HEREDITY AND OTOSCLEROSIS : A REVIEW

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ABSTRACT

A genealogical tree is presented of a family in which the dominant heredity of clinical otosclerosis was traced through three generations. Recent hypotheses for hereditary transmission of the disease have been advanced and evaluated. Chromosomal changes in otosclerotic subjects have been found by different workers to be conspicuously absent. Therefore the most convenient, and practical, way of ascertaining the exact mode of genetic ransmission in otosclerosis is through large-scale family studies. This particularly holds good for a vast country like India. The most recent genetic studies in the field indicate a polygenic and probably multifactorial mode of heredity of otosclerosis.

The hereditary nature of otosclerosis has been recognized for more than a century (Toynbee, 1861), yet the precise mode of inheritance has eluded any measure of scientific exactitude in a variety of postulated theories, all vying to conform to conventional mendelian norms.

Essentially, three hypotheses have been forwarded with regard to the nature of inheritance of otosclerosis: 1) a monohybrid autosomal dominant (Chumlea, 1942; Kabat, 1943; Pfandler, 1949; Larsson, 1960; Ruedi, **196.3);** ii) a dihybrid autosomal recessive (Tinkle, 1933; Kholmatov, 1973); and iii) a dihybrid inherited as a dominant in which one gene is in the sex chromosome, while the second is in one of the autosomes (Davenport et al 1933 a,b,c Fowler, 1963 ; Hernandez-Orozco and Courtney, 1964). In addition to this; some authors, while assuming that the inheritance of otos glerosis is dominant at the same time do not exclude the possibility of a recessive type of inheri. ance as well (Voyachek, 1925 ; Lindsay, 1973).

Such a diversification of opinion concerning the type of heredity by which otosclerosis is transmitted can be explained by the fact that the investigators by and large obtained their data on the basis of genetic anam-

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nesis. In such an investigation, actual cases of clinical otosclesrosis about which the patient did not know could have been missed. On the other hands hearing disorders of a completely different origin could have been attributed to otosclerosis.

In two-thirds of otosclerotic patients, upon adequate enquiry, there are secondary cases in the family and the disease can by traced directly or indirectly through two, three or even four generations (Marinelli and Marino, 1968).

The degree of otosclerotic manifestation varies from family to family, and even this appears to be genetically determined. Some families are encountered with 100 per cent manifestation, the full penetrance giving strict mendelian dominant ratios, while other families show degrees of manifestation of as little as 10 per cent. It is tempting to postulate that "sporadic" cases are simply a continuation of this process (Morrison, 1971), in any given case a detailed family history is the test guide to prognosis for the other family members, and this applies to the natural history as well.

It is worthwhile to begin a study on the genetic aspects of otosclerosis in families with many otoseloroiics amongst them. The family trees may clearly bring out the dominant autosomal inheritance, but the expression of the genes or set of genes may be variable. The chromosomal pattern on analysis of both the affected and unaffected members may be normal. Aberrations as reported by Tato et al., (1963) in Chromosome 13 and mesaicisms in Chromosomes 46/47/48 may not be noticed, nor any anomalous count found in any investigated otosclerotic cases (Koga et a!,, 1974).

Nitze (1967) analyzed leukocyte cultures from twenty two cases of otoselerosis and five normal controls, He found that both groups had normal chromosomal patterns and concluded that any structural changes which might be present are too small to be detected by numerical or morphological analyses. We must therefore conclude with Nitze (1967) that any systematic structural changes which might characteriza the genetic system of otosclerotics ate too subtle to be observed by available techniques if in fact they do exist.

Morrison (1967), reporting on nine cases of otosclerosis, found that of the few cases with anomalous counts there was no consistent abnormality and no evidence of mosaicism, trisomy or tetrasorny.

