Genetic Hearing Impairment

Its Clinical Presentations

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Clinical Presentation of DFNA8–DFNA12

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The phenotypic expression of mutations in the α-tectorin (TECTA) gene (DFNA8–DFNA12) is a nonsyndromic, sensorineural hearing loss, affecting all frequencies, but especially the mid-frequencies. The hearing loss is moderate to moderately severe, with a prelingual onset and without progression. The median hearing loss at onset is 51 dB (pure tone averages – PTA). The inheritance pattern is autosomal dominant and fully penetrant. Some differences in clinical expression may exist and may be related to different domains where the mutations are localized. The above description corresponds to mutations in the zona pellucida domain. Mutations in the zonadhesin domain may affect the high frequencies rather than the mid-frequencies.

Material and Methods

Family Study

The description of the clinical presentation of DFNA12 is based on the findings in a Belgian family whose pedigree (consisting of 10 generations and 238 members) was worked out and where mutation analysis revealed missense mutations in the zona pellucida domain of the α-tectorin gene in the DFNA8–DFNA12 region on chromosome 11q22–24) [1, 2]. Pure tone audiometry was performed on all affected family members and on part of the unaffected members. Air and bone conduction thresholds were established according to routine

procedures. In case of hearing loss, anamnestic data were obtained and previous audiograms collected if available.

Statistical Analysis

The audiometric data were statistically analyzed. Five-parameter statistics and box and whisker plots were used to describe the hearing loss [3]. PTA were defined as the average of the thresholds at 500, 1,000 and 2,000 Hz. To label an audiogram in terms of normality, the thresholds were compared to the age- and gender-related distribution as defined by the ISO 7029 standard [ISO 7029 (1984), 'Acoustics – Threshold of hearing by air conduction as a function of age and gender for otologically normal persons' (International Organization for Standardization, Geneva)]. For each frequency the threshold was expressed as the number of standard deviations below or above the median value for a given age and gender (further called 'hearing standard deviations' – HSD). From this number of standard deviations, the corresponding percentile can be found in any table of a normal distribution. For instance, the median hearing loss at 500 Hz for a normal male at age 70 years is 8 dB according to the ISO 7029 standard with a positive standard deviation of 10 dB. A hearing loss of 25 dB can be expressed as 1.7 HSD, namely 1.7 standard deviations (=17 dB) above the median, and this corresponds to the 96th percentile (or P96). Nonparametrical statistics (Mann-Whitney U test) were used to compare the hearing thresholds of affected with those of unaffected family members.

Results

Anamnestic Data

The anamnestic data and, if available, the audiometric history of the 17 affected family members are summarized in table 1. Three patients (18%) were not aware of any hearing loss at the ages of 22, 23 and 44 years respectively, whereas the audiometric data showed significant hearing loss. Three patients (18%) reported the onset of their hearing loss at ages ranging from 35 to 47 years. Four patients (24%) reported a hearing loss from primary school onward and 7 (41%) presumed their hearing loss to be prelingual. Of 4 patients an audiogram before the age of 10 years was available. The hearing loss ranged from 50 to 70 dB and no deterioration was measured during a follow-up time ranging from 2 to 14 years.

Statistical Analysis

The audiometric results of the 17 patients genetically diagnosed as affected are plotted in figure 1, which shows a mid-frequency sensorineural hearing loss of 57 dB as PTA. At all frequencies, the hearing loss of the genetically affected patients is significantly worse than that of the unaffected family members (Mann-Whitney U $p < 0.001$). To eliminate possible gender and age effect, the hearing loss of each individual was related to the age- and gender-related median (see Materials and Methods for details). Also, table 2 shows that the hearing

Table 1. Summary of the anamnestic and audiometric history of the 17 patients [from 2, with permission]

Patient	Actual age, years	Reported age of onset, years	Age of first audiogram, years	First PTA, dB	Evolution
1	40	0			
2	85	0			
3	36	0			
4	17	0	3.5	55	No deterioration
5	19	0	5	70	No deterioration
6	15	0	6	50	No deterioration
7	6	2.5	4	55	5 dB deterioration
8	47	10			
9	70	<12			
10	33	<12			
11	34	<12			
12	52	35			
13	53	40			
14	49	47			
15	44				
16	22				
17	23				

