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Etiological approach in patients with unidentified hearing loss

Ann N. Deklerck [a], Frederic R. Acke [a], Sandra Janssens [b], Els M.R. De Leenheer [a,*]

[a] Department of Otorhinolaryngology, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium
[b] Department of Medical Genetics, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium

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ABSTRACT

Objectives: Etiological diagnosis of hearing impairment is of great importance to ensure early and adequate management. Even after thorough history taking, clinical and audiometric evaluation, the cause of hearing loss remains unclear in a majority of patients. Further examinations can imply imaging, ophthalmologic investigations, laboratory tests, electrocardiography and genetic testing. Lately, the latter has taken an increasingly prominent place within this diagnostic work-up. However, clear guidelines about optimal implementation and sequence of these tests are required.
Methods: Records of patients who visited the consultation for otogenetics at Ghent University Hospital (Belgium) during the period 2006–2012 were retrospectively reviewed. In order to optimize the etiological-diagnostic work-up of unidentified hearing loss, application patterns and results of various diagnostic tests, audiometric and etiological data of each patient were collected and analyzed.
Results: Data of 191 patients were analyzed. In 81.2% of the patients, a cause of hearing loss could be determined or suspected. In total, 65.4% had a (presumably) genetic etiology, with connexin 26 (*GJB2*) mutations as the leading cause. Inquiry of risk factors, associated with congenital hearing loss, and pedigree analysis were found to have the highest diagnostic gain (61.3% and 41.8%). Connexin 26 gene mutations were only present in bilateral hearing impairment, whereas CT abnormalities were related to unilateral ($P = 0.003$), profound ($P < 0.001$) hearing loss. An enlarged vestibular aqueduct was present in 42.9% of all CT abnormalities. Ophthalmologic anomalies were detected in 35.7% of the studied patients.
Conclusions: A sequential approach for the etiological diagnosis of unidentified hearing loss could determine or suggest a cause in more than 80% of patients. The approach may vary based on the presenting phenotype.

1. Introduction

Approximately 2–4 in 1000 children are born with sensorineural hearing loss (HL), making it the most prevalent birth defect [1,2]. This high prevalence, together with the early-onset HL among school-aged children and young adults, causes a substantial direct disease burden. Overall, the consequences of hearing impairment are highly underestimated [1–4]. Problems are not only linguistic, but also interfere with professional, social and psychological well-being. In order to minimize these effects, timely detection and effective intervention is desirable [5–7]. Furthermore, determination of the cause of HL enables counseling, customized intervention, and anticipation of possible associated comorbidities [2].

Unlike acquired HL, the relative proportions of the various causes of congenital HL are well established. More than 50% of congenital HL is hereditary [1,2,8,9] of which the majority (2/3) is non-syndromic. The pattern of inheritance is autosomal recessive (AR) in 75% of these hearing losses. More than 50% of the AR non-syndromic losses are due to a mutation in the *GJB2* gene, encoding Connexin 26 (Cx26) [1,10,11]. Regarding syndromic HL, some authors cite Waardenburg syndrome as the most prevalent otogenetic syndrome [12,13], while others define Pendred syndrome (*SLC26A4* gene defect) as the most frequent [1]. Besides a genetic origin, environmental factors account for the remaining

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; BOR syndrome, branchio-oto-renal syndrome; CMV, cytomegalovirus; Cx26, connexin 26; ECG, electrocardiography; EVA, enlarged vestibular aqueduct; HL, hearing loss; MIDD, maternally inherited diabetes and deafness; MT, mitochondrial.

* Corresponding author. Tel.: +0032 9 332 23 32; fax: +0032 9 332 49 93.
E-mail address: Els.DeLeenheer@UGent.be (Els M.R. De Leenheer).

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Table 1
Neonatal risk indicators associated with sensorineural and/or conductive hearing loss [6].

1. Family history of childhood congenital hearing loss
2. Congenital infections such as the TORCH (Toxoplasmosis, Rubella, Cytomegalovirus, Syphilis, and Herpes)
3. Craniofacial anomalies, including morphological abnormalities of the pinna, ear canal, nose, and throat
4. Birth weight less than 1500 g
5. Hyperbilirubinemia requiring exchange transfusion
6. Ototoxic medications, including but not limited to aminoglycosides, used in multiple courses or in combination with loop diuretics
7. Bacterial meningitis
8. APGAR scores of 0–4 at 1 min or 0–6 at 5 min
9. Mechanical ventilation for 5 days or longer, ECMO, or persistent pulmonary hypertension
10. Stigmata or other findings associated with a syndrome known to include sensorineural and/or conductive hearing loss

causes of HL. Within these causes, we distinguish congenital infections as cytomegalovirus (CMV), rubella and syphilis, and other risk factors such as ototoxic medication, hypoxia during birth, birth weight <1500 g, and hyperbilirubinemia [14,15]. Of course, several factors can be involved simultaneously, and the most prevalent causes differ according to the studied age and region. Nevertheless, HL remains idiopathic in 25% of the cases [1,2].

