Objective: To analyze otologic features in patients with primary ciliary dyskinesia (PCD) aged 0 to 18 years and to evaluate the correlation between ultrastructural defects and severity of otologic features.

Design: Retrospective study.

Setting: Pediatric referral center.

Patients: Fifty-eight patients with PCD were evaluated in the following 4 age intervals: group 1, preschool (≤5 years [n=47]); group 2, school (6-11 years [n=50]); group 3, teenagers (12-17 years [n=34]); and group 4, young adults (≥18 years; 27 years for the oldest [n=10]). Follow-up was 2 to 6 years in each age group; 26 patients had total follow-up of more than 12 years. Ultrastructural defects occurred in the outer dynein arm (n=33), the inner dynein arm (n=13), and the central complex (n=11). One patient had typical Kartagener syndrome with typical PCD features but normal ciliary ultrastructure.

Main Outcome Measures: Frequency of acute otitis media, otitis media with effusion, otorrhea, chronic otitis media, hearing loss, and middle ear surgery and type of antibiotic regimen according to age and type of defect.

Results: Recurrent acute otitis media decreased from group 1 (32 of 47 [68%]) to group 4 (0 of 10 [0%]) (P<.001). Otitis media with effusion was more severe in groups 1 through 3 than in group 4 (P=.02). Otorrhea decreased in group 4: 30% vs 80% (3 of 10 vs 36 of 41) in the other groups (P<.001). Half of the patients with tympanostomy tubes eventually had tympanic perforation. Hearing loss was moderate in groups 1 through 3 and mild in group 4. Continuous antibiotic therapy could be slightly reduced only in group 4. Central complex defect was a significant marker of severity for all these criteria.

Conclusions: Despite continuous antibiotic therapy, the middle ear condition in PCD remained severe throughout childhood, with improvement only after age 18 years. Armstrong grommet placement did not improve the middle ear condition. Central complex defect is a marker of severity.

PATIENTS

A retrospective study was conducted between January 1, 1992, and December 31, 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 the patients, PCD was suspected on compatible clinical features and was confirmed by the results of ciliary ultrastructural analysis.

For analysis, children were evaluated in the following 4 age intervals: group 1, preschool (≤ 5 years [n = 47]); group 2, school age (6-11 years [n = 50]); group 3, teenagers (12-17 years [n = 34]); and group 4, young adults (≥ 18 years; 27 years for the oldest [n = 10]). This type of classification was chosen to allow longitudinal follow-up and clinical description of symptoms and diseases for each age group. According to this distribution, 12 patients were followed up in only 1 group, 20 were followed up in 2 groups, 18 were followed up in 3 groups, and 8 were followed up in 4 groups. Patient follow-up in each group ranged from 2 to 6 years; 26 patients had a total follow-up of more than 12 years. Mean (SD) follow-up was 11.8 (4.4) years (range, 2-18 years).

Otolologic features according to type of ciliary defect were analyzed by comparing patients with abnormalities of the ODA alone or associated with IDA defects (n = 33), abnormalities of the IDA alone (n = 13), and abnormalities of the CC (n = 11). One patient with typical Kartagener syndrome but normal ciliary ultrastructure was excluded from 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 biopsy samples were immersed in 2.5% glutaraldehyde in 0.045M cacodylate buffer at pH 7.4 and were processed for ultrastructural analysis. After fixation, samples were postfixed in osmium tetroxide and were 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.6 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 in the total number of abnormal cilia to define the main ultrastructural defect. Ciliary beat frequency was determined using videomicroscopy on at least 5 different areas of ciliated epithelium.

PULMONARY STATUS

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

OTOLOGIC EVALUATION

At each visit, clinical assessment included recording of symptoms, treatment history, and 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. Otolologic symptoms or diseases included recurrent acute otitis media (rAOM), defined as 3 or more episodes in 6 months or 4 or more episodes in 12 months, and otitis media with effusion (OME) when at least 1 episode was reported and persistent OME when OME lasted for 3 months or longer each year. Otorrhea (for ≥ 1 month) was noted and was considered recurrent when 2 or more episodes occurred each year.

