocardia	Bronchiectasis	Ears
	F-2	2	–	–	OME*
2	M-4	4	+	–	OME
3	M-4.5	4	+	–	OME
4	F-5	2.5	i		OME
5	M-7	7		–	OME
	M-8	4	+		OME
	F-8	3.5	+		OME
	F-9	9		+	OME
	M-9	3.5	+	–	OME
10	M-9.5	9.5		–	OME
11	M-11	4	+		OME
12	F-24	6	–	+	Cholesteatoma
13	F-34	34	–	+	Tympanosclerosis
14	M-44	20	–	–	Tympanosclerosis
15	F-47	47	–	–	Tympanosclerosis
16	M-53	33	–	+	Keratosis obturans & tympanosclerosis

*OME, otitis media with effusion. All patients had chronic or recurrent upper and lower respiratory tract infections. Patients 2 & 6 are brothers; 5 & 11 are first cousins.

No.	Sex	Age (years)	Follow-up period (years)	Number of tube reinsertion	Cause of reinsertion
1	F	2	1	—	—
2	M	4	2	1	Blockage
3	M	4.5	4	5	Blockage & extrusion
4	F	5	4.5	3	Extrusion
5	M	7	2	1	Blockage
6	M	8	1	—	—
7	F	8	2	2	Extrusion
8	F	9	1.5	—	—
9	M	9	2	—	—
10	M	9.5	2	2	Blockage
11	M	11	2	—	—

Table 2. Clinical course of 11 children with otitis media with effusion and primary ciliary dyskinesia

All patients had ventilation tubes inserted within 4 weeks following the otological diagnosis. Tube reinsertion was only performed after bilateral tube extrusion or blockage.

maxillary sinuses in all patients. The ethmoids and sphenoids were well aerated in most patients. The frontal sinuses were hypoplastic or absent in nine patients. Chest radiographs showed bronchiectatic changes in eight patients.

Electron microscopic examination showed deficiencies in the dynein arms in 14 patients: and two had a microtubular transposition defects. The dynein arm deficiencies involved various combinations of partial and complete lack of inner and outer arms. The microtubular transposition defects were non-persistence of the central core and tubules beyond the base of the cilium with one of the peripheral microtubular doublets transposed to the centre.

Discussion

Primary ciliary dyskinesia is a hereditary inborn defect in the ultrastructure of cilia that renders them incapable of normal beating. Different opinions prevail on the name of the disease. The term 'immotile cilia syndrome' was proposed by Eliasson *et al.* in 1976;[4] and has been advocated by several authors. However, this term has been criticized on the ground that some cilia may display some, even though erratic, movement.[10,11] Also, the term 'immotile cilia syndrome' would include a different disease like cystic fibrosis, where the cilia have a normal structure and function but are prevented from moving by too abundant and too viscous mucus. Therefore, the name 'primary ciliary dyskinesia' introduced by Sleigh in 1981, is considered to be more appropriate.[12]

Primary ciliary dyskinesia is not a common disease; the prevalence has been estimated as between 1 in 15 000 to 1 in 30 000 of the population.[13] The hereditary trait seems to be an autosomal recessive.[2]

Generally, symptoms start in childhood with recurrent respiratory tract infections leading to chronic sinusitis and bronchiectasis. The disease is frequently not diagnosed until the second or third decade of life when the bronchiectasis has reached a point where hospitalization may be required. Patients with Kartagener's syndrome, however, are usually diagnosed at an early age due to the presence of dextrocardia. In this series, the average age of diagnosis was 3.7 years for patients with dextrocardia versus 20.7 years for levocardia patients.

The otological aspects of primary ciliary dyskinesia have been described by a number of authors.[3,4,6–9] Greenstone *et al.*[6] found evidence of otitis media with effusion in 10 of 16 patients. Jahrsdoerfer *et al.*[7] reported four perforated tympanic membranes and one middle ear effusion among a series of six patients. Mygind and Pedersen[8] reported a 27 patients' series and found forty of 54 tympanograms to be flat; 12 of the 14 curves not suggestive of otitis media with effusion were from adults. Levison *et al.*[3] reported recurrent otitis media in all of a 33 patients' series. Ernstson *et al.*[9] reported a series of seven patients showing bouts of acute otitis media against an almost unceasing background state of otitis media with effusion. They noticed slowly declining activity during adolescence with most of their patients having aerated middle ears in adult life.

This study, in accord with some previous investigations[6–9] showed that most of the children with primary ciliary dyskinesia do suffer from protracted otitis media with effusion. The cause of this association is not clear. Ernstson *et al.*[9] postulated that impairment of mucociliary clearance leads to the accumulation of secretion in the middle ear which will be prone to infection by respiratory pathogens that are often carried in the nasopharynx in children. Also, the inadequate mucociliary clearance may cause persistence of the effusion caused by malfunction of the Eustachian tube which is generally considered a common factor associated with otitis media with effusion.

