EDITORIAL

Genetic hearing loss. Past and future

Research into the causes of hereditary hearing loss and hereditary deafness was first initiated in the second half of the 19th century. At this time the first reports appeared of a number of fairly common hereditary syndromes with hearing loss as one of the characteristic symptoms. These include Usher’s syndrome, Pendred’s syndrome, Treacher Collins syndrome and Branchio-oto-renal syndrome. In the last quarter of the 19th century the concept of heredity as a cause of hearing impairment was accepted, but it took until the beginning of the 20th century for Mendel’s Laws to be recognized as an explanation for the hereditary pattern.

In the first half of the 20th century research into the causes of deafness was continued on a large scale and several impressively large series were published in detail demonstrating autosomal recessive hereditary deafness. Our knowledge of the syndromal and non-syndromal forms of hereditary hearing loss have greatly increased over the last half century. In this period the first reviews appeared of the many and ever increasing number of hereditary syndromes (nowadays about 350) with deafness as a symptom. Attention was given to the degree of penetrance of the syndrome and the degree of expression of the separate symptoms.

Nowadays it is no longer sufficient simply to show that a certain disease is inherited in an autosomal or sex-linked recessive or dominant pattern. It is necessary to know the gene product of the mutated gene and the mechanism by which it causes the syndrome. Possible preventive and/or therapeutic approaches depend very much on a knowledge of the gene product.

In this last quarter of the 20th century, there is a worldwide effort to identify and sequence, or read, the code of the human genome, the complete set of genetic instructions for a human. In the past 5 years new genetic techniques have been used successfully to locate and characterize genes for many types of hearing loss. About 40 hereditary diseases with hearing loss or deafness as a feature have been mapped on a chromosome and the affected gene has been identified in about 10 of these 40. In 1994 in almost every month a new gene for deafness has been linked or identified. Compared to the X-linked and autosomal dominant disorders, autosomal recessive disorders, even syndromal ones, are difficult to study.

Usher’s syndrome is an autosomal recessive syndrome that accounts for about 50% of combined deafness and blindness. The blindness is due to retinitis pigmentosa. The incidence of Usher’s syndrome is estimated to be one in 30 to 40000 individuals. Based on clinical data it has already been subdivided into three types. Type I is characterized by profound early childhood deafness and absent vestibular responses. Type II by a non-progressive mild to profound hearing loss with normal vestibular responses. Type III is like type II with an ill-defined progressive sensorineural hearing loss. Based on gene linkage studies Usher’s syndrome proved to be even more heterogeneous and until now seven types have been recognized. Three loci have been identified for type I (la on 14q, Ib on 11q13 and one unlinked to these regions), two loci for type II (Ia on 1q and IIb unlinked) and type III on chromosome 3q. Gene linkage has been demonstrated for five types. For Usher’s type IB the gene myosin 7A has been cloned. Based on these close gene linkage results the clinical picture of each of these different types needs to be redefined. For Usher’s type IIA it has been shown that the deafness can also be progressive which is in disagreement with the previous clinical definition.

In 1994 for the first time genes have been linked to non-syndromal autosomal dominant and recessive types of deafness. Autosomal dominant progressive sensorineural deafness has been mapped to chromosome 11 and to 13. Many more locations are expected to be found, including those for otosclerosis.

Autosomal recessive congenital non-syndromal sensorineural deafness has been linked to chromosomes 13, 11 and to 17. Autosomal recessive congenital non-syndromal childhood deafness affects about one in three of the children with early childhood deafness. The incidence of this deafness in childhood is one in 700 children and so the incidence for autosomal recessive non-syndromal deafness is one in 2000. It is unknown how many different genes are involved, but estimates vary between five and 50. The most challenging part of this field of research is to link and clone these genes. The availability of enormous numbers of markers, new genetic techniques and international cooperation and competition led to a breakthrough in 1994 with three types of autosomal recessive early childhood deafness being linked to chromosomes. The first, called NSRD1, to chromosome 13, NSRD2 to chromosome 11 close to the area where Usher IB is located and NSRD3 to chromosome 17. Large consanguinous families with childhood deafness are present in the Islamic world. The Pasteur Institute of Paris had access to some of these families in Tunisia, resulting in linkage of NSRD1 and NSRD2.

This increasing new knowledge will, in the future, enable a genetic diagnosis of the deaf child, with genetic counselling based on facts and not empirical data. In the same way carrier detection will become available for the relatives. In Europe and North America the congenital deaf mostly marry deaf partners and thus, they may be counselled as to the chances of an affected child. In addition with knowledge of the gene product we will be able to understand better and at a more
fundamental level the pathophysiology of the inner ear which could lead to preventative and/or therapeutic approaches.

Individuals from around the world are demonstrating newfound interest, enthusiasm and support for research into genetic deafness. Nevertheless, still more help is needed from otorhynologists to study families with genetic deafness and to refer them for genetic linkage studies. Many positive steps have been taken to speed the progress of research in hereditary deafness. The establishment in 1988 of the National Institute on Deafness and other communication disorders has allowed the funding of this research in the USA.24,25

The human genome project also helps research into hereditary disorders. Research in human genetic deafness is accelerating at an increasing rate. Today's rapid advances coming from the field of genetic deafness will improve our understanding of hearing and deafness. It will bring the world closer to preventing and controlling some types of genetic deafness.

The European countries could contribute more by better international co-ordination, by a larger funding program from the European Common Market and by giving greater priority to the field of research into genetic deafness, giving deafness the same priority as to the central nervous system. Recently a European Working Group on Genetic Deafness has been founded. In many areas of Europe populations have lived for centuries in the same small areas whilst the high level of medical care provides well documented data. Europe is still in an excellent position to be of great help in this field of research.

References

1 Wilde W.R. (1853) Practical observation on auricular surgery and the nature and the treatment of diseases of the ear. Blanchard and Lea, Philadelphia


3 Uttermann V. (1869) de Dursturmmi Norge. Cammermeyer: Christiana

4 Hartmann A. (1880) Taubstummheit und Taubstummeneigung nach den vorhandenen Quellen, so wiefgegen Beobachtungen und Erfahrungen. Stuttgart


7 Pendred V. (1896) Deaf mutism and goiter. Lancet 2, 532

8 Thomson A. (1847) Notice of several cases of malformation of the external ear together with experiments on the state of hearing in such persons. Month J. Med. Sci. 7, 420.


10 Treacher Collins E. (1900) Case with symmetrical notches in the outer part of each lower lid and defective development of the malar bone. Trans. Ophthal. Soc. UK. 20, 190-192.

Appendix


12 Politzer A. (1882) Lehrbuch der Ohrenheilkunde für praktische Ärzte und Studierende. II. Bond, Ferdinand Enke. Stuttgart, Germany


C.W.R.J. Cremers

University Hospital Nijmegen

Philips van Leydenlaan 15

PO Box 1901

NL 6500 HB Nijmegen

The Netherlands