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A longitudinal evaluation of hearing and ventilation tube insertion in patients with primary ciliary dyskinesia

Tobias Nicolai Andersen*, [1], Mikkel Christian Alanin [1], Christian von Buchwald, Lars Holme Nielsen

Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Copenhagen University Hospital, Rigshospitalet, Denmark

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ABSTRACT

Introduction: Primary ciliary dyskinesia (PCD) is an autosomal recessive genetic disease, which primarily manifests with oto-sino-pulmonary symptoms. Otitis media with effusion (OME) is common from early childhood. The existing literature on OME management in PCD is conflicting.
The goals of the present study were firstly to evaluate the long-term hearing in PCD patients and secondly to determine the influence of ventilation tube (VT) insertion on hearing and postoperative otorrhoea.
Methods: A longitudinal retrospective study extracting the hearing level (pure tone average (0.5, 1, 2, 4 kHz, PTA)) and tympanometry from the medical records. Furthermore, the patient files were reviewed for VT insertion and postoperative otorrhoea. Postoperative otorrhoea was defined prolonged when it lasted for four weeks or longer.
Results: Fifty-seven patients were identified in a 30-year period, age 2–72 years, and 278 audiometries were evaluated. The median number of audiometries per patient was 3 (range 1–29) and the median follow-up was 60 months (range 0–351 months). The mean PTA was 34 dB HL in patients below six years of age and improved significantly ($p < 0.0001$) with age. VT insertion improved hearing; however, 48% of patients with VT insertion experienced prolonged otorrhoea.
Conclusion: In this study of PCD patients the hearing improved as a function of age as well as following VT insertion. However, VT insertion was also associated with prolonged otorrhoea.

1. Introduction

Primary ciliary dyskinesia (PCD) is an autosomal recessive, heterogenous group of disorders of ciliary ultrastructure and function [1,2]. Most studies report a prevalence of 1:10,000 to 1:30,000 [3,4]; however, many mild PCD phenotypes may remain undiagnosed indicating a higher prevalence [5]. Approximately 50% of the patients has Kartagener's syndrome characterized by the triad: chronic rhinosinusitis, bronchiectasis and situs inversus [6].

PCD is mainly an oto-sino-pulmonary disease. Common manifestations include otitis media with effusion (OME), rhinitis, chronic rhinosinusitis [5,7] and recurrent or chronic lung infections [8] with declining lung function [9,10].

OME in PCD is believed predominantly to be caused by the dysfunctional cilia and decreased mucociliary clearance in the Eustachian tube and middle ear [11,12]. Previous studies of non-syndromic patients have suggested allergy [13], blockage of the Eustachian tube [14,15] and infections of both bacteria [16,17] and viruses [18,19] as causes for negative ear pressure ensuing effusion and these may also contribute to the pathogenesis of OME in PCD patients. OME is a global health problem and the most common cause of acquired hearing loss in children [20]. It affects 10–30% of 1–3 year olds and 1.5–3.1% of 5–7 year olds [21,22]. In chronic OME, fluid without signs of inflammation persists in the middle ear for at least 12 weeks. The middle ear fluid reduces the transmission of sound through the middle ear leading to conductive hearing loss. Evidence from other contexts suggests that bilateral chronic middle ear effusion can significantly impair hearing, speech development and quality of life [23–26].

A major concern in PCD is persistent hearing loss that is linked to OME, which may persist into adulthood. Previous studies have shown that 81–95% of PCD patients have recurrent otitis media

* Corresponding author. Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark.
E-mail address: tobiasnicolaiandersen@gmail.com (T.N. Andersen).
[1] Denotes equal contribution.

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[7,11] and more than 80% of PCD patients have OME, which may not resolve with age [27,28].

Timely treatment of OME medically, with hearing aids, otovent [29] or with ventilation tubes (VT) is important to improve hearing and to prevent delayed speech and language development; however, treatment of OME in PCD is controversial and existing studies are conflicting [30]. VT insertion can improve hearing [27,30,31] but also lead to post-operative prolonged otorrhoea in 33–100% of patients with PCD [28,30]. In comparison, the prevalence of chronic otorrhoea in the general population after VT insertion is reported to be approximately four percent [32]. Further, PCD patients hearing loss may resolve spontaneously [33] and normalize before 12 years of age [27,34] suggesting conservative treatment of OME in PCD.

However, some reports question this spontaneous normalization of the middle ear and hearing in PCD. Sommer et al. [7] concludes that hearing does not resolve with age and other studies [28,33,35] have found that OME persists into adulthood promoting VT insertion as a treatment option, since complications as otorrhoea can be relatively easy treated.

The existing literature concerning the natural history of OME and OME management in PCD is conflicting [7,28,30,36]. Conclusions are based on cross-sectional studies [7,27,31,33,34,36–38] and only one longitudinal retrospective study including relatively few audiometries [28]. The primary aim of the present study was to evaluate the hearing level longitudinally in PCD patients. A secondary aim was to determine the effect of VT insertion on hearing and the extent of the following otorrhoea.

