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No evidence of cholesteatoma in untreated otitis media with effusion in children with primary ciliary dyskinesia

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ABSTRACT

Introduction: Primary Ciliary Dyskinesia (PCD) describes a group of inherited disorders that result in abnormal ciliary motion leading to mucous stasis. Clinical features include almost universally otitis media with effusion (OME), particularly in infants. PCD patients provide us with a cohort of patients with OME that is not treated with ventilatory tube (VT) insertion as these have been shown to result in frequent complications including chronic otorrhoea, early extrusion and persistent perforation without significant improvement to hearing in the long term. This cohort was used to investigate whether children with PCD and OME not treated with VT were predisposed to cholesteatoma formation in the setting of a paediatric quaternary referral centre.

Methods: A retrospective chart review was performed of all the children attending a multi-disciplinary PCD clinic at a national quaternary referral centre with a diagnosis of OME. We reviewed otoscopic findings, and audiometry and tympanometry results. We assessed the children in four groups: Watchful waiting, hearing aids, VT, and VT and hearing aids.

Results: One-hundred-and-one of 107 patients included in the study had a diagnosis of otitis media with effusion. No child with OME and PCD was diagnosed with a cholesteatoma during the follow up period. The only children who had insertion of a ventilatory tube were those who had the procedure prior to the formal diagnosis of PCD. We found a significant complication rate in the children with VT insertion. Hearing improved over time. The prevalence of retraction pockets in untreated OME was 1.72% (3 out of 174 ears).

Conclusions: In children with PCD, OME is an almost universal finding in younger children, but not in adolescents. The study supports the current preference to avoid VT insertion in children with PCD as it confers a significantly higher rate of complications. No cases of cholesteatoma were found in this cohort of PCD children with OME managed without VTs.

1. Introduction

Primary Ciliary Dyskinesia (PCD) describes a group of autosomal recessively inherited disorders that result in abnormal ciliary motion leading to mucous stasis. It affects 1 in 10,000 to 40,000 live births [1]. Ciliary structural defects include abnormalities of the outer or inner dynein arms, radial spokes or microtubule transposition into a dysfunctional location. Occasionally despite structural normality, there may be abnormalities in function, specifically reduced beat frequency, abnormal orientation or incoordination [2]. The diagnosis of PCD is based on a combination of clinical phenotype, nitrous oxide screening, light and electron microscopic inspection of mucosal cilia and genetic testing [3]. The atypical mucociliary function not only affects the lungs, causing recurrent chest infections, but also the middle ear, sinuses and nose making it an important condition for the otorhinolaryngologist. Otitis media with effusion (OME) is an almost universal finding in patients with PCD [4].

Theories of OME pathogenesis include eustachian tube (ET) dysfunction causing a negative middle ear pressure [5], chronic sterile middle ear inflammation e.g. secondary to chemical irritants, such as pepsin in gastric contents [6], or viral or bacterial infections leading to abnormal cilia function in the middle ear [7,8]. The prevalence of otitis media varies with age, season and geography. In Denmark, for example, Tos found peaks of prevalence at 18 months and 5 years of 19% and 18% respectively. After the age of 7 the prevalence rapidly declines [9]. Approximately 50% of cases of otitis media with effusion spontaneously resolve after 3 months [10]. Therefore in children without any other co-morbidity, if the OME and hearing loss persist after a 3-month period of conservative management, the first line management as recommended by the National Institute of Clinical Excellence (NICE) in the UK is the

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insertion of ventilatory tubes (VT) [11].

In children with PCD the ciliary function of the ET and the middle ear mucosa is impaired leading to mucous stasis and ET dysfunction. Despite this, the prevalence of deafness is much less common and hearing outcomes have been shown to improve with time (OME had resolved in most cases by the age of 12) [4,12]. Furthermore VT insertion in children with PCD has been shown to result in persistent or recurrent otorrhoea, multiple insertions, and permanent perforation [4,12,13]. This leads to a significant impact on quality of life without a long-term benefit to hearing. This is in comparison to a study of OME in patients with PCD in Saudi Arabia by El Sayed et al. [13] who found that out of 11 children treated with VTs, only 2 suffered from otorrhoea and so supported the use of VTs, although 6 required multiple insertions. Wolter et al. [14] in Canada also support the use of VTs and state that the otorrhoea in 8 out of 19 patients who had VT inserted was easily treated. They argued that the VT normalised hearing thresholds for the duration of their tenure, at an age when hearing is essential for speech development and that the risks were reasonable and recommended suitable counseling to parents regarding this. However the prevailing practice in the UK is to avoid VTs in these patients, as recommended by the European Respiratory Society Consensus Statement [15].

Studies in the literature suggest that chronically untreated OME is associated with significant retraction and perforation and a higher incidence of cholesteatoma [16,17]. It is unclear however whether the untreated OME results in the cholesteatoma or they are both a feature of the same underlying pathology. Interestingly, El Sayed et al. [13] found 1 patient at age 24 had bilateral cholesteatomas with PCD but there was no detail regarding whether they had previously been treated with VTs. Wolter et al. [14] found 3 patients with PCD had cholesteatomas. In 2 of these patients the cholesteatoma was found to be bilateral, despite having previously been treated with VTs. They suggest a possibility of PCD leading to an increased risk of cholesteatoma.