The presence of Armstrong grommets or Per-Lee tubes was noted, and placements were considered repeated when 2 or more grommet insertions were reported. The indication for tympanostomy tube insertion was persistent OME unresponsive to a 6- to 12-week course of medical treatment with conductive deafness (mean air conduction thresholds ≥ 25 dB) or rAOM (≥ 3 episodes in 6 months or ≥ 4 episodes in 12 months). For the first tympanostomy tube insertion, Armstrong grommets were used; Per-Lee tympanostomy tubes were used for all the remaining children with PCD. Otorrhea (for ≥ 1 month) in patients with grommets was noted (≥ 1 episode), and otorrhea was classified as recurrent when 2 or more episodes were observed. Chronic otitis media (COM) (including tympanic perforation, retraction pocket, or cholesteatoma) was noted, as was the presence of at least 1 episode of otorrhea (for ≥ 1 month) in these patients. The number of patients requiring tympanoplasty was recorded.

Audiograms were analyzed, and mean air conduction thresholds at 0.5, 1.0, and 2.0 kHz were calculated. Conductive deafness was considered significant when mean air conduction thresholds were at least 25 dB (all the patients had normal bone conduction). When several audiograms were available (range, 2-6 in each age bracket), only the worst was considered in each age group. Otolologic diseases according to age group or type of ciliary defect were analyzed using the same criteria.

ANTIBIOTIC REGIMEN

Patients treated with repeated discontinuous antibiotics (ie, ≥ 4 treatments per year) and patients receiving continuous alternating antibiotic therapy were considered separately.

STATISTICAL ANALYSIS

Linear trend χ² tests were used to compare proportions of symptoms and diseases between age groups to identify age-related trends. The inclusion of several patients in 2 or more groups may have introduced a bias in interpretation of the results but provided a unique opportunity for longitudinal follow-up. The Fisher exact t test was used to compare symptoms and diseases between the dynein arm defect and CC groups.

STUDY POPULATION

The mean (SD) age of patients at PCD diagnosis was 8.71 (0.63) years (age range, 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 age 5 years. The pulmonary status of the 58 patients was severe: 41 (71%) had bronchiectasis, and 37 (64%) required partial lung surgery. Cilia were totally immotile in all the 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 ciliary beat frequency). One patient with...
Table 1. Otologic Symptoms/Diseases and Treatments According to Age Groups*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age Group</th>
<th>*=5 y (n=47)</th>
<th>6-11 y (n=50)</th>
<th>12-17 y (n=34)</th>
<th>≥18 y (n=10)</th>
<th>Total (N=58)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent AOM, %</td>
<td></td>
<td>68.0</td>
<td>36.0</td>
<td>17.6</td>
<td>0.0</td>
<td>63.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>OME, %</td>
<td></td>
<td>97.7</td>
<td>93.8</td>
<td>93.9</td>
<td>70.0</td>
<td>98.2</td>
<td>.02</td>
</tr>
<tr>
<td>Long lasting</td>
<td></td>
<td>81.8</td>
<td>86.9</td>
<td>87.0</td>
<td>85.7</td>
<td>91.0</td>
<td>.08</td>
</tr>
<tr>
<td>Otorrhea, %</td>
<td></td>
<td>87.8</td>
<td>82.2</td>
<td>71.9</td>
<td>30.0</td>
<td>87.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Recurrent</td>
<td></td>
<td>44.4</td>
<td>45.9</td>
<td>34.8</td>
<td>66.7</td>
<td>56.2</td>
<td>.82</td>
</tr>
<tr>
<td>Armstrong grommets, %</td>
<td></td>
<td>45.2</td>
<td>51.1</td>
<td>46.8</td>
<td>30.0</td>
<td>69.0</td>
<td></td>
</tr>
<tr>
<td>With repeated surgery</td>
<td></td>
<td>52.6</td>
<td>47.8</td>
<td>46.6</td>
<td>33.3</td>
<td>63.1</td>
<td>.55</td>
</tr>
<tr>
<td>With otorrhea</td>
<td></td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>.07</td>
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<tr>
<td>With recurrent otorrhea</td>
<td></td>
<td>52.6</td>
<td>56.5</td>
<td>40.0</td>
<td>66.6</td>
<td>63.1</td>
<td></td>
</tr>
<tr>
<td>Chronic otitis media, %</td>
<td></td>
<td>9.3</td>
<td>28.6</td>
<td>31.2</td>
<td>20.9</td>
<td>31.0</td>
<td></td>
</tr>
<tr>
<td>With otorrhea</td>
<td></td>
<td>100.0</td>
<td>92.6</td>
<td>100.0</td>
<td>0.0</td>
<td>100.0</td>
<td>.07</td>
</tr>
<tr>
<td>Requiring surgery</td>
<td></td>
<td>25.0</td>
<td>35.7</td>
<td>30.0</td>
<td>0.0</td>
<td>41.2</td>
<td></td>
</tr>
<tr>
<td>Conductive deafness</td>
<td></td>
<td>Mean air conduction thresholds ≥25 dB, %</td>
<td>64.3</td>
<td>55.5</td>
<td>45.8</td>
<td>16.7</td>
<td>62.5</td>
</tr>
<tr>
<td>Antibiotic regimen, %</td>
<td></td>
<td>Repeated discontinuous</td>
<td>42.8</td>
<td>8.3</td>
<td>2.9</td>
<td>30.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Continuous</td>
<td></td>
<td>52.4</td>
<td>89.6</td>
<td>94.1</td>
<td>70.0</td>
<td>96.5</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Abbreviations: AOM, acute otitis media; OME, otitis media with effusion.

