

# Otologic features in children with primary ciliary dyskinesia

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## **ABSTRACT**

**OBJECTIVE:** To evaluate otologic features in children with primary ciliary dyskinesia (PCD).

**DESIGN:** retrospective study

**SETTING:** pediatric referral center

**PATIENTS:** 58 PCD patients, distributed in four age-groups (I: 0-5 years; II: 6-11 years; III: 12-17 years and IV: above 18 years with 47, 50, 34 and 10 cases, respectively). Follow-up: 2 to 6 years in each age-group. Ultrastructural defects of outer or inner dynein arms, and central complex (CC): 33, 13 and 11 cases, respectively.

**MAIN OUTCOME MEASURES:** Frequency of: acute otitis media (AOM), otitis media with effusion (OME), otorrhea, chronic otitis media, hearing loss, middle ear surgery and type of antibiotic regimen according to age and type of defect.

**RESULTS:** Recurrent AOM decreased from group I (68%) to group IV (0%),  $p < 0.00001$ . OME was more severe in groups I to III than in group IV,  $p = 0.02$ . Otorrhea decreased in group IV: 30% versus 80% in other groups,  $p < 0.001$ . One half of patients with tubes eventually had tympanic perforation. Hearing loss was moderate in groups I to III and mild in group IV. Continuous antibiotics could be slightly reduced only in group IV. CC defect was a significant marker of severity for all of these criteria.

**CONCLUSIONS:** Despite continuous antibiotics, the middle ear condition in PCD remained severe throughout childhood with improvement only after the age of 18 years. Grommet placement failed to improve the middle ear condition. CC defect is a marker of severity.

## INTRODUCTION

Primary ciliary dyskinesia (PCD) is an autosomal recessive disease characterized by abnormal ciliary structure and function and associated in about 50% of cases with *situs inversus* corresponding to Kartagener syndrome (1).

In normal airways, the structural components of the core of the cilium, known as the axoneme, include 9 peripheral doublet microtubules with attached dynein arms and radial spokes, and 2 central single microtubules (central complex - CC). Inner and outer dynein arms (IDA and ODA, respectively) are the transducers of mechanical force necessary for ciliary motion. Several types of axonemal defect have been identified, including lack of ODA and/or IDA or CC abnormalities (2, 3). Failure of ciliary structure and function in PCD impairs mucociliary clearance in the airways and can be responsible for respiratory tract infections including severe otologic features (4-6). To date, the characteristics of otologic features in PCD according to age and type of ciliary defect have not been reported. The aims of this study were to analyze otologic features in PCD patients from 0 to 18 years of age and to evaluate the correlation between ultrastructural defects and severity of otologic features. A better knowledge of otologic features in children with PCD according to age and type of ciliary defect could help physicians to more effectively manage these patients and prevent otologic complications.

## PATIENTS AND METHODS

### *Patients*

A retrospective study was conducted from 1992 to 2006 on 58 children and young adults with an established diagnosis of PCD (including 11 patients with Kartagener syndrome) treated in the Department of Pediatric Otolaryngology, Armand-Trousseau Children's Hospital (Paris,

France). For all patients, PCD was suspected on compatible clinical features and confirmed by the results of ciliary ultrastructure.

For analysis, children were evaluated in four different age intervals: I: preschool age 0 to 5 years (47 patients); II: school age 6 to 11 years (50 patients); III: teenagers 12 to 17 years (34 patients) and IV: young adults above 18 years (27 years for the oldest) (10 patients). This type of classification was chosen to allow longitudinal follow-up as well as clinical description of symptoms/diseases for each age-group. According to this distribution, 12 patients were followed in only one group, 20 were followed in two groups, 18 were followed in three groups, and 8 were followed in four groups. Patient follow-up in each group ranged from 2 to 6 years and 26 patients had a total follow up of more than 12 years. Mean of follow up was  $11.8 \pm 4.4$  years and ranged from 2 to 18 years.

Otologic features according to type of ciliary defect were analyzed by comparing patients with abnormalities of ODA alone or associated with IDA defect (n=33), IDA alone (n=13) and CC (n=11). One patient with typical Kartagener syndrome but normal ciliary ultrastructure was not included in this part of the study.

