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Genetics of otosclerosis

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Abstract
Otosclerosis is an early-middle adult life genetic disease affecting bone remodelling in the ear. Current knowledge of otosclerosis as an inherited disease dates to the mid-19th century, and we report here an attempt to understand the genetics of otosclerosis and detect its heterogeneity. The analysis was conducted on 151 otosclerotic families. The results of our study indicate that while heredity plays an important role in the manifestation of the disease a substantial portion of otosclerotic cases could arise due to non-genetic causes.

Key words: Otosclerosis, genetics

Introduction

Otosclerosis causes progressive hearing impairment in early and middle adult life (McPhee *et al.*, 1993). The ICMR study conducted in 1983 showed that 10 per cent of people in India suffer hearing impairment i.e. about 90 million. In India, otosclerosis is more common in the south than it is in the north where its prevalence varies from one to three per cent (Kapur and Patt, 1967; Rajendra Kumar, 1975). It is more commonly observed in Caucasians than in Mongoloids and Negroids (Morrison, 1967; Hall, 1974; Brobby, 1986).

The role of heredity in otosclerosis is well established. The prevalence of this disorder among relatives of otosclerotic patients was much greater than that observed in the general population (McKay, 1986). It is generally believed that otosclerosis is dominantly inherited with variable penetrance (Larsson, 1962; Morrison, 1967). It is also well established that clinical symptoms of the disorder set predominantly, between 15 to 40 years of age, with higher prevalence in women than men (James, 1989, 1991; McPhee *et al.*, 1993). Although this is the general outcome of most studies, heterogeneity with respect to mode of inheritance, degree of penetrance and age at onset is also reported in the literature. Studies on the genetics of otosclerosis from India are few (Kapur and Patt, 1967; Rajender Kumar, 1975; Raman *et al.*, 1991).

The present study has been conducted with the objective of understanding the genetics of otosclerosis and to detect heterogeneity if any, with particular reference to the populations of India.

Materials and methods

The present investigation is based on a sample of 151 otosclerotic families (153 probands) taken from various hospitals in Madras city during the period between September 1992 and May 1993.

Names and telephone numbers of 99 ENT surgeons listed in the yellow pages of the Madras city telephone directory were obtained. Information with respect to the place of work and willingness to co-operate in the study was sought either by personal visits or telephone conversation. Most of the surgeons had affiliation with seven leading hospitals belonging to either private, corporate or Government Institutions. Additionally a direct appeal to otosclerotic patients was also made in a local English newspaper and vernacular magazine. Addresses of otosclerotic patients who underwent stapedectomy were obtained by regular visits to hospitals. Initially a total of 618 addresses from all the above sources were collected. Clinical information and addresses of patients were recorded on a basic questionnaire. Family information was obtained either by mailing a detailed questionnaire to those patients who consented to participate in the study or by visiting houses located within the city. The questionnaire covered all clinical details and the family tree for at least three to four generations. Out of the total 618 patients contacted only 178 responded. Of these, only 153 provided satisfactory information suitable

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for inclusion in the study. Thus about 25 per cent of the patients whose addressess were ascertained were able to provide satisfactory information.

Of the 522 letters mailed nearly 79 per cent were returned as address untraceable. Response was good when patients and the family members were contacted in person. Compared to 21.3 per cent response by correspondence the response by personal visit was about 44 per cent (42 out of the 96 visited). However, the majority of the patients (73 per cent) included in the study were those who had responded by mail.

The affected status of the secondary cases has been determined by the respondents statement, who have been 'similarly' affected like them. The affected status of the secondary cases was further assessed based on available medical records. Relatives of the propositii who were reported to have normal hearing were not clinically examined. This may introduce some bias in the way of understating the familial cases. There is however no systematic bias introduced that excluded familial cases. All the propositii whose addresses have been ascertained have undergone standard clinical examination (otoscopic examination, pure tone audiometry and impedence audiometry) and stapedectomy.

The cases were classified based on mating of parents (normal hearing × normal hearing (N × N), affected hearing × affected hearing (A × A), affected hearing × normal hearing (A × N) and normal hearing × normal hearing other relatives affected (N × N − OR)). Analysis was performed employing the proband method given by Weinberg (Cavalli-Sforza and Bodmer, 1971).