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

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

*cLinear trend χ² test.

*dThese 2 patients had already undergone surgery with a closed eardrum.

OTOLOGIC SYMPTOMS/DISEASES AND TREATMENTS ACCORDING TO AGE GROUPS

Recurrent AOM decreased significantly from group 1 through group 4, whereas OME was almost always present throughout groups 1 to 3 and was still frequent in group 4 (Table 1). More than 80% of patients with OME had persistent OME regardless of age group (ie, group 1: 36 of 44 patients; group 2: 40 of 46 patients; group 3: 27 of 31 patients; and group 4: 6 of 7 patients). Otorrhea significantly decreased from group 1 through group 4. Armstrong grommets were placed throughout childhood in 50% of cases (ie, group 1: 19 of 42 patients; group 2: 23 of 45 patients; group 3: 15 of 32 patients; and group 4: 3 of 10 patients). For the 58 patients with PCD, the mean (SD) number of tympanostomy tubes inserted was 2.5 (1.0) (range, 0-6). In children who received tympanostomy tubes, the mean (SD) number of tympanostomy tube insertions was 3.5 (1.0). Repeated grommet placements were required in half of the patients in each group (groups 1–3). All the patients with grommets developed at least 1 episode of otorrhea, and 40% to 66% of patients experienced more than 2 episodes depending on age group (ie, group 1: 10 of 19 patients; group 2: 13 of 23 patients; group 3: 6 of 15 patients; and group 4: 2 of 3 patients).

The percentage of patients with COM significantly increased from group 1 through group 3, and almost all of these patients experienced otorrhea. Of 17 patients with COM, 1 had a retraction pocket, 1 had a cholesteatoma (these 2 patients underwent surgery), and 15 had tympanic perforation, requiring tympanoplasty in 5 cases. Tympanic perforation healed in 3 patients between ages 12 and 17 years and was concomitant with the disappearance of persistent OME. For the other 7 patients, tympanic membrane perforation persisted associated with persistent OME until age 17 years. For the 15 patients with tympanic perforation, the mean (SD) number of tympanostomy tube insertions was 4.5 (1.5) between ages 0 and 11 years.

The percentage of children who had conductive deafness with a mean air conduction threshold of 25 dB or greater progressively decreased with age. None of the patients developed sensorineural hearing loss. Discontinuous antibiotic treatments in group 1 were gradually replaced by continuous antibiotic regimens in groups 2 through 4, once the diagnosis of PCD was established.