#### *Evaluation of ciliary structure and function*

Ultrastructural analysis of ciliary defects was performed by transmission electron microscopy on nasal or bronchial epithelial cells. Airway biopsies were immersed in 2.5% glutaraldehyde in 0.045 M cacodylate buffer at pH 7.4 and processed for ultrastructural analysis (7). After fixation, samples were postfixed in  $\text{OsO}_4$  and routinely processed. Ultrathin sections were studied at a final magnification of 60,000. At least 50 transverse sections through the body of ciliary shafts of different cells were analyzed in each specimen to study the internal axonemal structure according to a quantitative method (8). Dynein arms were considered to be absent from sections when the structure was missing from at least 5 of

the 9 peripheral doublets. For each ciliary study, axonemal abnormalities were quantified and expressed as a percentage of each ultrastructural defect among the total number of abnormal cilia, in order to define the main ultrastructural defect. Ciliary beat frequency (CBF) was determined by videomicroscopy on at least five different areas of ciliated epithelium.

#### *Pulmonary status*

Pulmonary status, evaluated by radiologic deterioration and corresponding to bronchiectasis (internal diameter of bronchus larger than that of an adjacent artery assessed on CT scan), and lung surgery were recorded.

#### *Otologic evaluation*

At each visit, clinical assessment included recording of symptoms and treatment history, as well as otoscopy using a microscope. Audiograms (with the use of free-field audiometry techniques in young children, if necessary) and tympanometry were performed for each patient in each age-group. Otologic symptoms or diseases included: recurrent acute otitis media (rAOM) defined as 3 episodes or more in 6 months or 4 or more episodes in 12 months; otitis media with effusion (OME) when at least one episode was reported and persistent OME when OME lasted for 3 months or longer each year. Otorrhea (for 1 month or more) was noted and considered recurrent when two or more episodes occurred each year.

Presence of grommets was noted and placements were considered repeated when two or more grommet insertions were reported. The indication of tympanostomy tube insertion was: persistent OME that has not responded to a 6 to 12 week course of medical treatment with conductive deafness (mean air conduction thresholds  $\geq 25$  dB) or recurrent AOM (at least 3 episodes in 6 months or 4 or more episodes in 12 months). For first insertion, Armstrong grommets were used, following placements were conducted with Per-Lee Tubes for all PCD children. Otorrhea (for 1 month or more) among patients with grommets was noted (at least one episode) and otorrhea was classified as recurrent when two or more episodes were

observed. Chronic otitis media (including tympanic perforation, retraction pocket or cholesteatoma) was noted as well as the presence of at least one episode of otorrhea (for 1 month or more) among these patients. The number of patients requiring tympanoplasty was recorded.

Audiograms were analyzed and the mean air conduction thresholds at 0.5, 1, 2 kHz were calculated. Conductive deafness was considered to be significant when mean air conduction thresholds was  $\geq 25$  dB (all patients had normal bone conduction). When several audiograms were available (range from 2 to 6 in each age bracket), only the worst was considered in each age-group.

Otologic diseases according to each age-group or type of ciliary defect were analyzed according to the same criteria.

#### *Antibiotic regimen*

Patients treated by repeated discontinuous antibiotics (meaning four or more treatments per year), and patients receiving continuous alternating antibiotics were considered separately.

### **STATISTICAL ANALYSIS**

Linear trend chi-square tests were used to compare proportions of symptoms/diseases between age-groups in order to identify age-related trends. The inclusion of several patients in two or more groups may have introduced a bias in interpretation of the results, but provided an unique opportunity for longitudinal follow-up.

Fisher's exact t test was used to compare symptoms/diseases between dynein arm defect and CC groups.

### **RESULTS**

#### *Study population*

The mean age of patients at PCD diagnosis was  $8.71 \pm 0.63$  years (range from 6 months to 16 years) and did not vary according to the type of ultrastructural defect. Only 4 of the 11

patients with *situs inversus* were diagnosed before the age of 5 years. Pulmonary status of the 58 patients was severe: 41 (70%) had bronchiectasis and 37 (63%) required partial lung surgery. Cilia were totally immotile in all patients with ODA and IDA defects and in 5 of the 11 patients in the CC group (the other 6 patients had a normal or decreased CBF). One patient with *situs inversus* had normal ciliary ultrastructure but cilia were totally immotile.

