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Clinical Record

Family cluster of cholesteatoma

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Abstract

Objective: We report an extremely rare case of family clustering of cholesteatoma.

Method: Case reports and a review of the world literature concerning cholesteatoma and heredity are presented.

Results: The family consists of parents and seven siblings of whom the mother and three sons have been surgically treated for cholesteatoma. All cholesteatomas in the family are acquired and all have a history of otitis media. Cholesteatomas occur with an incidence of 5/100 000 in Greenland, corresponding to two to three new cholesteatoma patients per year among the 57 000 inhabitants of Greenland. The family is very exceptional and interesting for further research concerning heredity in the pathogenesis of acquired cholesteatoma.

Conclusion: To our knowledge this is the first report in the world literature of family clustering of acquired cholesteatoma. This case indicates that hereditary factors interplay with other factors in the pathogenesis of cholesteatoma.

Key words: Cholesteatoma; Hereditary Disease; Otitis Media; Greenland

Introduction

Cholesteatoma is a rare disease and has been reported with incidence rates of 5–10/100 000 in various countries and populations.[1–3] The aetiopathogenesis of acquired cholesteatoma is still debated and much research is undertaken concerning this disease.[4] The disease is bilateral in approximately 10–15 per cent of cases in Caucasians which suggests inborn anatomical, cellular or immunological mechanisms are involved in the development of cholesteatoma.[3] So far, heredity has not been thought to be involved in the pathogenesis of cholesteatoma even though genetic and intrinsic molecular factors are involved in the immunoreactivity and inflammatory process, osteoclast activity and fibroblast and keratinocyte behaviour in patients with cholesteatomas are believed to play an important pathogenetic role.[4–6] Also, studies have indicated that chromosome alterations such as trisomy 7 and aneuploidy of chromosome 8 may play an important role in the prognosis of cholesteatoma.[7,8] Cholesteatoma has been reported in patients with branchio-oto-renal syndrome, which again suggests inborn mechanisms to be important.[9]

By searching the databases Medline and Embase with the MeSH words: cholesteatoma and heredity, family cluster, cluster or genetics we only found two reports of family clustering of cholesteatoma in the world literature. Only one of these reports could be found. Ray in 1973 described two brothers aged three and a half years and eight and a half months old with intramastoid congenital cholesteatomas.[10] The brothers were diagnosed within a three-month period and presented with the same symptoms of mastoiditis without a prior history of otitis media. Surgery revealed in both cases cholesteatoma. The other report is from Japan and is entitled 'Cholesteatomas in dizygotic twins' by Naito *et al*. 1986, but this paper could not be traced. Thus, to the best of our knowledge there are no reports of family clustering of acquired cholesteatoma.

Case reports

In 2004 during an ENT visit to Greenland a family consisting of nine persons in one of the 16 health districts (for ethical reasons the exact place cannot be published) was found to have a clustering of cholesteatoma. A boy, 14 years old, was otomicroscopically diagnosed with cholesteatoma in his left ear. Anamnestic evaluation revealed that one older brother and their mother had had surgery for the same disease and examining the medical records, which were available for all family members, an additional brother in the family was found to have undergone surgery for cholesteatoma. Thus, four of nine family members have been surgically treated for acquired middle-ear cholesteatoma between 2002 and 2005. Of those without cholesteatoma, the father and one sister were without history of otitis media, the latter had a normal otomicroscopy, while two sisters had a medical history of otitis media but without any signs of cholesteatoma. One female child died in early infancy. We have personally seen five of the nine family members and all five have a phenotypically obvious dolichocephal appearance including the sister without cholesteatoma. Due to ethical reasons we have not personally seen the remaining three living family members. However, one sister was seen by a local physician and another sister was seen by a third ENT specialist but their phenotypical appearances were not described.

The medical histories of the four family members with cholesteatomas are as described.

