Cholesteatoma and family history: An international survey

Abstract

Objective

To explore the relative frequency of a family history of cholesteatoma in patients with known cholesteatoma, and whether bilateral disease or earlier diagnosis are more likely in those with a family history. Associations between cleft lip or palate and bilateral disease and age of diagnosis were also explored.

Design

An online survey of patients with diagnosed cholesteatoma was conducted between October 2017 and April 2019.

Participants

The sample consisted of patients recruited from two UK clinics and self-selected respondents recruited internationally via social media.

Main outcome measures

Side of cholesteatoma, whether respondents had any family history of cholesteatoma, age of diagnosis and personal or family history of cleft lip or palate were recorded.

Results

Of 857 respondents 89 (10.4%) reported a positive family history of cholesteatoma. Respondents with a family history of cholesteatoma were more likely to have bilateral cholesteatoma (p=0.001, odds ratio (OR) 2.15, 95% confidence interval (CI) 1.35 to 3.43), but there was no difference in the age of diagnosis (p=0.23). Those with a history of cleft lip or palate were not more likely to have bilateral disease (p=0.051, OR 2.71, CI 1.00 to 7.38), and there was no difference in age of diagnosis (p=0.11).

Conclusion

The relatively high proportion of respondents that reported a family history of cholesteatoma offers supporting evidence of heritability in cholesteatoma. The use of social media to recruit respondents to this survey means that the results cannot be generalised to other populations with cholesteatoma. Further population-based research is suggested to determine the heritability of cholesteatoma.

Key words; Cholesteatoma, genetic, family history, cleft lip, cleft palate, bilateral

Introduction

Background

Cholesteatoma is a well-defined erosive lesion of the middle ear, composed of keratinising squamous epithelium. It is a chronic condition affecting both children and adults with the only definitive treatment being microsurgery to clear it from the middle ear cleft.

Cholesteatoma occurs in approximately 9.2 in 100,000 people per year in Northern Europe [1] with a peak incidence in the age group 5-15 years [2]. Cholesteatoma incidence is higher in men compared to women [1, 3] and also reported to be higher in white than non-white populations [4]. While cholesteatoma can be described as a rare disorder it is an important cause of acquired deafness.

A systematic review of the genetics of cholesteatoma [5] was conducted and identified a range of studies reporting familial clustering. Whilst supportive of a genetic predisposition to cholesteatoma there was not enough evidence to describe cholesteatoma as a heritable trait. The review hypothesised that subtypes of cholesteatoma may exist with different aetiological pathways and suggested there may be rare genetic variants that underlie the disease in some families.

Subsequently, the Genetics of Cholesteatoma (GoC) project (https://www.uea.ac.uk/rhinology-group/research/active-projects) established a database and sample bank with the aim of identifying candidate genetic variants of interest that co-segregate with a cholesteatoma diagnosis in families with several affected individuals. Whole exome sequencing of DNA collected from participants in one family revealed variants of interest in two genes [6]. However, these are preliminary studies, and the variants are of unknown significance to the disease pathology. Any inherited risk for a complex trait like cholesteatoma is likely to be polygenic in origin; but a rare variant with a major functional effect may be a significant risk factor in some families.

There have been numerous reports of associations between cholesteatoma and congenital conditions, namely cleft palate disorders and Turner syndrome. A Danish study found a 20-fold increase in the risk of cholesteatoma for those with cleft palate [7] and a Canadian study reported an even higher 200-fold increase in the rate of acquired cholesteatoma when comparing children with cleft lip and palate to the baseline rate [8]. There have also been reports that individuals who have a sibling with palate problems are more likely to have cholesteatoma [7]. Similarly, strong associations between cholesteatoma and Turner syndrome have been reported [9, 10]. One study found that 7 out of 179 (3.9%) individuals with Turner syndrome had cholesteatoma [10] and another reported 26 out of 173 (15%) individuals with Turner syndrome had cholesteatoma [9].

Objectives

This study aims to explore the relative frequency of a family history of cholesteatoma in patients with established cholesteatoma, and whether bilateral disease or earlier diagnosis are more likely in those with a positive family history. Associations between cleft lip or palate and bilateral disease and age of diagnosis were also explored.