Results

Of the 153 otosclerotic patients who responded, 132 (86 per cent) were from Tamil Nadu State, 17 (11 per cent) from neighbouring states Andhra Pradesh, Kerala and Pondicherry and the remaining four (three per cent) were from Assam and West Bengal. About 53 per cent of the respondents who hailed from Tamil Nadu state were residents of Madras city.

The male to female ratio of probands was 1.35:1. The age of male probands ranged from 15 to 70 years with an average of 36.1 years. The range of female was 14 to 62 years with an average of 34.7 years.

The mean age at onset in males was 24.1 years (range 2 to 63 years) and females was 25.7 years (range two to 52 years). About 14 per cent of respondents suffered hearing loss before they attained 15 years of age and 68 per cent of respondents suffered hearing loss between 15 to 34 years.

Mating type analysis

Of the 153 otosclerotic patients 98 of them had both parents with normal hearing (N × N), in 44 only one parent was affected (A × N) and in one family both parents were affected (A × A). In the remaining 10 families although both parents were normal, affected relatives were found outside the sibship (N × N − OR).

N × N mating.

Of the 98 families with both parents of normal hearing, in four (4.1 per cent) of them the proband was the only child. These four families have not been considered for the purpose of analysis. Seventy-eight families (about 79.5 per cent) were sporadic or simplex in which case the proband was the only affected and 16 families (16.3 per cent) had more than one affected member. Of the 468 offspring, 118 (25 per cent) were affected. When the Weinberg correction was applied (where probands are excluded) the proportion of affected offspring of N × N mating was 5.4 per cent. In matings of two normal parents who had affected relatives outside the sibship, there were 58 children. In this subgroup about 28 per cent of children were affected. Applying the Weinberg correction the proportion of affected children was 12.5 per cent. In this group the sex ratio of male/female is 0.72.

A × N mating.

In this group there were 38 matings ascertained through 39 propositi, one sibship being ascertained twice. Of the total 187 offspring, 60 (32 per cent) were affected. Applying the Weinberg correction, the proportion of affected children reduced to approximately 14 per cent. In this group the sex ratio of male/female amongst affected children is 1.5.

In families where the father was otosclerotic (20 families ascertained through 21 propositi) the proportion of affected children was 31.2 per cent (34 affected out of 109 children), which reduced to about 15.7 per cent with Weinberg correction.

When the mother was otosclerotic (18 families ascertained through 18 propositi) the proportion of affected children was about 33 per cent (27 affected out of 82 offspring) which reduced to about 14 per cent with correction.

A × A mating.

There was only one family in which both parents were otosclerotic. There are only two offspring of whom one was affected (50 per cent).

Degree of manifestation of otosclerosis

If otosclerosis is a truly dominant character, 50 per cent of the first degree relatives (parents, siblings and offspring of propositi) and 25 per cent of second degree relatives (uncles and aunts of propositi) are expected to be affected. The proportion of the observed to those of expected among these relatives, indicates the degree of expression of disorder. This analysis has been carried out combining all types of matings. The analysis indicates a very low expression

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TABLE I
ANALYSIS OF N × N; A × N; A × A; N × N − (OR) MATING (TOTAL DATA OF 153)

Relationship to propositi	No. of affecteds	No. of normals	Total affecteds + normals	Expected ratio	Expected no. of affecteds	Degree of manifestation (%)
Parents	46	260	306	1/2	153	30.1
Sibs > 15	67	535	602	1/2	301	22.25
(−) < 15*	67	530	597	1/2	298.5	22.44
Offspring > 15	06	239	245	1/2	122.5	4.9
(−) < 15	04	121	125	1/2	62.5	6.4
Uncle/aunt	34	159	193	1/4	48.3	70.5

*NB (–) indicates exclusion of individuals less than 15 years of age.

rate among offspring (about five to six per cent), siblings (about 22 per cent) and parents (30 per cent). The expression rate in second degree relatives is about 70 per cent (Table I). The expression rate among siblings was 22.35 per cent and improved to over 50 per cent when N × N matings with proband alone affected have been excluded (Table II). This further improved to about 61 per cent if siblings below 15 years have been excluded (Table II). Similar calculations could not be carried out on offspring because of the small sample size. Considering only parents of A × N, A × A and N × N − OR matings (excluding N × N matings) the expression rate among parents was 71 per cent and in sibs 37 per cent (Table III). However, in offspring irrespective of the exclusion or inclusion of children below 15 years, the expression rate remained low at about 10 to 12 per cent (Table III).