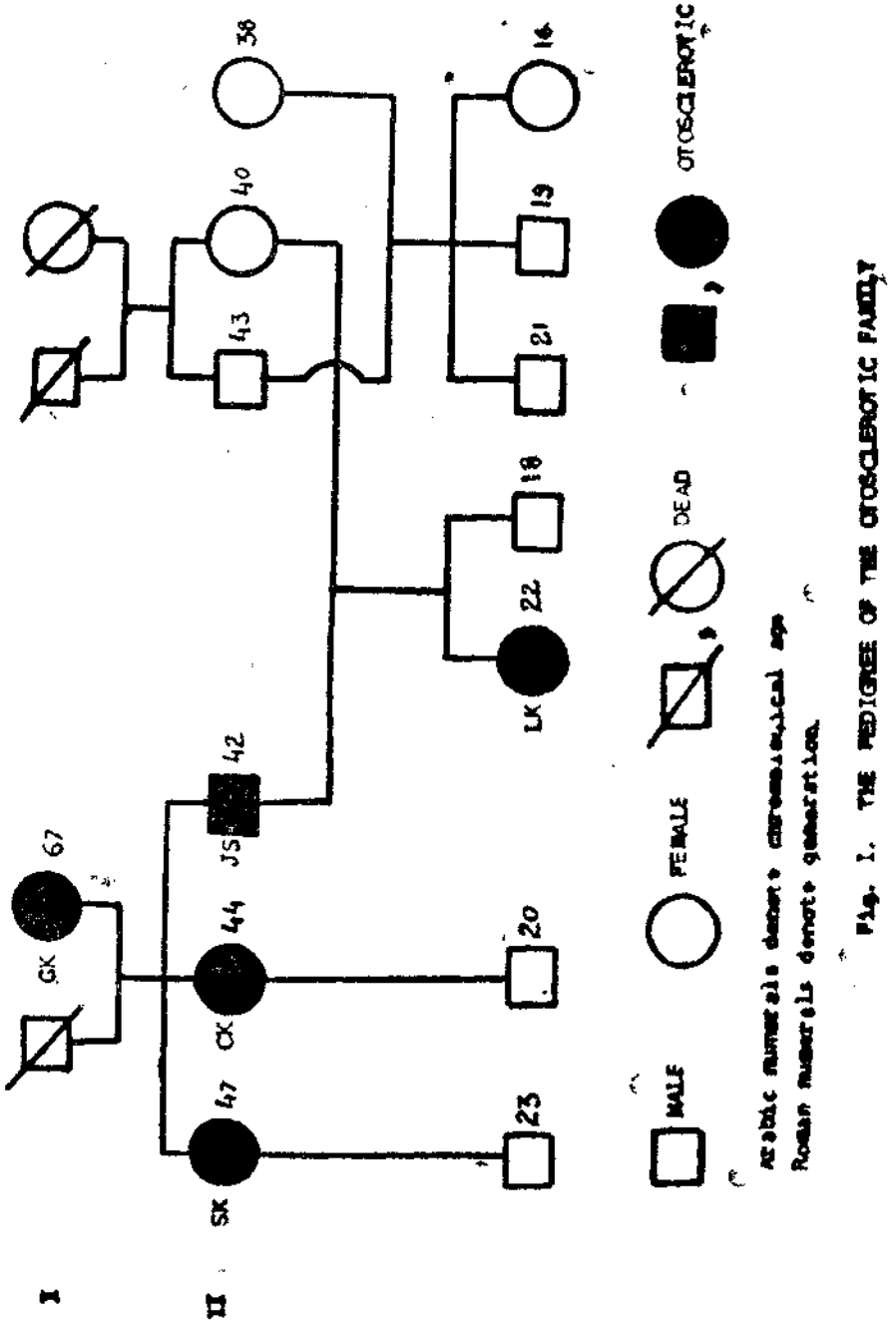

Fig. 1. THE PEDIGREE OF THE OTOSCLEROTIC FAMILY

Similarly, Cada and Soudek (1968) could not find the aberrations claimed by Tato and his co-workers (1963) in four cases of otosclerosis and one with van der Hoeve's syndrome.

In India a chromosomal study was undertaken between 1968 and 1973 at Calcutta by Mukherjee (1976) on twenty eight otosclerotics with positive family histories. It is significant that no chromosomal aberrations were observed in any of the twenty eight patients. It was concluded that genetic influence probably occurred at the gene level and was probably caused by the pleomo/phic character of a single mutant gene, detectable only by large family studies.

METERIALS AND METHODS

The authors' interest in the heredity of otosclerosis was stimulated through a i'amily in which five members in three generations were affected with moderate to severe conductive hearing loss. The family was pieced together through personal contacts and postal correspondence A family chart (Figure 1) was then compiled with the co-operation of normal relatives. This helped to clarify relationships and fill in missing links The authors had to collect the information concerning the penetrance of otosclerosis in the family through exhaustive history-taking. We had to depend heavily on heresay for the history of dead relatives. We could not trace the pedigree of deafness back through more than three generations. Nevertheless, a clear picture emerged of an inherited form of conductive deafness manifesting itself through three generations of a family.

RESULTS

Inheritance of the otosclerotic tendency in this family conformed to characteristically dominant type. The affected persons included the grand mother, her three siblings and the daughter of the youngest sibling. The sex ratio of deafness showed a classical female preponderance.

The audiological presentation revealed bilateral hearing losses in five members of the family. The grandmother had sensorineural loss in addition to conductive loss of hearing. This, in all probability, was due to presbyacutic changes. All the other affected members had mixed hearing losses to a certain degree, indicating probable involvement of the cochlea by the otosclerotic process. While there was no gross anatomical aberration or pathological finding on systematic otorhinolaryngological check-up of the affected subjects, SISI and Tone Decay tests were negative.