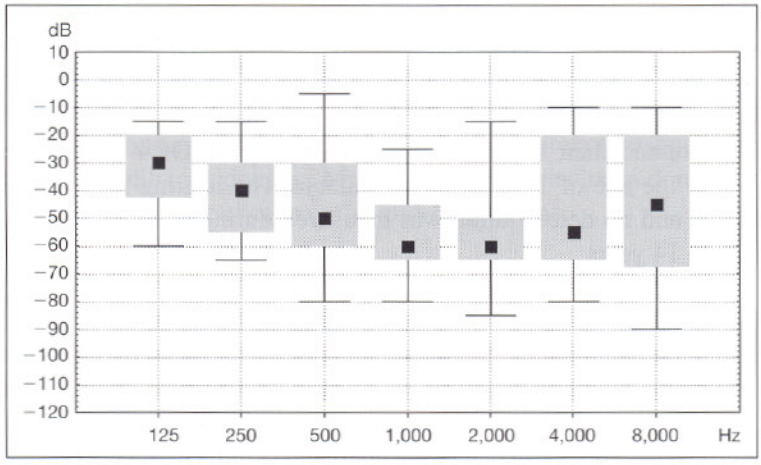

Fig. 1. Box and whisker plot of the audiometric data of 17 affected family members. Bars: minimum to maximum; large rectangles: 25–75%; small squares: median values. The hearing loss is highest over the mid-frequencies (500–2,000 Hz) [from 2, with permission].

Frequency, Hz	HL (HSD)
125	4.2
250	5.0
500	6.9
1,000	7.6
2,000	5.9
4,000	3.2
8,000	2.1

Table 2. Median hearing loss (expressed as HSD) of the 17 genetically affected patients for each tested frequency [from 2, with permission]

loss of the affected patients expressed as HSD is significantly worse than that of the unaffected family members (Mann-Whitney U $p < 0.001$).

Because this study represents a cross-sectional audiometric evaluation, it is not possible to describe the progression of the hearing loss for each patient. However, plotting the hearing threshold of each individual on an age-hearing loss plot gives a good approximation of the evolution with age. This is done for the frequencies 250, 1,000 and 4,000 Hz in figure 2. The best linear fit can be calculated according to the ISO formula:

$$H_{md,Y} = \alpha\,(Y - 18)^2 + H_{md,18}$$

where the median hearing threshold for a person of age Y ($H_{md,Y}$) is expressed as a function of age $(Y - 18)^2$ with $H_{md,18}$ being the median hearing threshold at age 18 years and α being the slope of the linear function (expressed as deterioration in dB/year^2). The values of coefficient α are smaller in the affected patients than in the normal population, from which it can be inferred that the average hearing deterioration with age in the affected patients does not exceed the normal deterioration with age.

Discussion

This analysis yields approximate values for both the 'onset' hearing loss and the slope of the hearing deterioration with age. The 'onset' hearing loss can be inferred from the value of $H_{md,18}$, as calculated by the linear fit according to the ISO formula. This is the hearing loss at age 18 years. In the normal population, $H_{md,18}$ equals 0 dB at all frequencies. In the affected patients, $H_{md,18}$ equals between 31 and 55 dB, with an average of 51 dB as PTA. To be comparable with the ISO 7029 data, the onset age was set at 18 years. Yet, when the calculations are performed with an age of onset being 0 years, the results are quite similar, with the same hearing loss at onset (PTA 51 dB). In addition, anamnestic data confirm the early onset. A majority of patients (11/17 or 65%) mention the