Discussion

The tendency for otosclerosis to run in families has been known for a long time. The condition has autosomal dominant inheritance with varying degrees of penetrance. In addition, the percentage of sporadic (non-familial) cases of otosclerosis have been variously described.

The age at onset of otosclerosis has been studied by many authors. Most authors agree that the main period of risk is roughly between the ages of 15 and 45 (Michael, 1989). In accordance with Ludman (1988) and Michael (1989), 68 per cent of our respondents also suffered hearing loss between 15 to 34 years. Out of 153 families studied there were 98 (64.05 per cent) of them in whom there was no history of otosclerosis. This implies that in the majority of patients in our study the disease was sporadic as compared to Michael (1989) who reported only 40 to 50 per cent and Ludman (1988) who reported 30 per cent. However, Morrison estimated the mutation rate at only 21/1 000 000 (0.0021 per cent).

The high proportion of sporadics seen in our data could be due to our inability to screen all the reportedly 'normal' relatives. It is also possible that those who are actually at the early stages of hearing loss may have not realised their hearing loss themselves until told by their immediate relatives and friends. This could have resulted in an underestimation of the actual proportion of familial cases and thus an overestimation of sporadics.

According to Morrison and Bundey as quoted by Michael (1989) sporadic cases of otosclerosis could arise due to phenocopies, new mutations, incomplete penetrance and alternative modes of inheritance.

If otosclerosis is inherited only in a dominant pattern, 50 per cent of first degree relatives should be affected. Our analysis of A × N matings showed that even when father or mother was affected there was very low expression among offspring (with and without correction) and it was nowhere near the expected percentage of expression. This indicates that otosclerosis could be inherited in some other mode also (other than dominant alone) and incomplete expression of the gene is probably playing a vital role in skipping generations. Some persons probably carrying the gene had not shown expression at the time of study.

In this particular sample analysis we present a similar expression rate (of 37 per cent) among siblings of propositi in familial cases to earlier workers. Morrison (1967) and Causse and Causse (1984) reported 40 per cent expression, while Larsson (1962) reported 25 per cent expression.

TABLE II
ANALYSIS EXCLUDING ALL N × N MATINGS WITH PROBAND ALONE AFFECTED

Relationship to propositi	No. of affecteds	No. of normals	Total affecteds + normals	Expected ratio	Expected no. of affecteds	Degree of manifestation (%)
Parents	—	26	26	1/2	13	—
Sibs > 15	19	54	73	1/2	36.5	52.1
(−) < 15	21	47	68	1/2	34	61.1
Offspring > 15	—	23	23	1/2	11.5	—
(−) < 15	—	11	11	1/2	5.5	—
Uncle/Aunt	—	—	—	—	—	—

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TABLE III
ANALYSIS EXCLUDING ALL N × N MATINGS (INCLUSIVE OF ONLY A × N; A × A AND N × N − OR)

Relationship to propositi	No. of affecteds	No. of normals	Total affecteds + normals	Expected ratio	Expected no. of affecteds	Degree of manifestation (%)
Parents	46	84	130	1/2	65	70.8
Sibs > 15	42	185	227	1/2	113.5	37
(−) < 15	42	183	225	1/2	112.5	37.3
Offspring > 15	04	73	71	1/2	38.5	10.4
(−) < 15	02	30	32	1/2	16	12.5
Uncle/aunt	27	80	107	1/4	26.8	100

Conclusion

Although otosclerosis is widely believed to be dominantly inherited with incomplete penetrance, this analysis of populations in India in recent times, shows that otosclerosis is a heterogenous disease. The role of non-genetic factors is probably a lot more important than previously thought. The role of genetic/non-genetic factors in manifestation of otosclerosis needs to be explored on a larger sample size.

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