The current theories of pathogenesis of cholesteatoma are based on the outer squamous epithelium of the tympanic membrane entering and being entrapped in the middle ear. The most popular theory of cholesteatoma formation is invagination of the tympanic membrane due to a negative middle ear pressure, as found in OME. More recently mucosal coupling has been postulated, which refers to the TM mucosa adhering to the mucosa of the ossicles following TM retraction [26]. In all theories, chronic inflammation is thought to stimulate and propagate this process.

We used this cohort to investigate whether children with PCD and OME managed by avoidance of VT insertion were predisposed to cholesteatoma formation.

2. Method

A retrospective chart review was performed of children attending a multi-disciplinary PCD clinic at a national quaternary referral centre. All children were reviewed by the senior author of the paper (JH) or the audio-vestibular consultant attending the clinic. Our primary outcome was to identify whether avoiding VT insertion increases the risk of acquired cholesteatoma in OME.

The department's database of all children with PCD in January 2016 was searched. Only children with a confirmed diagnosis via electron microscopy or genetic analysis and a diagnosis of OME were included in our study. Our exclusion criteria were those who had an unconfirmed or presumed PCD diagnosis.

OME was diagnosed clinically via otoscopy by finding a dull TM and confirmed with tympanometry (type B curve). From our review of the medical records we were able to identify whether any children had ever been found to have a cholesteatoma. To statistically analyse the incidence of cholesteatoma between those who had a VT inserted and those who didn't, we performed a Chi squared test.

Otoscopic findings from the first and last appointment were recorded. They were reported as normal, dull, wax, otitis externa (OE), persistent perforation, chronic suppurative otitis media (CSOM), retraction or presence of cholesteatoma. If the perforation was wet and lasted over 2 weeks, we classified it as CSOM rather than a simple perforation. If no specific comment for otoscopy was made, the assumption was that it was normal. We categorised first four findings as being neutral, and the last three as a possible complication of the management option which we would then statistically analyse.

Secondary outcomes included persistence of OME, complications of VTs and hearing thresholds. Pure tone audiometry (PTA) was performed for air conduction and often bone conduction. We only recorded the air conduction hearing thresholds as OME results in a conductive hearing loss. This is represented as $PTA_{AC\ and}$ the average was calculated as the mean hearing level at 500, 1000, 2000 and 4000 Hz for each ear. Audiometric data at both initial and last appointment was also collected if available. Some children did not have a PTA at our institute.

Details of the management of these children was recorded. Children were categorised into four groups: those who were managed with 'watchful waiting' (group a), 'hearing aids' (group b), 'VT only' (group c) or 'VTs then subsequent hearing aids' (group d). In the department, a hearing aid was given to patients based on the NICE guidance for children with Down's Syndrome and Cleft Palate; both conditions which also result in persistent OME with complications after VT insertion [11]. Children with bilateral OME with a hearing level in the better ear of 25–30 dB or worse averaged over 0.5, 1, 2 and 4 kHz were offered a hearing aid. As per NICE guidance, hearing aids were also prescribed if there was a hearing level worse than 25–30 dB but where the impact of the hearing loss on a child's developmental, social or educational status was deemed to be significant. Children in the 'hearing aid' group included those that were offered hearing aids at any point during their follow up in the clinic. All the children were monitored for deterioration in their hearing in the 'watchful waiting' group. Children who had a VT inserted at any time were assigned to the 'VT only' group. Those who had a VT inserted at any time and subsequently required further intervention with a hearing aid, were categorised in the 'VT then subsequent hearing aid' group. We used a parametric paired *t*-test for statistical analysis.

For completion demographic data was also collected which included age and sex.

3. Results

One-hundred-and-twenty-seven out of the 144 children on the departmental PCD database had a confirmed diagnosis of PCD. Despite our best efforts, we were unable to find the charts of 20 patients. Of the 107 patients we reviewed, 101 (94%) were diagnosed with OME during follow up and included in the study. Fifty-one were females and 50 males, with a mean duration of follow up in clinic of 4 years and 10 months. The mean age of OME diagnosis was 5 years and 2 months for those in the 'watchful waiting' and the 'hearing aid' group. OME diagnosis predated the first PCD clinic in those who had had VTs inserted.

Fifty-three (52%) of children were managed by watchful waiting alone (group a), 34 (34%) were offered hearing aids at some point during their follow up (group b) and 14 (14%) had had VTs inserted, all of which were inserted prior to the diagnosis of PCD. Six (6%) of these children subsequently went on to be offered hearing aids (group d), leaving 8 (8%) in the 'VT only' group (group c).

With review of the medical notes we confirmed that none of the 101 children with OME had a cholesteatoma. This zero value meant it was not amenable to statistical analysis.

On reviewing the otoscopic findings, we found that of the 4 groups, the groups with children who had a VT inserted (groups c and d), had a significantly higher incidence of non-audiological ear problems compared to conservatively managed groups (groups a and b); 35.57% compared to 2.87% X^2 (1, N = 202) = 37.84, $p < .0001$ (Table 1).

From reviewing the medical notes, we were able to establish any