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# Genetic hearing loss: a study of 228 Brazilian patients

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*Abstract*

We studied 228 patients, with suspected or confirmed genetic hearing loss, in order to determine the clinical and genetic diagnoses and etiology of each case. Deafness with no associated abnormalities was found in 146 patients (64%) belonging to 112 families. Syndromic deafness was diagnosed in 82 patients (36%) belonging to 76 families. The genetic etiology was as follows: autosomal recessive inheritance in 40.8% of syndromics and non-syndromics, autosomal dominant inheritance in 13.2% and X-linked recessive in 1.3%. In 44.7% of the cases, the etiology of the hearing loss could not be determined. Monogenic causes are the most possible etiology in the latter cases. Parental consanguinity was found in 22.4% of the cases, and deafness was bilateral, profound and neurosensorial in 47.4% of the patients. An early onset of hearing loss (< 2 years of age) occurred in 46.5% of the cases. These results are similar to previous literature reports.

## INTRODUCTION

The incidence of hearing loss varies among populations and, in the developed countries, it is estimated that approximately 1 in 1000 infants have a hearing loss (Fraser, 1964; Feinmesser *et al.*,1986; Newton, 1989; Steel and Brown, 1994).

Kloenfer *et al.* (1970) suggested that 46-60% of the causes of profound deafness are genetic disorders, a claim supported by Nance and McConnell (1974). Konigsmark and Gorlin (1976) estimated that 35-50% of their cases had a genetic cause, and that in congenital or genetically determined, early-onset deafness, the inheritance was autosomal recessive (AR) in 60-70% of the cases, autosomal dominant (AD) in 20-30% and X-linked (XL) in 2%. Similar findings were reported by Chung and Brown (1970). More recently, Marazita *et al.* (1993) reported that 47% of the cases of hearing loss were caused by autosomal recessive inheritance, and 15% by autosomal dominant inheritance.

Most cases involve isolated hearing loss. Arnos *et al*. (1992) claimed that 71% of their cases represented isolated hearing loss (29% autosomal recessive, 24% autosomal dominant and 3% X-linked) with the remaining 29% being syndromic forms.

The lack of such studies on Brazilian samples and the expressive number of patients with hearing loss referred for investigation in our center prompted us to perform this study in order to determine the genetic diagnoses of each case.

## SUBJECTS AND METHODS

Two hundred and twenty-eight patients from 188 families were studied between 1972 and 1994. Of these, 116 (50.9%) were evaluated between 1989 and 1994. Clinical and genetic analysis approaches were done and complementary tests excluded enviromental causes. All patients with a confirmed or suspected genetic cause for the hearing loss were included. All the patients underwent clinical and audiological tests. Patients with no morphological defects and/or neurological deficits were classified as cases of isolated hearing loss whereas the others were classified as cases of associated hearing loss.

Sporadic patients with consanguineous parents or an affected sib were considered as autosomal recessives in the isolated group. An AD or XL pattern of inheritance was established by the patient's pedigree. More than one etiology meant that concurrent factors (genetic and environmental) played a role in the development of hearing loss.

The hearing impairment was classified as described by Northern and Downs (1989), but intermediate groups, such severe-profound, were also considered. Classification as non-coincident meant that the hearing loss was not the same in both ears.

Indirect ophthalmoscopy was done in 39% of the patients, and 33.8% underwent computed tomography of the temporal bones.

## RESULTS

The etiological and clinical diagnoses are summarized in Tables I and II.

Consanguinity occurred in 22.4% of the cases, and in 37.3% of the families there was recurrence.

The hearing loss was bilateral in 88.6% of the cases and unilateral in 6.1%. In 5.3% of the cases, laterality was not informed. Sensorineural hearing impairment accounted for 86% of the cases, and conductive loss occurred in 3.9%. The hearing loss was mixed in 3.1% and non-coincident in 2.2%. In 4.8%, the information was absent. The

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**Table I** - Probable etiological diagnosis of isolated hearing loss among 146 patients of 112 families.

| Etiology | N | % |
|---|---|---|
| Autosomal recessive | 70 | 48.0 |
| Autosomal dominant | 13 | 8.9 |
| X-Linked | 1 | 0.7 |
| Other forms | 6 | 4.1 |
| More than one form | 3 | 2.0 |
| Supposed monogenic | 53 | 36.3 |
| Total | 146* | 100 |

*Corresponds to 64% of the total number of individuals examined.

**Table II** - Probable etiological diagnosis of associated hearing loss among 82 patients of 76 families.

| Etiology (inheritance) | Diagnosis | N | % |
|---|---|---|---|
| Autosomal recessive | | 23 | 28 |
| | Fraser | 1 | 1.2 |
| | Oculocutaneous albinism | 1 | 1.2 |
| | Optico-cochleo-dentate | 1 | 1.2 |
| | External ear anomaly | 3 | 3.7 |
| | Usher | 6 | 7.3 |
| | Jervel-Lange-Nielsen | 1 | 1.2 |
| | Pigmentary anomaly and hearing loss | 1 | 1.2 |
| | Pendred | 1 | 1.2 |
| | Unknown | 8 | 9.8 |
| Autosomal dominant | | 17 | 20.7 |
| | Waardenburg | 5 | 6.1 |
| | Branchio oto | 8 | 9.8 |
| | Treacher-Collins | 2 | 2.4 |
| | Townes-Brocks | 1 | 1.2 |
| | Multiple exostoses | 1 | 1.2 |
| X-Linked recessive | | 2 | 2.4 |
| | Lesh-Nyhan | 1 | 1.2 |
| | Jubert-Marsidi | 1 | 1.2 |
| Chromosomal | 10q- | 1 | 1.2 |
| Etiology unknown | | 39 | 47.7 |
| | Goldenhar (OAV spectrum) | 3 | 3.7 |
| | Wildervank | 1 | 1.2 |
| | Pigmentary anomaly | 4 | 4.9 |
| | External ear anomaly | 11 | 13.5 |
| | Klippel-Feil | 1 | 1.2 |
| | Probable syndromes | 19 | 23.2 |
| Total | | 82* | 100 |