2. Material and methods

2.1. Study design

We performed a longitudinal retrospective observational study, where we investigated the hearing level and middle ear function of all patients with definitive PCD diagnosis and at least one evaluable audiometry performed at the Department of Otorhinolaryngology, Head & Neck Surgery and Audiology, Copenhagen University Hospital, Rigshospitalet, Denmark during a 30-years period (1985–2015).

2.2. Patients

All Danish PCD patients are affiliated with the Danish PCD Centre at Rigshospitalet, Copenhagen. Annual clinical visits to the ear, nose and throat outpatient clinic including audiometry is common routine but not universal. Only patients with at least one evaluable audiometry were included in the study. Confirmed PCD diagnosis requires presentation of the characteristic clinical phenotype in combination with ciliary ultrastructural defects recognized on electron microscopy, abnormal ciliary movement verified by high-speed video recordings of ciliary movements or a genetic mutation recognized to cause PCD [5].

Patients were then divided into four age groups (<5 year, 6–11 years, 12–17 years and >17 years) and allowed to be included in one or more of these groups depending on follow-up period.

2.3. Hearing evaluation

The evaluation of hearing included pure tone thresholds for air conduction (AC) and bone conduction (BC), and tympanometry. Pure-tone audiometry at frequencies 0.25, 0.5, 1, 2, 4 and 8 kHz was carried out in accordance with ISO 8253-1 [39]. The modified Hughson-Westlake technique (−10/+5 dB) is employed using a Madsen Astera Audiometer with Sennheiser HDA 200 circumaural earphones. The equipment was calibrated in accordance with IEC 60319-2 [40], ISO 389-5 [41] and ISO 389-8 [42] using a Brüel and Kjær measuring amplifier with a 4144 microphone in a 4152 coupler. Immittance measurements, including middle ear air-pressure, were carried out using the Madsen Electronics Zodiac 901 middle-ear analyzer. To categorize the outcome of immittance measurements, the tympanogram types defined by Jerger [43] were used.

The pure tone average (PTA) was calculated for both AC (PTA_{AC}) and BC (PTA_{BC}) and included the average of pure tones at 0.5, 1, 2 and 4 kHz. Values reported are in decibel hearing level (dB HL). Since some of the measurements were missing, PTA was only calculated if at least 2 pure tone thresholds were available. PTA difference (PTA_{DIF}) was calculated by subtracting PTA_{BC} from PTA_{AC}. This is equivalent to the air-bone gap. This was only done for ears with PTA_{BC} measurements.

We defined normal hearing as PTA <25 dB HL. OME was defined as flat curves (B-curve) on tympanometry [43,44] in combination with a low middle ear volume (<0.9 mm^3 in children [45,46] and <1.6 mm^3 in adults). If a patient had multiple audiometries available in an age group, the mean PTA of audiometries in this agegroup was used in calculating the percentage of patients with normal hearing, while all audiometries were included in the mixed model for longitudinal evaluation of hearing. In addition, patients were reported as having OME if this was present in >50% of the tympanometries in one age group.

Perforation of the tympanic membrane was defined as B-curves in combination with a large volume [43]. Perforation was recategorized as VT if the treating physician had reported this in the patients' record.

For this study, hearing evaluation was done independently by two audiological technicians and conflicting values were corrected afterwards by one of the authors (TNA). The degree of otorrhoea after VT insertion was noted from the patients' medical records when possible. Patients were listed as having chronic otorrhoea if this diagnosis was given by an ENT doctor in the medical records. Prolonged otorrhoea was defined as patients having either chronic otorrhoea or episodes lasting more than four weeks [47].

2.4. Statistics

Data were analyzed using SAS (SAS Institute Inc., version 9.4, NC, USA). The longitudinal quantitative variable (PTA) was analyzed in a mixed model using the two qualitative variables (age group and VT/perforation) in repetitive measures ANOVA. Only one variable was used for VT and perforation status. A value of $p < 0.05$ was considered statistically significant. Model assumption was checked by plotting the residuals in a Q-Q plot.

2.5. Ethics

Data collection was approved by the Danish Data Protection Agency (2014-41-3499).

3. Results

3.1. Patients and follow-up

A total of 57 PCD patients were included in the study (30 males and 27 females, median age 13 years, range 2–72 years). A total of 300 audiometries on 600 ears were evaluated. Twenty-two audiometries were excluded because of missing VT/perforation status, resulting in 278 evaluable audiometries on 556 ears. The median number of audiometries per patient was 3 (range 1–29) and the median follow-up was 60 months (range 0–351 months).

The median number of audiometries per age group was 77 (range 23–102). Thirty-one patients were followed in only one age