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Mother: Age 44 at diagnosis and operation. Right side flaccida/sinus/antrum cholesteatoma. There was a facial nerve dehiscence and a spontaneous atticostomy. Pneumatisation was present in the temporal bone and the incus was eroded. A combined approach tympanomastoidectomy with interposition of the incus between the malleus and the intact stapes was performed. The flaccida region was reinforced with bone. Pre-operative/post-operative hearing pure tone average (average of 500, 1000, and 2000 Hz): 25/25 dB. Any history of otitis media in early childhood was unknown. Ear discharge and hearing loss were the symptoms leading to the diagnosis of cholesteatoma.

Brother one: He was age 22 at diagnosis and 23 at operation. He had a right side flaccida cholesteatoma with deep retraction pocket into the atticus and antrum. Pneumatisation was reduced and the head of the malleus and part of the incus were resorbed. A combined approach tympanomastoidectomy with interposition of the incus between the handle of the malleus and the intact stapes was performed. The flaccida region was reinforced with tragus perichondrium. Pre-operative/post-operative hearing pure tone average: 40/30 dB. A history of otitis media since early childhood was reported and at age 14 secretory otitis media was present. Ear discharge was the symptom leading to the diagnosis of cholesteatoma.

Brother two: Age 13 at diagnosis and 15 at operation. He had right side flaccida cholesteatoma with deep retraction and destruction of the roof of the external ear canal. At diagnosis in Greenland the retraction pocket was cleaned of cholesteatomatous material but at operation no cholesteatoma was found except for the deep epithelial retraction pocket. The head of the malleus and part of the incus were resorbed. Via a Herrmann incision a tympanoplasty with interposition of the incus between the handle of the malleus and the intact stapes was performed. The flaccida region was reinforced with tragus perichondrium. Mastoidectomy was not performed. Pre-operative/post-operative hearing pure tone average: 40/35 dB. No history of otitis media was reported before age 10. Ear discharge was the symptom leading to the diagnosis of cholesteatoma.

Brother three: He was age 14 at diagnosis and operation. He had on the left side a very large flaccida cholesteatoma, with deep retraction pocket into the atticus and antrum and anterior extension into the eustachian tube. There was extensive destruction of the roof of the external ear canal. Mucous and fibrous membranes were found in the anterior attic and removed. The pneumatisation of the mastoid was of mean size and part of the incus was eroded. A computed tomography (CT) scan prior to operation was performed (see Figure 1). A combined approach attico-antromastoidectomy with interposition of the incus between the malleus and the intact stapes was performed and a piece of autograft mastoid bone was used to reconstruct the external ear canal. Pre-operative/post-operative hearing pure tone average: 22/22 dB. No history of otitis media was reported but hearing problems were apparent from age 12. Two years prior to the diagnosis of cholesteatoma the patient was found to be at risk of developing a cholesteatoma as an almost clean retraction pocket was observed at otomicroscopy. Hearing problems and later ear discharge were the symptoms leading to the diagnosis of cholesteatoma. A slight flaccida retraction was found in the opposite ear.

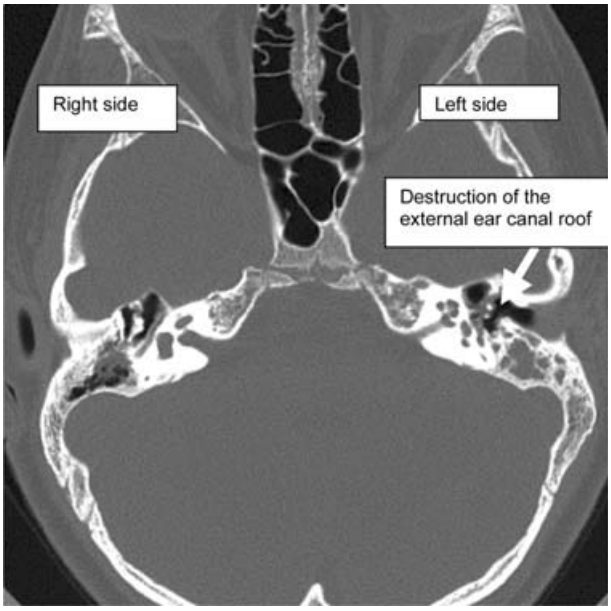

FIG. 1

Left side cholesteatoma with destruction of the roof of the external ear canal (arrow) and cholesteatomatous masses in the middle ear and mastoid. Pneumatisation is rather poor and similar to the right ear.