OTOLOGIC SYMPTOMS/DISEASES AND TREATMENTS ACCORDING TO THE TYPE OF CILIARY DEFECT

Recurrent AOM was significantly more frequent in patients in the CC group compared with the ODA and IDA groups, with no significant differences between the ODA and IDA groups (Table 2). All the patients with CC defects had persistent OME, which was less frequent in the ODA and IDA groups. Armstrong grommet placements were reported in 81.8% of patients (9 of 11) in the CC group and in approximately 60% and 70% of patients in the ODA (19 of 33 patients) and IDA (9 of 13 patients) groups, respectively. Repeated tympanostomy tube placement, the presence of tympanostomy tube–induced otorrhea, and recurrent otorrhea were more frequent in the CC group. The frequency of COM was significantly higher...
Table 2. Otologic Symptoms/Diseases and Treatments According to Ciliary Defect Type

<table>
<thead>
<tr>
<th>Variable</th>
<th>CC (n=11)</th>
<th>ODA±IDA (n=33)</th>
<th>IDA Alone (n=13)</th>
<th>Total (N=57)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent AOM, %</td>
<td>72.7</td>
<td>54.5</td>
<td>53.8</td>
<td>63.6</td>
<td>.18</td>
</tr>
<tr>
<td>OME, %</td>
<td>100</td>
<td>96.9</td>
<td>92.3</td>
<td>96.2</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Long lasting</td>
<td>100</td>
<td>81.8</td>
<td>92.3</td>
<td>89.3</td>
<td></td>
</tr>
<tr>
<td>Grommets, %</td>
<td>81.8</td>
<td>57.5</td>
<td>69.2</td>
<td>68.5</td>
<td></td>
</tr>
<tr>
<td>With repeated surgery</td>
<td>63.6</td>
<td>33.3</td>
<td>38.4</td>
<td>42.6</td>
<td>.30</td>
</tr>
<tr>
<td>With otorrhea</td>
<td>81.8</td>
<td>57.5</td>
<td>69.2</td>
<td>68.5</td>
<td></td>
</tr>
<tr>
<td>With recurrent otorrhea</td>
<td>54.5</td>
<td>33.3</td>
<td>46.1</td>
<td>42.6</td>
<td></td>
</tr>
<tr>
<td>Chronic otitis media, %</td>
<td>81.8</td>
<td>15.1</td>
<td>15.4</td>
<td>29.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>With otorrhea</td>
<td>81.8</td>
<td>15.1</td>
<td>15.4</td>
<td>29.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Requiring surgery</td>
<td>36.4</td>
<td>0</td>
<td>0</td>
<td>11.1</td>
<td>.01</td>
</tr>
<tr>
<td>Antibiotic regimen, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeated discontinuous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous</td>
<td>81.8</td>
<td>100</td>
<td>92.3</td>
<td>96.4</td>
<td>.09</td>
</tr>
</tbody>
</table>

Abbreviations: AOM, acute otitis media; CC, central complex; IDA, inner dynein arm; ODA, outer dynein arm; OME, otitis media with effusion.

In the CC group (81.8% vs 15.1% [9 of 11 patients vs 5 of 33] in the ODA and 15.4% [2 of 13] in the IDA groups), COM with otorrhea requiring middle ear surgery was more frequent in the CC group (P < .001). The 2 patients with a retraction pocket or cholesteatoma belonged to the CC group.

Otologic features in patients with PCD are generally explained by the defective ciliary function in the Eustachian tube and middle ear cleft, impairing mucociliary clearance, thereby predisposing patients to repeated bacterial infections. To our knowledge, otologic features in patients with PCD according to age and type of defect have never been previously documented. This lack of knowledge about the natural history of otologic features in patients with PCD 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 to evaluate the frequency and severity of each symptom and disease.

All patients 5 years and younger had at least 1 episode of AOM or OME. In a context of suggested PCD in children, the absence of episodes of AOM or OME can, therefore, probably be considered a clinical argument against this diagnosis. Recurrent AOM was observed during early childhood but persisted after age 6 years and up to age 17 years, which is fairly unusual in non-PCD populations. Similarly, the frequency of persistent OME decreased only after age 18 years in patients with PCD, whereas it resolved by age 8 years in most children without PCD.