#### *Otologic symptoms/diseases and treatments according to age-groups (Table 1)*

Recurrent AOM decreased significantly from group I to group IV, while OME was nearly always present throughout groups I to III and still frequent in group IV. Interestingly, more than 80% of patients with OME had persistent OME regardless of age-group. Otorrhea significantly decreased from group I to group IV. Grommets were placed throughout the childhood in 50% of cases. For the 58 PCD patients, the mean number of tubes inserted was  $2.5 \pm 1$  (range from 0 to 6). Among children who received tubes, the mean number of tube insertion was  $3.5 \pm 1$ . Repeated grommet placements were required in one half of patients in each group (groups I to III). All patients with grommets developed at least one episode of otorrhea and 40 to 66% of patients experienced more than two episodes depending on age-group.

The percentage of patients with chronic otitis media significantly increased from group I to III and almost all of these patients experienced otorrhea. Among 17 patients with chronic otitis media, one had a retraction pocket, one had a cholesteatoma (these two patients were operated) and 15 had tympanic perforation, requiring tympanoplasty in 5 cases. Tympanic perforation healed for 3 patients between 12 and 17 years and was concomitant with disappearance of persistent OME. For the other 7 patients tympanic membrane perforation persisted associated with persistent OME until 17 years. For the 15 patients with tympanic

perforation, the mean number of tympanostomy tube insertion was  $4.5 \pm 1.5$  between 0 to 11 years.

The percentage of children who had conductive deafness with a mean air conduction thresholds equal to or greater than 25 dB progressively decreased with age. None of the patients developed sensorineural hearing loss.

Discontinuous antibiotics treatments in group I were gradually replaced by continuous antibiotics regimen in groups II to IV, once the diagnosis of PCD was established.

#### *Otologic diseases and treatments according to the type of ciliary defect (Table 2)*

Recurrent AOM was significantly more frequent in patients in the CC group compared to the ODA and IDA groups with no significant differences between ODA and IDA. All patients with CC defects presented persistent OME, which was less frequent in ODA and IDA groups. Grommet placements were reported in 81.8% of patients in the CC group and in about 60% and 70% of patients in the ODA and IDA groups, respectively. Repeated tube placement, presence of tube-induced otorrhea and recurrent otorrhea were more frequent in the CC group. The frequency of chronic otitis media was significantly higher in the CC group (81.8% versus 15.1% in ODA and 15.4% in IDA).

Chronic otitis media with otorrhea requiring middle ear surgery was more frequent in the CC group ( $p < 0.001$ ). The 2 patients with retraction pocket or cholesteatoma belonged to the CC group.



## DISCUSSION

Otologic features in PCD patients are generally explained by the defective ciliary function in the Eustachian tube and middle ear cleft, impairing mucociliary clearance, thereby predisposing to repeated bacterial infections (9). Otologic features in PCD patients according to age and type of defect have never been previously documented. This lack of knowledge about the natural history of otologic features in PCD patients may hinder optimal follow-up and care of these patients. This retrospective study was therefore designed to analyze the otologic features according to age and evaluate the frequency and severity of each symptom and disease.

All patients under the age of 5 years presented at least one episode of AOM or OME. In a context of suspicion of PCD in children, the absence of episodes of AOM or OME can therefore probably be considered to be clinical argument against this diagnosis. Recurrent AOM was observed during early childhood but persisted after the age of 6 years and up to the age of 17 years, which is fairly unusual in non-PCD populations (10). Similarly, the frequency of persistent OME only decreased after the age of 18 years in PCD patients, while it resolves by the age of 8 in most children without PCD (11).

However, the few available large clinical series on both adult and pediatric patients with PCD did not present detailed data on otitis media (9, 12). A history of recurrent AOM is reported in the vast majority of patients but the duration of these episodes has never been documented. A significant proportion of school age children and teenagers appeared to suffer from AOM. OME was also almost universal in the present study, as previously reported by other authors (9, 13) but the supposed spontaneous improvement before adulthood was not observed, as a significant proportion of patients still suffered from OME in the oldest group. Persistent OME leads to conductive deafness, which was disabling until the age of 17 years in the present study. In a previous study, hearing thresholds were reported to return to normal by

the age of 12 in PCD patients (13). However, patients with tympanic perforations or grommets were excluded (8 ears out of 71 patients) and the study design did not provide any longitudinal follow-up.

