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Main Article

Familial cholesteatoma in East Anglia, UK

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Abstract

Objective: To report a cluster of families affected by cholesteatoma in the East Anglia region of the UK.

Setting: Otology service for the population of Norfolk and North Suffolk, East Anglia, UK.

Method: Prospective and systematic collection of family history data for patients presenting with cholesteatoma over 10 years.

Result: Several families were identified with affected individuals over several generations.

Conclusion: There is likely to be a genetic propensity for cholesteatoma in some individuals.

Key words: Cholesteatoma; Genetic Diseases; Aetiology

Introduction

Since 1996, the author has worked as a consultant otolaryngologist, appointed with a 'specific role to assist in the provision of a specialist otology service to a population of 750 000 people in parts of Norfolk and Suffolk'.

Surgical otology has formed a major part of this work, with many cases being surgically treated for chronic otitis media and cholesteatoma. This paper presents the observation that a number of the patients diagnosed with and/or undergoing surgery for cholesteatoma, over a 10-year period, were either related to each other or related to other, previously operated upon patients.

The population of East Anglia, a region of east England, is mainly rural, with small towns and cities. It is a more settled and stable population than those of the more urbanised and metropolitan areas of the country. It is not unusual to encounter extended families living fairly close together, with medical records at the same hospital stretching back several generations. This fact facilitated access to old records of previously operated upon patients.

Methods and results

The first family (family Ha; Figure 1) was detected following presentation of a set of non-identical twins, Ga and C, aged five years, who both presented with cholesteatoma, one bilaterally and one unilaterally. The mother volunteered the fact that the twins' elder brother and a cousin had undergone surgery for the condition. The brother happened to be present at the consultation, and on examination had a dry and healthy ear cavity (having undergone surgery in the same hospital some years previously). The mother also reported that a brother of her father had died in childhood in the 1920s as a result of an 'ear infection'.

This family history prompted the author to begin to ask specifically about family history of cholesteatoma or surgery for ear problems, whenever a new patient with cholesteatoma was encountered.

Soon afterwards, two other affected families were discovered (families Sm and Ri), containing many affected individuals.

Family Sm came to light as a result of a local clinic nurse (K) requesting an ear examination, as she was having difficulties using her stethoscope. The nurse had undergone surgery some years previously for perforation of the ear drum. Endoscopic examination of the nurse's ear showed intratympanic cholesteatoma (Figure 2).

Nurse K was the sister of another patient with cholesteatoma, and the daughter of another. She said that cholesteatoma 'ran in the family'. Her son and two of her nieces had been diagnosed and operated upon for cholesteatoma.

Both K and her sister C had bilateral disease, as shown in Figure 3.

The strongest family pedigree was found in family Ri (Figure 4).

Patient D had been operated upon by the author for left-sided cholesteatoma in 1997, and then again in 1998 for right-sided disease. He reported that his elder brother T had been operated upon for right-side cholesteatoma in 1974 and for left-sided cholesteatoma in 1981. This was readily confirmed by inspecting the hospital record. Patient D's younger brother Ji had also been operated upon for

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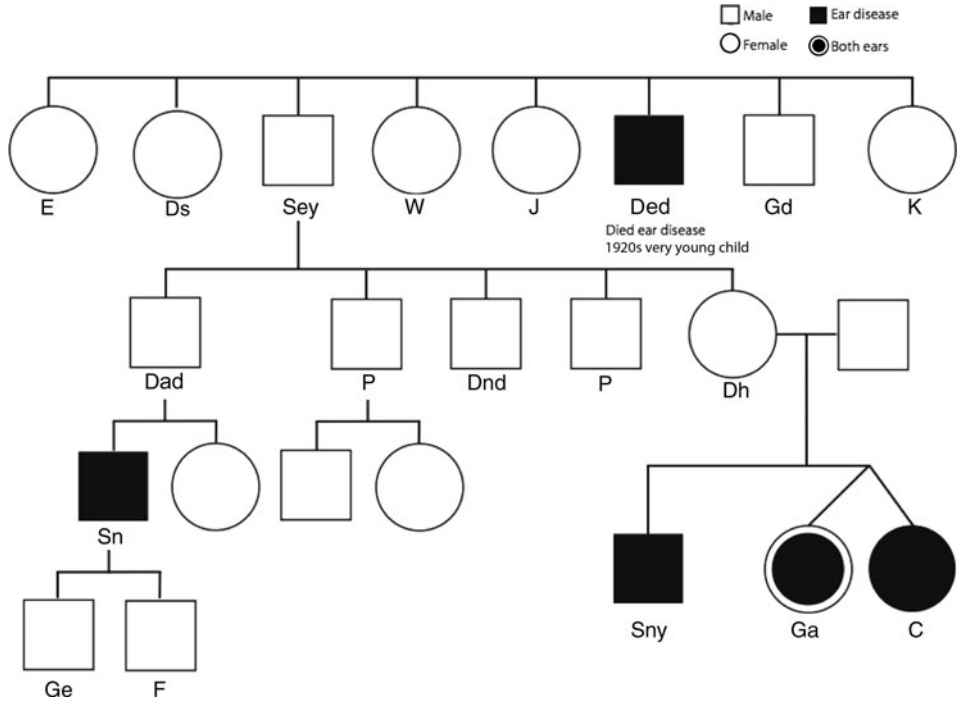