In the diagnostic work-up, history taking, physical examination, and more extensive audiometric testing are routinely performed. Case history usually implies a pedigree analysis, focus on pregnancy/birth/development, and considering risk factors for HL [16]. However, without additional testing, the etiology of about 80% of HL remains uncertain [17]. Consequently, additional diagnostic tests are imposed, of which genetic testing, imaging and ophthalmologic examination are most frequently performed.

Several studies examined the optimal use of the large range of diagnostic tests [3,12,17–22]. These have shown that sequential decision-making is recommended, instead of performing all tests simultaneously. This study aims to describe the etiological approach of HL in a quite unique population: patients exhibiting HL at young age without clear cause (e.g. meningitis, ototoxic medication, congenital HL due to congenital CMV infection,... are already excluded). A specific otogenetic consultation with an otorhinolaryngologist and a medical geneticist has been established for these patients, who are often referred to our tertiary center. Inherent in the name of the consultation, the population mainly consists of patients with HL of presumably genetic origin, as several obvious environmental causes have already been excluded in advance.

2. Materials and methods

The study patients were recruited from the consultation for otogenetics at Ghent University Hospital (Belgium), during the period July 2006–May 2012. Inclusion criteria were the presence of confirmed HL and established diagnostic work-up, regardless of the type of HL or demographic features of the patients. Of the 356 patients attending the consultation, 53.7% (n = 191) met these inclusion criteria. The remaining patients were only looking for counseling or proved to have a more straightforward cause of hearing loss (e.g. inflammatory), and thus did not need a thorough etiological work-up. A retrospective chart review of the included patients was performed in search for demographic and audiometric features, utilization of diagnostic tests, their results, and etiology of HL. Data processing and statistical analysis were performed with SPSS version 20.0 (SPSS Inc, Chicago, USA). For inferential statistics, Fisher's Exact, χ^2-test and Spearman correlation coefficient were used. The significance level was set at $P < 0.05$. Approval by the Ethics Committee of the Ghent University Hospital was obtained. The HL was established by several audiometric techniques, depending on the patient's age. HL was classified into mild (26–40 dB), moderate (41–55 dB), moderate severe (56–70 dB), severe (71–90 dB) and profound (>90 dB). In case of asymmetric bilateral HL (in which both ears demonstrate a hearing threshold of >25 dB but are classified in another severity category), the best hearing side was used for statistical analysis. In unilateral HL, however, the affected ear was used. The threshold separating pre- and postlingual HL was set at 4 years of age. The risk factors for congenital HL, defined by the Joint Committee on Infant Hearing (JCIH) in 2007 (Table 1) supplemented with some environmental risk factors such as noise exposure [6] were systematically assessed. Even if no molecular confirmation could be established, HL was considered syndromic if it was associated with certain comorbidities, dysmorphic features and/or a positive family history for a known otogenetic syndrome. Familial involvement was assessed by history and pedigree drawing.

Not all etiological tests were performed in every patient. The sequential approach of etiological testing, based on available literature and our own experience, is shown in Fig. 1. A diagnosis was made by a combination of the different clinical and testing results. Factors influencing the choice for a specific test and factors influencing the retention of a certain diagnosis were considered

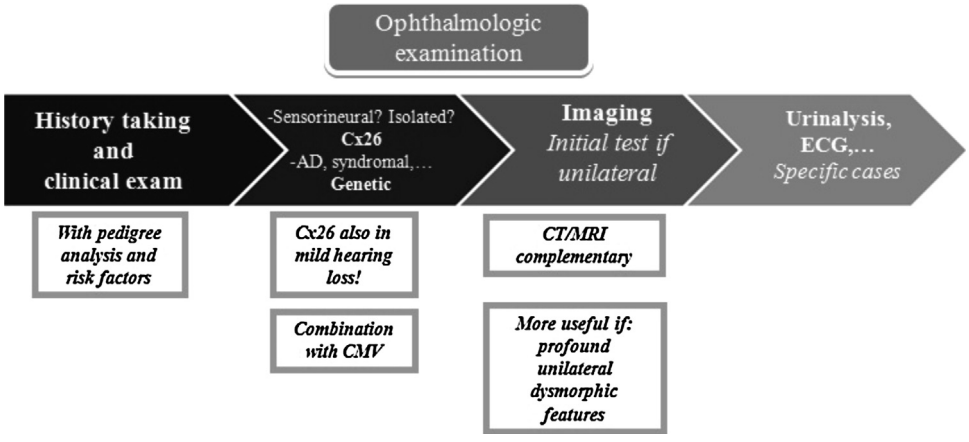

Fig. 1. Flowchart of the etiological diagnosis of hearing loss.