Significant hearing loss associated with OME usually constitutes an indication for grommet placement, but this approach may not be recommended PCD (13). Repeated grommet placements were performed in all groups due to the severity of OME. The presence of grommets may induce otorrhea which is common in young children (14, 16) but all patients in the present study experienced otorrhea, regardless of the age-group. The frequency of otorrhea correlated with the duration of grommet placement, reaching 83% after 18 months in the general pediatric population (15) but otorrhea appears to be even more frequent (87.6%) in PCD patients, regardless of the duration of grommet placement.

One half of patients with a history of grommet placement eventually developed tympanic perforation, which is much more frequent than in the general pediatric population (around 0.5 to 10% of cases depending on type of grommets and the duration) (14, 17) but could be explained by repeated placements of Per-Lee tubes in this cohort. Grommet placement in PCD has a limited efficacy to improve hearing in these patients, as otorrhea and/or obstruction by sticky fluid of middle ear are almost systematic and persistent. Repeated insertions are associated with a high risk of persistent tympanic perforation. Nevertheless, unlike in serous otitis media of healthy population, the problem is not a consequence of poor ventilation of middle ear and that could explain the low rate of success of grommets placement in PCD. In patients with hearing loss of more than 25 dB, the treatment decision should weigh up the risks and benefits of grommet insertion and hearing aids for each patient with PCD. The use of hearing aids was also proposed by Bush *et al*, who emphasized the almost inevitable otorrhea after grommet insertion (18).

A significant number of complications of chronic otitis media would be expected in view of this high rate of persistent OME. However, the number of retraction pockets and cholesteatomas remained very low (2 cases in this study, 11.7% of patients with chronic otitis media). Majithia (13) also reported no case of cholesteatoma in a series of 91 patients. One could argue that tympanostomy tubes could prevent severe chronic otitis media in PCD children. Only seven of the 17 patients with chronic otitis media were operated, and all other patients were closely monitored for recurrent otorrhea. Tympanoplasty in PCD patients achieves a high perforation closure rate, but is associated with a 66% OME recurrence rate (19), which is obviously a drawback even when hearing is preserved after surgery.

Although the vast majority of the patients in this series were treated by continuous alternating antibiotics, this treatment does not appear to prevent persistence of OME or otologic complications such as otorrhea or tympanic perforation.

Lastly, a correlation between the type of ciliary defect and otologic features was investigated. CC abnormalities are less common than the absence of dynein arms and, although not all cilia are affected (30 to 50% usually), they are considered to be congenital (7, 20) when a similar pattern is observed on all affected cilia. These abnormalities of CC appear to be a criterion of severity for otologic disease. The frequencies of recurrent AOM, persistent OME and repeated grommet placement, as well as chronic otitis media and the number of patients subsequently requiring tympanoplasty were significantly higher in this group.

Interestingly, CC defect has already been demonstrated to be a marker of severity in PCD in relation to lower respiratory tract disease (20). The pathophysiologic basis of this pejorative pattern is unknown, but this difference suggests that ciliary immobility universally observed in dynein arm defects is not the only mechanism involved in PCD patients, as one half of our CC patients presented motile cilia. No difference was found throughout childhood

between ODA (+/- IDA) and isolated IDA defects, suggesting a common mechanism of symptoms in these cases.

In this long-term study, many patients were studied in several age-groups, allowing a description of symptoms in each age-group and an estimation of the duration of these symptoms, but this methodology may also have induced a bias. Each group had not the same number of patients, some were lost of follow up (particularly at young adult age), and some entered the cohort only by the age of 6 or 12 years. More, we cannot exclude that patients who came at consultation for a longer period of time had worse clinical presentation. The conclusions of this study should therefore ideally be confirmed by prospective data.