The subjects were retested over a period of twelve months with the same audiometer and the results obtained were essentially the same as those obtained before, the maximum deviation at any one frequency being 5 dB The audiometer employed was Arphi Model 700 MK IV, whieh had been periodically calibrated to I.S O. specifications and was operated on A. C. mains All audiometry tests were carried out under ideal soundproof conditions in the audiological wing of the E.N.T. Department of New Dayanand Hospital, Ludhiana.

DISCUSSION

First of all, we must concede that genetic anamnesis has its limitations. Since the subject of deafness may evoke fear and denial among individuals with deaf relatives, it is possible that the complete picture had not been obtained. Social taboos concerning obvious physical handicaps in India militate strongly against willing cooperation between investigators and members of the public under survey. A more accurate presentation would have accrued from a study in which, ideally, all family members were willing to subject themselves to hearing tests. This was not possible in the survey.

Theoretically, the heredity of otosclerosis could best be observed at the chromosomal level. Any chromosomal abnormalities which might be associated with otosclerosis would be most likely to appear among persons from families riddled with otosclerosis, i.e. from persons who could be said to exhibit familial otosclerosis. On the other hand, cases with chromosomal changes usually display no constant hereditary pattern.

The methods of chromosome analysis available to us at the moment are unable to detect the changes that occur in the chromosome at the gene level and so the chromosomes appear normal. Therefore, further study of chromosomal patterns in otosclerotics by current methodology does not appear promising and the only way to observe the pattern of genetic transmission is by family studies (Mukherjee, 1976). Such studies may indicate autosomal dominant inheritance with a penetration of about 50 per cent, yet the chromosomes may not show any abnormalitv. This, perhaps, is due to inheritance of mutant genes of large effect and their genetic determination is possible mainly from family studies and followed in some cases by refined biochemical tests for the detection of subclinical cases of otosclerosis (Gukovich, 1969; 1976 and 1977).

Morrison (1967) was of the opinion that otosclerosis, like osteogenesis imperfecta, belongs to a group of hereditary collagen disorders with a similar mode of inheritance, incomplete manifestation, varying degrees of

expressivity, and possibly a common abnormal enzyme system (Martin and Chevance, 1976).

The most recent genetic studies on the familial transmission of otosclerosis point to a polygenic (Gapanavichyus, 1971 ; Causse and Causse, 1980) and probably a multifactorial phenomenon (Mendlowiz and Hirschhorn, 1976), A number of different genetic determinants, involving such factors as collagen and calcium metabolism, parathormone activity, bone structure, etc., might combine to produce a clinical syndrome. One or more of the genes involved may show a dominance effect (Falconer, 1972). However, the additive effects of other genes (as well as environmental factors) might be necessary for clinical expression of trait (Mc Kusick, 1972). Such a hypothe. sis explains the wide range of traif (Mc Kusick, 1972). Such a hypothesis explains the wide range of severity and age of onset that occurs in different affected families. Among environmental factors nutrition, emotional stress, hormonal stimulation and infection probably also play a role. If the work of Shambaugh and Petrovic (1968) on the ability of fluoride to prevent this diseise proves accurate, fluoride intake may also come to be considered as a variable. Hence the heredity of otosclerosis is probably multifactorial as well as polygenic.

As for the explanation regarding the different modalities in the inheritance of otosclerosis, pleomorphism of the variable multiple effects of a single mutant gene is likely. There are several hereditary forms of clinical otosclerosis which are regulated by different mutations of a single or different mutations of a single or different genes governing the development of the osseous labyrinth. Different forms of such mutations are responsible for different frequencies of the disease in individual genealogies. So the presence of a dominant form of clinical otosclerosis does not preclude the possibility of the existence in the same population of a recessive form of the disease. In the light of the fact that genetic investigations showt hat such diseases as hemophilia and albinism have somewhat different forms because of different gene mutations, this argument is not unfounded.

CONCLUSIONS

Quite a number of cases of otosclerosis are encountered with positive family histories. While it may be possible for only a small number of them to show demonstrable chromosomal anomalies, a very large number furnish definite evidence of transmission of pleomorphic mutant genes detectable only by family studies (Mukherjee, 1982) In a vast country like India a large amount of this data remains to be investigated. Medical

geneties is attaining enormous importance in investigation for casual agents of diseases and we are likely to hear a lot about it in the 1980's in deciphering the etiology of diseases. Considering this, it is felt that organized study on genetics in otosclerosis will be worthwhile in the various centres of our country.

To elucidate the genetic transmission at least two types of studies need to be undertaken viz. (i) identification of the gene, if possible by biochemical and electron microscope studies and (ii) large-scale field studies to trace the pedigree of otosclerotics and elucidate the precise mode of inheritance.

When the exact mode of genetic transmission can be established, it should be possible to reduce the incidence of otosclerosis by Family Welfare Planning Services.

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