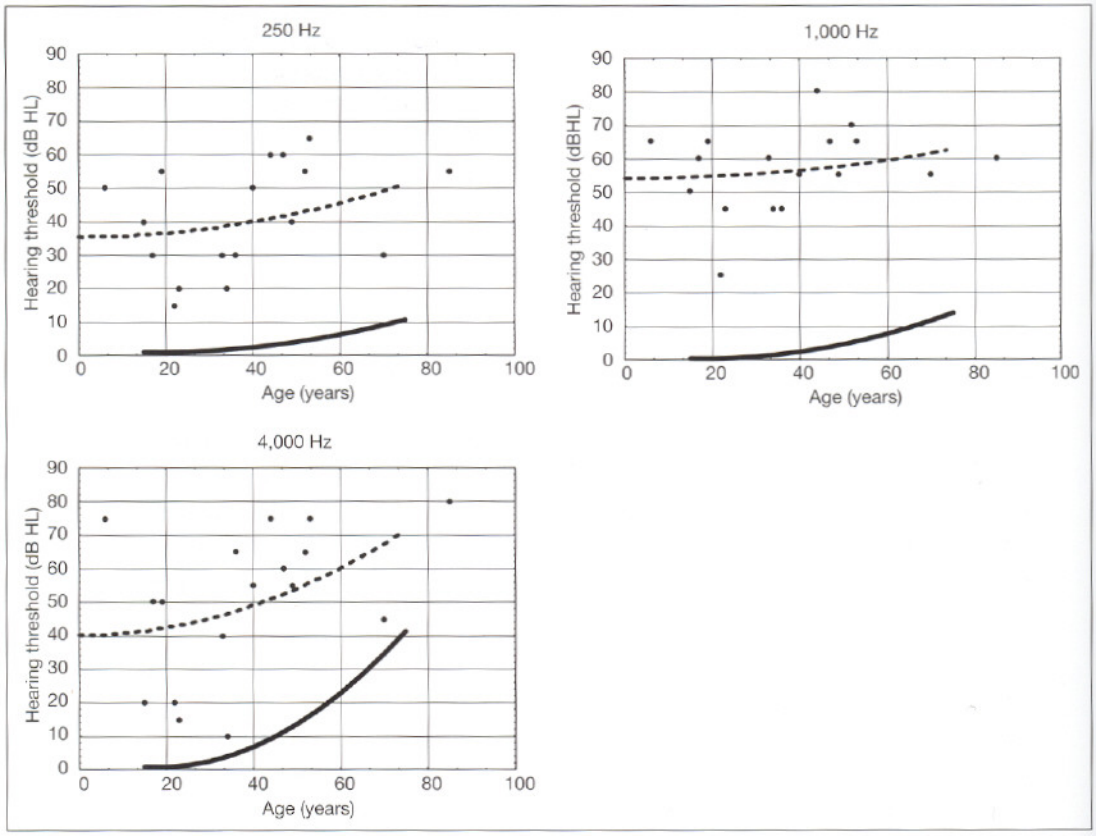

Fig. 2. Hearing thresholds (dBHL) for 250 Hz (top), 1,000 Hz (mid) and 4,000 Hz (bottom) plotted in function of age. The dots represent the thresholds of the affected patients. The dotted line is the best linear fit through the affected patients according to the ISO 7029 formula (see text). The solid line is the best linear fit of the normal population according to the ISO 7029 standard. At all frequencies the slope of the dotted line is similar to the slope of the solid line. Thus the hearing deterioration of the affected patients does not exceed the normal hearing deterioration with age and is therefore stable. The 'onset' hearing loss (at birth) is therefore likely to be the same as the hearing at age 18 years and is 38 dB at 250 Hz, 55 dB at 1,000 Hz and 43 dB at 4,000 Hz [from 2, with permission].

hearing loss to be first noticed before or at primary school, and where audiometric data at this age are available, they show hearing losses of over 50 dB (age 3.5–6 years) with no further deterioration.

The hearing loss is sensorineural and most prominent in the mid-frequencies, although all frequencies are affected. The slope of the linear fit at different frequencies is smaller than the slope of the linear fit of the normal population.

This means that the hearing deterioration in the affected patients does not exceed the normal age-dependent hearing deterioration. Consequently, the hearing loss in this family may be labeled as nonprogressive or stable. This is in line with the anamnestic data, since most affected persons mention no or only slight progression with age. In addition, in patients with audiometric follow-up data, no deterioration is seen.

This phenotype has also been described in an Austrian family with a mutation in the same zona pellucida domain of the α-tectorin gene [4]. The hearing loss in this family seems to be a bit more pronounced (60–80 dB) but no correction is made for age. The phenotype of a French family with a mutation in the zonadhesin-like domain of the α-tectorin gene has been reported to be slightly different [5]. It is also a nonsyndromic, sensorineural hearing loss with a prelingual onset. But it is reported to preferentially affect the higher frequencies and to be progressive. The report however does not include the evidence of these latter features. The progression is said to be 0.7 dB per year in the higher frequencies, but this is the same order of magnitude as the natural progression with age. No correction for this seems to be made. It is thus likely that this also is a nonprogressive hearing loss. The affection of the higher frequencies may be a particular feature of the mutation in the zonadhesin-like domain.

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