FIG. 1
Pedigree for family Ha.

cholesteatoma, as had both of D's parents, A (in both ears) and G (in one ear). Born in 1913, A had last been seen at the ear clinic in 1996 with bilateral, trouble-free ear cavities. The hospital records showed that she had been seen regularly at the Norfolk and Norwich Hospital ENT department for 60 years. In addition, D later reported that his son DJ was affected by cholesteatoma, and also his granddaughter (DJ's daughter) Ja. Although neither of these latter patients has been examined by the author, if they were indeed affected by cholesteatoma then family Ri would contain four affected generations.

Simple enquiry about any family history of ear problems in all patients seen with cholesteatoma revealed four other individual families with three affected members and eight other individual families with two affected individuals, as shown in Table I.

Discussion

The aetiology of cholesteatoma is unknown, but genetic causes are not usually emphasised.

Conventionally, so-called congenital cholesteatoma arising behind an intact drum is considered distinct from acquired cholesteatoma associated with drum abnormalities. In this article, no formal

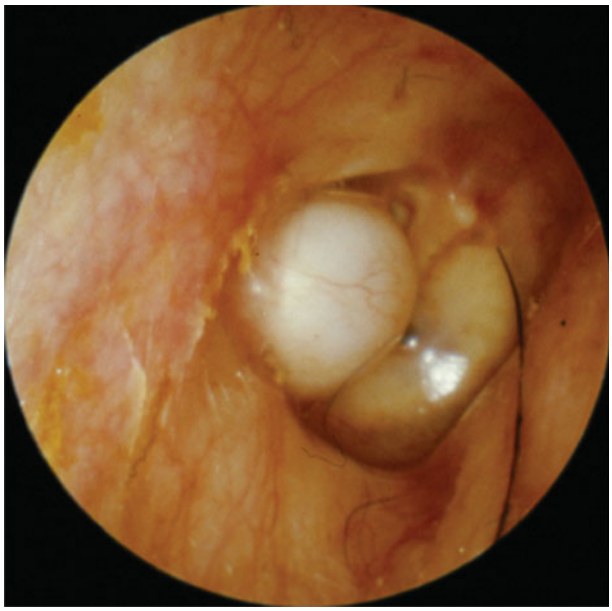

FIG. 2
Endoscopic view of K's ear (family Sm).

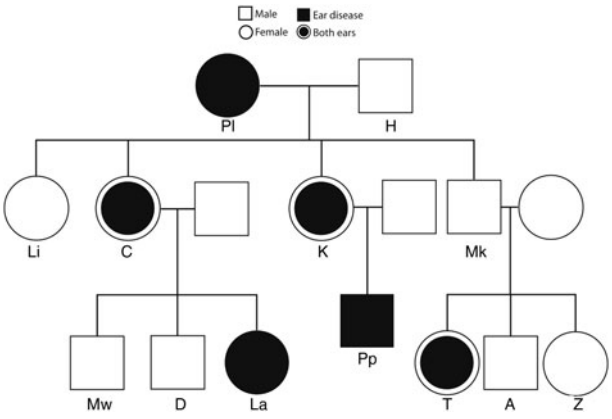

FIG. 3
Pedigree for family Sm.

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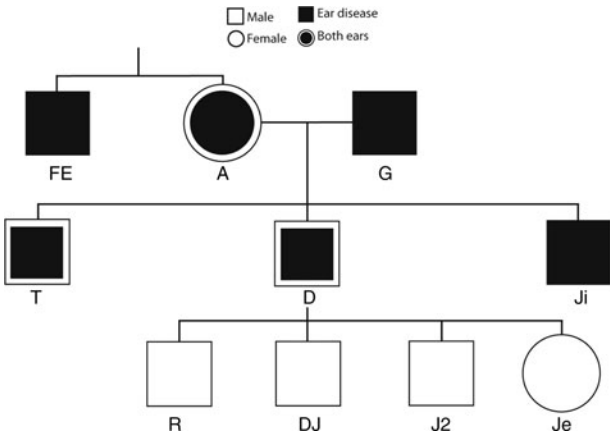

FIG. 4
Pedigree for family Ri. (Missing from the chart is DJ's cholesteatoma-affected daughter Ja.)

distinction is made between the two conditions, although the great majority of cases were associated with drum abnormalities and would not therefore normally be considered 'congenital'. Interestingly,