*Corresponds to 36% of the total number of individual examined.

hearing impairment was profound (47.4%), severe-profound (4.8%), severe (11%), moderate-severe (4.8%), moderate (9.2%), mild-moderate (1.7%), mild (0.9%), or non-coincident (13.6%).

## DISCUSSION

Consanguinity (22.4%), onset of loss before two years of age (46.5%) and profound, bilateral and sensorineural hearing loss (47.4%) were the main general characteristics. The rate of consanguinity was extremely high compared to that of the urban Brazilian population (around 1%) (Agostini and Meirelles-Nasser, 1986). Parental consanguinity varies widely among deaf children, from 8% in a Brazilian study (Bento *et al.*, 1986) to 37.6% in a large study from India (Majumder *et al.*, 1989).

The most common type of hearing loss found in this study, profound, bilateral and sensorineural, agrees with other reports (Salerno *et al*., 1979; Castro Jr. *et al*., 1980; Bento *et al*., 1986; Feinmesser *et al*., 1986). A profound sensorineural hearing loss accounts for most cases of genetically determined hearing loss (Gorlin *et al*., 1995).

In a study of over 3,100 patients with hearing loss, Fraser (1976) reported rates of 66% for AR, 30% for AD and 4% for XL inheritance. These figures vary in the other studies (Chung and Brown, 1970; Konigsmark and Gorlin, 1976; Majumder *et al*., 1989; Reardon, 1990; Marazita *et al*., 1993). Morton (1991) suggested that AR = 77%, AD = 22% and XL = 1%. Considering our cases in which the etiology (pattern of inheritance) was determined (126 cases), 93 (73.8%) were AR, 30 (23.8%) were AD and 3 (2.4%) were XL. These values are within the range reported in the literature. We are unaware of a similar sample group studied in Brazil.

The supposed monogenic cases (Table I) were all physically normal, sporadic patients with no consanguineous parents and had profound, bilateral sensorineural deafness. In these cases, the most probable etiology was autosomal recessive inheritance. Mondini dysplasia and Meniére syndrome were classified as other forms, as described by Gorlin *et al*. (1995).

Hearing loss of unknown causes occurs in 20-50% of the cases (Fraser, 1976; Konigsmark and Gorlin, 1976; Ruben *et al*., 1982; Reardon, 1990; Marazita *et al*., 1993). In Brazilian patients, hearing loss of undetermined etiology varies from 13.5-38.8% (Salerno *et al*., 1979; Castro Jr. *et al.*, 1980; Castagno and Carvalhal, 1985).

In our patients with an unknown etiology and/or clinical diagnosis (33% or 75 patients out of 228), a genetic cause was supposed. In the group “probable syndromes” (Table II) the patients had dysmorphic signs and represented sporadic cases. Their chromosomal study was normal. In these cases, a monogenic, unknown syndrome must be the explanation.

Ophthalmological evaluation was very important for defining diagnosis of some syndromic cases, such as Usher syndrome. Ophthalmological alterations were the only anomaly associated with hearing loss. The exclusion of certain non-genetic cases helped to define acquired conditions, such as congenital rubella in older patients.

Computed tomography of the temporal bones was also helpful in diagnoses where there were anatomical anomalies. In these cases, a knowledge of the normal dimensions of the tomographic structures of temporal bones in Brazilians is necessary in order to avoid subjective interpretation.

Our results indicate that a clinical study and delineation of the family history are the main approaches for evaluating hearing loss patients; also, the genetic diagnosis of hearing loss in the Brazilian patients are similar to those referred in the literature.

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## RESUMO

Estudamos 228 pacientes, pertencentes a 188 famílias, com deficiência auditiva genética, suspeita ou confirmada, já excluídas causas ambientais, no sentido de determinar o diagnóstico clínico e genético e a etiologia em cada caso, já que estudos deste tipo são escassos em pacientes brasileiros. A surdez sem anomalias associadas compreendeu 146 pacientes (64%) pertencentes a 112 famílias. Deficiência auditiva sindrômica foi diagnosticada em 82 pacientes (36%) pertencentes a 76 famílias. Em 44,7% deles, não foi possível determinar a etiologia da deficiência auditiva e a origem monogênica foi suposta baseada em dados de freqüência. Com relação ao padrão de herança, 40,8%, entre sindrômicos e não-sindrômicos, foram recessivos, 13,2% foram dominantes e 1,3%, ligados ao X. Algumas variáveis foram analisadas: consangüinidade parental foi encontrada em 22,4% dos casos, surdez neurosensorial profunda bilateral em 47,4%, e o início precoce da perda auditiva (até 2 anos) em 46,5%. O estudo clínico e a história familiar revelaram-se como os principais métodos para a definição diagnóstica. As causas genéticas de surdez em pacientes brasileiros são similares aos estudos referidos na literatura.

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