The treatment of otitis media with effusion in primary ciliary dyskinesia is controversial. On one hand, some authors[6,8] suggested that insertion of tympanostomy tubes should, as a rule, be avoided because when they inserted tubes the ears continued to discharge until they were either extruded or

removed. Mygind and Pedersen[8] advised temporary use of a hearing aid. On the other hand. a previous investigation[7] as well as this study. demonstrated that a dry ear and hearing improvement can be achieved following ventilation tube insertion. This finding is believed to be related to the change in the middle ear-nasopharyngeal pressure relationship following insertion of the tube so that the middle ear secretion drains down the Eustachian tube even in the absence of a normal mucociliary transport system.[7] Insertion of tympanostomy tube produces hearing gain that is of particular importance for those patients because of the earl!- onset. the relatively long duration. and the bilateral nature of the disease. Also. treatment of otitis media with effusion may prevent development of complications. Paparella *et al.*[14] hypothesized that all categories of otitis media (serous. purulent. mucoid. and chronic) represent different stages in a continuum of events. A number of authors"." demonstrated a strong association between otitis media n-ith effusion and pathological structural changes in the tympanic membrane{ atrophy, atelectasis. and attic retraction). However, the role of ventilation tubes. if any. in preventing these possible sequelae is not known. Schilder et *al.* (1995) found more frequent sequelae in patients treated by ventilation tube insertion compared with untreated patients.[16]

Many patients with this disorder may require repeated ventilation tube insertion throughout their childhood. Tos *et al.*[17] and Maw[18] demonstrated that one-time insertion of a ventilation tube brings about the same likelihood and sev erity of tympanosclerosis as repeat tube insertion. Long-term ventilation tubes (e.g. Goode T-tubs. Per-Lee tube or Shah Permavent tube) merit consideration for use in these patients to diminish the need for repeated insertions.

In this series, one patient with bilateral keratosis obturans was seen. The prevalence of keratosis obturans in primary ciliary dyskinesia patients is nor known. However. several authors have documented a definite relationship between keratosis obturans. bronchiectasis and sinusitis especially in children. Black and Clayton[19] found an incidence of 89% of either sinus suppuration or chronic respiratory infection or both in 90 children with keratosis obturans. Morrison[20] in a series of 50 patients. found 77% of his juvenile patients and 20% of the adults to have either bronchiectasis or sinusitis. The pathogenesis of keratosis obturans is unclear. Morrison[20] presented a theory that the underlaying cause was bronchiectasis that caused reflex stimulation of the ceruminous glands by the sympathetic autonomic nerv ous system. leading to hyperemia of the external canals and an epidermal plug.

The early diagnosis of primary ciliary dyskinesia is highly desirable so that appropriate management (physiotherapy. bronchodilator and antibiotic therapy) might prevent or delay the onset of life-threatening irreversible pulmonary damage. The diagnosis has also importance for counseling the patients and their parents regarding the genetic implications.

The appreciation of the otological aspects of the disorder may lead to early recognition of the disease. Persistent or recurring otitis media in association with early appearance of recurrent or persistent upper and lower respiratory tract infections. should raise clinical suspicion.

The pathological diagnosis of primary ciliary dyskinesia is usually made on the ultrastructural appearances of cilia in a respiratory mucosa biopsy specimen. The most common ciliary abnormality is the absence or gross deficiency of dynein arms. Other types of ciliary defect may exist such as radial spoke linkage defect. microtubular transposition defect, and supernumerary microtubules.[3] In men. it is also important to evaluate the ultrastructure and motility of spermatozoa.'.'

One has to be extremely careful in interpreting ciliary ultrastructural abnormalities. Son-specific ciliary defects are observ ed in many patients with a respiratory infection. These defects commonly include deletion of tubules and the presence of supernumerary tubules as well as most commonly, the fusion of cilia to form compound or megacilia.[21] These nonspecific defects show no consistent pattern and occur sporadically in the respiratory tract. The technique and the recommended criteria for the evaluation of ciliary ultrastructure are discussed by Levison *et al.*[3]

Functional studies of ciliary movement will contribute in the diagnosis of the rare cases of the disease with normal ciliary ultrastructure.[10] The nasal saccharin test" is a simple, sensitive. inexpensive. and reproducible screening procedure. Compliance of young children. however, is difficult to achieve. Mucociliary activity can also be studied by measuring the movement velocity of a radioactive tracer placed anteriorly in the nose.[23] Furthermore. the frequency and the pattern of ciliary beats in a nasal biopsy can be viewed by phase contrast microscopy and recorded by a video camera.[11]

In conclusion. otitis media is a prominent part of the primal-)7 ciliary dyskinesia syndrome. Most of the affected children suffer from unrelenting bilateral otitis media with effusion. Treatment by ventilation tube insertion seems appropriate to restore normal hearing; and it may prevent the development of complications. Many of these children n-ay require repeat tube insertion until adulthood. Long-term follow-up in a larger number of patients is needed to evaluate the value of this treatment.

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