TABLE I
FAMILIES WITH CHOLESTEATOMA

Family	Affected individuals
Fx	CF, female, 8 y, cholesteatoma*
	LF, female, 8 y, identical twin of CF, CAT Holland*
	KF, mother of twins, mastoidectomy 1991 Sunderland
Al	MA, male, revision typmanoplasty 2000, 2nd revision 2005*
	AA, brother of MA, atticotomy 1994, revised 2003*
	MA, grandmother of brothers, mastoidectomy
Gl	VG, female, age ?, attic retraction*
	EL, brother of VG, mastoidectomy 1975
	GY, maternal grandfather, died of ear abscess 1951 Great Yarmouth
Go	JG, female, 10 y, mastoidectomy 2003*
	MC, father of JG, cholesteatoma*
	JC, grandfather of JG, mastoidectomy
Ca	BC, mastoid obliteration 1998*
	PB, cousin of BC, mastoidectomy 1971, 1999*
Fa	DF, cholesteatoma 2006*
	PF, mother of DF, mastoidectomy 1954
Ni	GN, female, 8 y, tympanoplasty for cholesteatoma 2003*
	Grandmother had mastoidectomy 1950s Blackburn
Bu	MB, male, 30 y, mastoidectomy 2005*
	Father of MB had mastoidectomy Germany
We	TW, female, mastoidectomy 2005*
	MH, father of TW, mastoidectomy Northern England
Ph	SP, female, 62 y, mastoidectomy 2004*
	DS, brother of SP, mastoidectomy 1987
Do	DD, mastoidectomy 1978
	DR, brother of DD, mastoidectomy 1994
Ba	JB, female, cholesteatoma 2006*
	LB, mother of JB, mastoidectomy 1984 Southend

*Treated by the author. Y = years; CAT = combined approach tympanoplasty

the endoscopic appearance of K's ear (Figure 2) might suggest a congenital cholesteatoma in the presence of an intact drum, but the history of previous surgery implies a possible secondary acquired mechanism. Lesinkas *et al.*,[1] writing in Lithuania in 2002, reviewed the theories of congenital cholesteatoma development, which include ectopic cell rests, ingrowth of meatal epidermis and metaplasia of refluxed amniotic cells. Theories of acquired cholesteatoma development include retraction pocket disease, basal cell proliferation, immigration of epithelium through a perforation, and squamous metaplasia of the middle-ear epithelium. A 2000 literature review by Tos[2] also suggested a variety of ways in which epithelial cell inclusions within the mesotympanum may develop in acquired cholesteatoma in children. These relate to an increase in the dynamics of the tympanic membrane, eustachian tube problems, otitis media and retractions, rather than congenital inclusions. A family history of the condition, however, is not usually considered to be of importance. However, an epidemiological study of kibbutz dwellers in Northern Israel in 1986 did identify a family history in 64 per cent of cholesteatoma patients.[3] In 2006, Homoe and Rosborg[4] claimed to publish the first report of an affected family, with a mother and three of seven children having cholesteatoma, in Greenland.

The three East Anglian families described in the present study also support the theory of a genetic cause in some cases of cholesteatoma.

Bilateral cholesteatoma may be partly explained by genetic factors. Family Ri included a mother with bilateral disease and a father with unilateral disease who produced three children, all with cholesteatoma (two of whom had bilateral disease). If there is a strong genetic propensity, as there seems to be in this family, then it might be reasonable to suppose that the chance of bilateral disease would be greater.

- **The aetiology of cholesteatoma is unknown, but genetic causes are not usually emphasised**
- **This observation of familial clustering of cholesteatoma patients in East Anglia is remarkable**
- **It supports the suggestion that a genetic predisposition exists for cholesteatoma**

The mechanism of genetic influence, if one exists, is unknown. One proposal is that cholesteatoma may be due to altered genetic control of cellular proliferation. Recent molecular biology research suggests mechanisms by which genes might influence the behaviour of epithelial cells within the middle ear. Ectodermal remnants or cellular ingrowths are normally eliminated in mesenchymal tissue by apoptosis. This process may fail in cholesteatoma. Genes which control epithelial cell proliferation and differentiation have been studied. Albino *et al.*[5] found increased expression of the nuclear phosphoprotein

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p53 tumour suppressor gene in cholesteatoma, compared with postauricular skin. This gene is involved in the regulation of the cell cycle and apoptosis. Tokurika *et al.*[6] used complementary deoxyribonucleic acid arrays to compare the cell biology of cholesteatoma tissue with that of skin taken from the retroauricular sulcus during surgery on the same patients. They described up-regulation of proliferation and differentiation genes in the cholesteatoma cells. A similar comparative study of cholesteatoma and retroauricular skin, by Kwon *et al.*,[7] used microarrays and also identified a large number of up-regulated genes in the cholesteatoma tissue.

Conclusion

This observation of familial clustering of cholesteatoma patients in East Anglia is remarkable. It supports the suggestion that a genetic predisposition exists for this condition.

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Mr P Prinsley takes responsibility for the integrity of the content of the paper.
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