Other hypothesis-generating associations are described in supplementary tables, namely whether a history of grommet insertion or tonsillectomy is associated with a younger age of cholesteatoma diagnosis.

Materials and Methods

Ethical considerations

Ethical approval was granted by the Health Research Authority, East of England, Cambridge Central Research Ethics Committee (reference REC 16/EE/0131, IRAS ID 186786).

Study design

An online survey (http://smartsurvey.co.uk/s/cholesteatoma) was created to gather information from those who have been diagnosed with cholesteatoma and gathered retrospective data on demographics, genetic factors and condition specific factors.

Setting

Initially data collection focused on patients presenting in Norfolk to ENT clinics at two sites. Patients with a diagnosis of cholesteatoma were personally invited to complete the questionnaire. Subsequently the project was expanded globally, whereby anyone in the world could complete the survey if they had access to an online computer. The survey continues to collect responses from participants.

Participants

Participants were included if they had a diagnosis of cholesteatoma, had the capacity to consent to participation and were English speaking. There was no age restriction with some parents completing the survey on their child's behalf. Participants were excluded if they did not complete the majority of the questionnaire (at least 11 questions).

Variables

Demographic questions encompassed; age, sex, ethnic background, geographic distribution, occupation and level of qualification. Questions regarding the genetic nature of the condition focused on whether there was any family history of cholesteatoma, palate problems or inherited medical conditions. Condition specific questions were also included in the survey and explored side of disease, age of diagnosis, history of other ear, nose or sinus conditions (including grommet insertion and tonsillectomy/adenoidectomy) and handedness (supplementary tables 1 and 2). Survey questions are summarised in supplementary table 4.

Data sources

Data were collected via a web based questionnaire over a 19-month period between October 2017 and April 2019. The survey consisted of 24 closed questions each with a selection of available answers. Twelve questions provided open text boxes with the option to provide further details. Respondents could provide their postcode or country of origin in a free field text box. Participants were either invited following a hospital clinic visit or self-selected through invitations posted in patient support groups on social media. Social media groups were identified by searching social media sites for groups with the word 'cholesteatoma' in their title. These groups were then contacted and asked if they would share the invitation to participate, and the survey link, with their members.

Bias

To ensure respondents had a cholesteatoma diagnosis they were asked at the beginning of the questionnaire to confirm if they had been invited to participate following a clinic visit or that they had a diagnosis of cholesteatoma and came across the survey online.

Study Size

Data collection was based on an online survey and no pre-set target was set.

Quantitative variables

Most of the questionnaire consisted of questions with categorical answers. Quantitative variables collected included age at completion of survey and age at diagnosis of cholesteatoma.

Statistical methods

The software package SPSS was used to generate descriptive statistics and conduct t-tests, chi-squared tests and logistic regression. Independent samples t-test was used to compare the average age and Chi-squared tests were conducted for each demographic category to compare differences between participants recruited online and from clinic. Subsequent analysis was conducted on the sample as a whole – combining participants from clinic and online.

Logistic regression was performed to compare unilateral and bilateral disease to any family history of cholesteatoma, having a first degree relative with cholesteatoma and personal or family history of cleft lip/palate. T-tests were conducted to determine any difference in

mean age of diagnosis for those with a family history of cholesteatoma and other past medical history (supplementary table 3).

Results

Participants

A total of 859 participants completed the survey. Two respondents were excluded as they failed to complete the survey, answering at most 5 of 22 questions. The sample consisted of 857 participants, 581 (68%) of which were female. The majority, 796 (93%), were recruited online as opposed to clinic. The mean age of diagnosis was 24.6 years of age, with a range of 0 to 80 years (table 1). There was a peak in the age of diagnosis in childhood in the age range 3-10 years old.

Descriptive data

Participants recruited online had a different gender distribution compared to the clinic participants; with a higher proportion of females (69.2%) than males (30.7%) compared to the almost even distribution of the clinic sample (table 1; p=0.002). Clinic and online recruits had a similar age range, though the mean ages differed (table 1; 44.5 years and 33.1 years retrospectively, p<0.001). Both samples had the same mean age of diagnosis (table 1; 24.6 years, p=0.98).