However, the few available large clinical series of adult and pediatric patients with PCD did not present detailed data on otitis media. A history of rAOM is reported in most patients, but the duration of these episodes has never been documented. A significant proportion of school-aged children and teenagers seemed to have AOM. Otitis media with effusion was also almost universal in the present study, as previously reported, but the supposed spontaneous improvement before adulthood was not observed because a significant proportion of patients still experienced OME in the oldest group. Persistent OME leads to conductive deafness, which was disabling until age 17 years in the present study. In a previous study, hearing thresholds were reported to return to normal by age 12 years in patients with PCD. However, patients with tympanic perforations or Armstrong grommets were excluded (8 ears of 71 patients), and the study design did not provide longitudinal follow-up.

Significant hearing loss associated with OME usually constitutes an indication for grommet placement, but this approach may not be recommended for PCD. Repeated grommet placements were performed in all the groups owing to the severity of OME. The presence of grommets may induce otorrhea, which is common in young children, but all the 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, but otorrhea seems to be even more frequent (88%) in patients with PCD, regardless of the duration of grommet placement.

Half of the patients with a history of grommet placement eventually developed tympanic perforation, which is much more frequent than in the general pediatric population (approximately 0.5%-10% of cases depending on the type of grommets and the duration) but could be explained by repeated placements of Per-Lee tympanotomy tubes in this cohort. Grommet placement in PCD has limited efficacy to improve hearing in these patients because otorrhea and obstruction by sticky fluid of the middle ear are almost systematic and persistent. Repeated insertions are associated with a high risk of per-
sistent tympanic perforation. Nevertheless, unlike in serous otitis media of the healthy population, the problem is not a consequence of poor ventilation of the middle ear, and that could explain the low rate of success of grommet placement in PCD. In patients with hearing loss of more than 25 dB, the treatment decision should weigh 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.

Many complications of COM would be expected in view of this high rate of persistent OME. However, the number of retraction pockets and cholesteatomas remained low (2 cases in this study, approximately 12% of patients with COM). Majithia et al. also reported no cases of cholesteatoma in a series of 91 patients. One could argue that tympanostomy tubes could prevent severe COM in children with PCD. Only 7 of the 17 patients with COM underwent surgery, and all other patients were closely monitored for recurrent otorrhea. Tympanoplasty in patients with PCD achieves a high perforation closure rate but is associated with a 66% OME recurrence rate. Although most patients in this series were treated by continuous alternating antibiotic administration, this treatment does not seem to prevent the persistence of OME or otologic complications, such as otorrhea or tympanic perforation.

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

The CC defect has already been demonstrated to be a marker of severity in PCD in relation to lower respiratory tract disease. The pathophysiologic basis of this progressive pattern is unknown, but this difference suggests that ciliary immobility universally observed in dynein arm defects is not the only mechanism involved in patients with PCD, as half of the present patients with CC had motile cilia. No difference was found throughout childhood between ODA (with or without 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 method may also have induced a bias. Each group had different numbers of patients, some were lost to follow-up (particularly at the young adult age), and some entered the cohort only by age 6 or 12 years. Moreover, we cannot exclude that patients who came to consultation for a longer period had a worse clinical presentation. The conclusions of this study should, therefore, ideally be confirmed by prospective data.

In conclusion, patients with PCD 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, because repeated grommet placement can predispose patients to chronic otitis and worsen the prognosis. Hearing aids should be considered as an alternative. Moreover, patients with CC defects must be carefully monitored owing to the risk of potentially more severe otologic complications.

Submitted for Publication: June 8, 2009; final revision received February 19, 2010; accepted March 30, 2010.

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Financial Disclosure: None reported.

Funding/Support: This work was supported by grants ANR-05-MRAR-022 from Agence Nationale de la Recherche et Association Française contre les Myopathies, PHRC AOM 06 053 from Assistance Publique–Hôpitaux de Paris, Legs Poix 2006.

Previous Presentation: This study was presented at the 21st Meeting of the American Society of Pediatric Otolaryngology; May 20, 2006; Chicago, Illinois.

REFERENCES