Discussion

Cholesteatomas occur in a more or less random fashion in humans. This is true whether the mechanism is migration, retraction, proliferation or congenital and it is not possible to predict whether a retraction pocket will develop into a cholesteatoma or not. Although closely associated with secretory otitis media it is still an enigma why some patients develop a cholesteatoma while the vast majority do not. Anatomic factors related to cranial angles, rhinopharyngeal dimensions, eustachian tube morphology, temporal bone pneumatisation and middle-ear morphology have been associated with the development of cholesteatomas.[11] Recent studies have focused on immunological and inflammatory processes including genetic studies of chromosomes in the cholesteatomas, growth factors and proliferation markers such as various overexpressed proteins; for example Ki-67, p53, p21 and ErbB-2 and lately proteomic analysis of cholesteatomas.[4–8,12,13] The cells involved are fibroblasts, keratinocytes and osteoclasts in addition to inflammatory cells. Animal models contribute the most experimental information whereas experimental studies in humans are limited to immunohistological and molecular biological laboratory examinations of samples, epidemiological studies, and anatomical studies mainly using CT scans. Therefore it is still important to report human cases which may be of special interest.

- **This paper describes an extremely rare case of family clustering of cholesteatoma**
- **The family consists of parents and seven siblings of whom the mother and three sons have been surgically treated for cholesteatoma**
- **This case indicates that hereditary factors in interplay with other factors may play a role in the pathogenesis of cholesteatoma**

Family clustering of acquired cholesteatoma has not been reported before and we found only one report of family clustering of congenital cholesteatoma (two brothers).[10] We cannot claim a genetic disposition to cholesteatoma in our Greenlandic family as the only factor. Several independent factors in the family and the

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surrounding environment may all predispose to the development of cholesteatoma. The most important of these environmental factors is the very frequent and early episodes of upper respiratory tract infections among Greenlandic children often resulting in secretory otitis media and later retraction pockets and chronic otitis media.[14,15] Thus, Greenlandic children less than two years old have on average been found to spend more than 40 per cent of their lifetime having upper respiratory tract infections which is associated with crowding and use of daycare.[14,15] However, cholesteatomas do not occur with higher incidence among the Inuit population in Greenland than in, for example, the populations in Denmark and Finland.[1–3] A recent study concerning cholesteatoma incidence in Greenland during a 16-year period revealed incidence rates of 6.6 cases per 100 000 children between 0 and 14 years old and 4.4 cases of 100 000 adults, corresponding to two or three new cholesteatoma cases every year.[1] The family from Greenland may contribute with more important information if anatomical, genetic and molecular biological examinations can be carried out in addition to further exploration into the ancestral disease history of the proband. We hope to be able to do this in the future.

Conclusion

This rare case of family clustering of cholesteatomas in an Inuit family leaves many unsolved questions concerning anatomy and genetics. However, as four of nine family members have been treated for the same very rare disease it is unlikely that this phenomenon is just a coincidence. Our finding strongly indicates that hereditary factors play an important role in the pathogenesis of cholesteatoma and that coexistence of phenotypical anatomical features, infection and inborn genetic molecular factors may be necessary for the development of cholesteatomas in humans. Further anatomical, genetic and molecular studies in this family might reveal new knowledge about the aetiopathogenesis of middle-ear cholesteatoma.

Summary

We present a very rare case of family clustering of acquired middle-ear cholesteatoma. This case story adds to the aetiopathogenesis of cholesteatoma as a disease triggered by a combination of inborn factors and environmental circumstances.

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