A substantial proportion of participants stated they lived in the UK (552/857,64.4%). Over a quarter of participants (215/857, 25.1%) did not state where they originated from. There clinic recruits were all from the UK, whereas the online recruits consisted of both UK and international participants (table 1; p<0.001).

There was a range in the level of qualifications for the participants, with most having achieved GCSE or above. It must be noted that the sample included children, whom naturally will not have gained qualifications. The online recruits had on average higher levels of qualifications compared to the clinic recruits (table 1, p<0.001). There was an almost equal distribution in terms of right or left ear affected (40% and 37% retrospectively), 194/857 (23%) had both ears affected and there was no difference between online or clinic participants (Table 1; p=0.46).

Outcome data

When participants were asked whether they had a family member with cholesteatoma 89 of 857 (10.4%) answered 'yes', 47 (5.5%) of these stating it was a first degree relative. In terms of cleft palate or lip condition, 39 (4.6%) said they had a family history of cleft lip/palate and 16 (1.9%) stated they had this condition.

Main results

There was a positive association between participants reporting an affected family member (any relation) and bilateral cholesteatoma, those with an affected family member were more likely to have bilateral cholesteatoma than those with no such family history (table 2; OR 2.15, CI 1.35 to 3.43). Similarly, those with an affected first degree relative were more

likely to have bilateral disease compared to those without such history (table 2; OR 2.04, CI 1.10 to 3.80). Those with a personal history of cleft lip/palate were not more likely to have bilateral disease (table 2; p=0.051,OR 2.71, CI 1.00 to 7.38). There was no association between having a family history of cleft lip/palate and bilateral disease (table 2; OR 1.55, CI 0.77 to 3.13).

There was no difference in mean age of diagnosis between those with a family history (any relative and first degree relative) and those without such history (p=0.23 (CI -1.39 to 6.08) and p=0.52 (-6.62 to 3.36) retrospectively). Similarly, there was no difference in mean age of diagnosis for those with a cleft lip/palate or a family history of this condition (p=0.11 (CI -1.61 to 15.12) and p=0.78 (CI -4.68 to 6.23) retrospectively).

Discussion

Key results

Given that cholesteatoma is present in approximately 0.01% of the population it is interesting that 89 (10.4%) of 857 of respondents report an affected family member, 47 (5.5%) of whom are first degree relatives. The association between family history of cholesteatoma and bilateral disease is a novel finding of this study.

There was no evidence in the sample of a positive association between a personal history of cleft lip/palate and bilateral ear disease, though the small number of participants with such history suggests these results should be considered with caution. There was also no

evidence in the sample that a family history of cholesteatoma or a history of cleft lip/palate resulted in a younger mean age of cholesteatoma diagnosis.

Interpretation

The number of respondents whom reported a family history of cholesteatoma is consistent with studies that report familial clustering and the suspicion of cholesteatoma as a heritable trait [5]. The association between family history of cholesteatoma and bilateral disease may represent a genetic liability, whereby those with a genetic predisposition are more likely to have more severe disease. It might be expected that those with a genetic predisposition for cholesteatoma would have a younger mean age of diagnosis, though this data does not support this hypothesis.

Various studies have reported an association between cleft lip/palate and cholesteatoma [7, 8]. The sample of this study is consistent with this; with 16/857 (1.9%) reporting to have had a cleft lip/palate problem themselves. Given that the incidence of cleft lip/palate in newborn babies in the UK is 1.7 per 1000 [12], or 0.17%, the proportion of people in the sample who report to have cleft lip/palate is higher than would be expected

This sample includes a large number of participants with a wide age range of 1-80 years. The 2.1 to 1 female to male ratio differs from the widely reported higher incidence in men [1, 3, 11]. The gender ratio may represent a bias in the sampling technique whereby there is likely to be gender differences in health seeking behaviour and social media engagement. The distribution of the age of diagnosis is consistent with other studies, with a peak in childhood [2, 3].

Limitations

The opportunistic sampling method presents challenges in how widely the results can be generalised. Participants were self-selected and, for the majority, their diagnosis of cholesteatoma was self-reported. However, it can be argued that, given the rare nature of cholesteatoma, participants are unlikely to have self-diagnosed or have come across the survey by chance. Nevertheless, the survey relied on participants recalling details of their own diagnosis and past medical history.