## **CONCLUSION**

PCD patients have severe, early-onset, otologic symptoms that persist throughout childhood. Close follow-up is therefore required and physicians must adopt a specific therapeutic approach, notably concerning the treatment of persistent OME, as repeated grommet placement can predispose to chronic otitis and worsen the prognosis. Hearing aids should be considered as an alternative. Moreover, patients with CC defects must be carefully monitored due to the risk of potentially more severe otologic complications.

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**Table 1. Otologic symptoms/diseases and treatments according to age groups**

	0-5 years	6-11 years	12-17 years	>18 years	Total	p <sup>\$</sup>
	n=47	n=50	n=34	n=10	n=58	
<b>Recurrent AOM (%)</b>	68	36	17.6	0	63.7	<0.00001
<b>OME (%)</b>	97.7	93.8	93.9	70	98.2	0.02
<i>Of which long lasting (%)</i>	81.8	86.9	87	85.7	91	
<b>Otorrhea (%)</b>	87.8	82.2	71.9	30	87.3	<0.001
<i>Of which recurrent (%)</i>	44.4	45.9	34.8	66.7	56.2	NS (0.82)
<b>Grommets (%)</b>	45.2	51.1	46.8	30	69	NS (0.55)
<i>Of which with repeated surgery (%)</i>	52.6	47.8	46.6	33.3	63.1	
<i>Of which with otorrhea (%)</i>	100	100	100	100	100	
<i>Of which with recurrent otorrhea (%)</i>	52.6	56.5	40	66.6	63.1	
<b>Chronic otitis media (%)</b>	9.3	28.6	31.2	20	31	NS (0.07)
<i>Of which with otorrhea (%)</i>	100	92.8	100	0*	100	
<i>Of which requiring surgery (%)</i>	25	35.7	30	0*	41.2	
<b>Conductive deafness</b>						
mean air conduction thresholds $\geq$ 25dB (%)	64.3	55.5	45.8	16.7	62.5	NS (0.06)
<b>Antibiotics regimen</b>						
Repeated discontinuous (%)	42.8	8.3	2.9	30	3.5	<0.001
Continuous ATB treatment (%)	52.4	89.6	94.1	70	96.5	<0.01

As data for each item were available for all patients, the percentages are expressed in relation to available data.

Each patient who experienced the event during at least one six-year period is shown in the total column (for antibiotics, the worst 6-year period was considered).

NS (not significant), AOM (Acute Otitis Media), OME (Otitis Media with Effusion), ATB (antibiotic), dB (decibel).

<sup>\$</sup> linear trend chi-square test

\*These 2 patients had already been operated with a closed eardrum



**Table 2. Otologic symptoms/diseases and treatments according to ciliary defect type**

	CC	ODA (+/- IDA)	IDA alone	Total	p <sup>\$</sup>
	n=11	n=33	n=13	n=57	
<b>Recurrent AOM (%)</b>	72.7	54.5	53.8	63.6	NS (0.18)
<b>OME (%)</b>	100	96.9	92.3	98.2	NS (1.00)
<i>Of which long lasting (%)</i>	100	81.8	92.3	89.3	
<b>Grommets (%)</b>	81.8	57.5	69.2	68.5	NS (0.30)
<i>Of which with repeated surgery (%)</i>	63.6	33.3	38.4	42.6	
<i>Of which with otorrhea (%)</i>	81.8	57.5	69.2	68.5	
<i>Of which with recurrent otorrhea (%)</i>	54.5	33.3	46.1	42.6	
<b>Chronic otitis media (%)</b>	81.8	15.1	15.4	29.6	<0.0001
<i>Of which with otorrhea (%)</i>	81.8	15.1	15.4	29.6	<0.0001
<i>Of which requiring surgery (%)</i>	36.4	0	15.4	11.1	0.01
<b>Antibiotics regimen</b>					
Repeated discontinuous (%)	18.2	0	0	3.6	NS (0.12)
Continuous ATB treatment (%)	81.8	100	92.3	96.4	NS (0.09)

Total number of patients is 57 instead of 58, as one patient with *situs inversus* had normal ciliary ultrastructure and was therefore excluded from this analysis.

<sup>\$</sup> Fisher's exact test, grouping ODA (+/- IDA) + isolated IDA versus CC.

NS (not significant), AOM (Acute Otitis Media), OME (Otitis Media with Effusion), ATB (antibiotic).