In addition, there were limitations in the survey design including that questions regarding qualifications were originally formatted for UK respondents, subsequent international distribution of the survey resulted in respondents having to convert their education level into UK answers. Ethnicity data had to be excluded due to ambiguity in the available categorical answers.

Despite the limitations this study is a relatively large survey of people with cholesteatoma. The sample captured people throughout the world affected by the condition from the very young to older generation and included a wide range of data on demographic, genetic and condition specific factors.

Generalisability

The approach of gathering participants through social media may result in capturing a particular social demographic, as evidenced by the higher proportion of females that completed the survey. It is also possible that such an approach recruited individuals who are

more affected by their condition, with more severe symptoms or who have more affected friends and family since those with cholesteatoma who have affected family members may be more likely to complete and share the survey. Nevertheless, the percentage that report an affected family member is much greater than what would be expected by chance.

Conclusion

This study aimed to explore genetic factors in cholesteatoma. A larger number than would be expected reported a positive family history of cholesteatoma and a personal or family history of cleft lip or palate. There was a positive association between having a family history of cholesteatoma and bilateral cholesteatoma.

Implications of research

This study offers further support for a genetic component to cholesteatoma and possible association with more severe disease. Preliminary findings of genetic based research have identified two gene variants of interest in cholesteatoma [6]. Further population based research is suggested to determine the heritability of cholesteatoma.

Conflicts of Interest

No conflicts of interest to declare

Key points

- 89 of 857 (10.4%) of respondents with cholesteatoma reported an affected family member.

- This study found a positive association between family history of cholesteatoma and bilateral cholesteatoma.
- Further population based research is suggested to determine the heritability of cholesteatoma.

References

1. Heikki O. Kemppainen, H.J.P.P.J.L.M.M.S.M.P.M.P.H.K., *Epidemiology and Aetiology of Middle Ear Cholesteatoma.* Acta Oto-Laryngologica, 1999. **119**(5): p. 568-572.
2. Rosenfeld, R.M., R.L. Moura, and C.D. Bluestone, *Predictors of Residual-Recurrent Cholesteatoma in Children.* JAMA Otolaryngology–Head & Neck Surgery, 1992. **118**(4): p. 384-391.
3. Djurhuus, B.D., C.E. Faber, and A. Skytthe, *Decreasing incidence rate for surgically treated middle ear cholesteatoma in Denmark 1977-2007.* Dan Med Bull, 2010. **57**(10): p. A4186.
4. Bhutta, M.F., I.G. Williamson, and H.H. Sudhoff, *Cholesteatoma.* BMJ, 2011. **342**: p. d1088.
5. Jennings, B.A., et al., *The genetics of cholesteatoma. A systematic review using narrative synthesis.* Clinical Otolaryngology, 2018. **43**(1): p. 55-67.
6. Prinsley, P., et al., *The Genetics of Cholesteatoma Study. Loss-of-function variants in an affected family.* Clinical Otolaryngology, 2019. **0**(ja).
7. Djurhuus, B.D., et al., *Cholesteatoma risk in 8,593 orofacial cleft cases and 6,989 siblings: A nationwide study.* Laryngoscope, 2015. **125**(5): p. 1225-9.

8. Harris, L., et al., *Impact of cleft palate type on the incidence of acquired cholesteatoma.* International Journal of Pediatric Otorhinolaryngology, 2013. **77**(5): p. 695-698.
9. Bergamaschi, R., et al., *Hearing loss in Turner syndrome: Results of a multicentric study.* Journal of Endocrinological Investigation, 2008. **31**(9): p. 779-783.
10. Lim, D.B., et al., *Cholesteatoma has a high prevalence in Turner syndrome, highlighting the need for earlier diagnosis and the potential benefits of otoscopy training for paediatricians.* Acta Paediatr, 2014. **103**(7): p. e282-7.
11. Olszewska, E., et al., *Etiopathogenesis of cholesteatoma*. Vol. 261. 2004. 6-24.
12. Mossey, P.A., et al., *Cleft lip and palate.* Lancet, 2009. **374**(9703): p. 1773-85.