

Aetiological Diagnosis of Childhood Deafness: 2015 CODEPEH Recommendations

Diagnóstico etiológico de la sordera infantil: Recomendaciones CODEPEH 2015

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ABSTRACT

The important breakthrough in the field mainly of molecular genetics and in the field of diagnostic imaging, together with the lack of a consensus protocol for guiding diagnostic process after confirmation of deafness by neonatal screening, have led to this new document drafted by the Commission for the Early Detection of Infant Deafness (CODEPEH). This 2015 Recommendations Document, which is based on the most recent scientific evidence provides guidance to professionals in order to support them in decision making regarding aetiological diagnosis. This aetiological diagnosis should be performed without hindering or delaying early care. Early identification of the causes of deafness offers many advantages: prevention of unnecessary troubles to the families; reduction of health system expenses caused by performing different tests; and provision of prognosis information which may guide therapeutic actions.

KEY WORDS

Deafness, Diagnosis, Aetiology, Genetics, Hearing Loss, Early Care

RESUMEN

El importante avance en el campo de la genética molecular, fundamentalmente, así como en el diagnóstico por imagen, junto a la ausencia de un protocolo consensuado que oriente el proceso diagnóstico una vez confirmada la presencia de una sordera tras el cribado neonatal, motivan este nuevo trabajo de la Comisión para la Detección Precoz de la Sordera Infantil (CODEPEH). El Documento de Recomendaciones 2015, que se basa en la más reciente evidencia científica, ofrece orientaciones de apoyo al profesional en la toma de decisiones en relación con el diagnóstico etiológico que, en todo caso, debe llevarse a cabo sin entorpecer ni retrasar la intervención temprana. Identificar precozmente la causa de la hipoacusia aporta numerosas ventajas: evita molestias innecesarias a las familias, reduce el gasto sanitario derivado de la realización de numerosas pruebas y proporciona información pronóstica, que puede guiar la actuación terapéutica.

PALABRAS CLAVE

Sordera, Diagnóstico, Etiología, Genética, Hipoacusia, Atención Temprana

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INTRODUCTION

The importance of early diagnosis of hearing loss has been recognised for decades, both scientifically and empirically, for decades.

Today, many countries have rolled out universal newborn hearing screening programmes for hearing loss in line with the recommendations of the Joint Committee on Infant Hearing (2007: 120: 898-921), which establishes that detection should not be delayed beyond the first month of life and that diagnostic confirmation should be available in the third month of life to ensure that children receive adequate treatment before six months, since the main objective is to achieve the acquisition of spoken language and the maximum development of children with a hearing deficit at all levels: personal, cognitive, educational and social. As part of this process, the need for an aetiological diagnostic protocol has become one of the main focuses of interest of the professionals involved.

The boundary between genetic and environmental hearing loss is not clearly defined. Although it is estimated that 60% of early-onset deafness is of genetic cause and 40% environmental, the presence of one of the latter causes does not exclude the existence of a genetic predisposition (Kochhar et al., 2007: 9: 393-408) (Cabanillas and Cadiñanos, 2012: 63: 218-29). In a study conducted in newborns with confirmed hearing loss (Declau et al., 2008: 121: 1119-26), an aetiological factor was found in almost half of cases, of which more than 60% corresponded to genetic causes, 20.8% to perinatal problems and 18.8% to congenital cytomegalovirus infection.

An early identification of the cause of hearing loss has many advantages: it prevents costly and unnecessary testing, reduces the stress of the parents and the child, allows genetic counselling, if appropriate, and provides us with information about the prognosis, being able to identify and even anticipate potential co-existing medical problems. It also serves as a guide for successful therapeutic action.

At this point, as opposed to the practice of carrying out a battery of expensive tests simultaneously in every child with hearing loss, it is necessary to establish an algorithm that guides the professional to arrive at an aetiological diagnosis efficiently, bearing in mind that it must be carried out in a way that does not hinder or delay early intervention.

The CODEPEH therefore considers it necessary to make recommendations on the matter, given the important breakthroughs mainly in the field of molecular genetics, mainly, as well as in diagnostic imaging.

These recommendations are based on the latest scientific evidence and are intended to bring order to a process for which no consensus protocols are available, resulting in cases that remain undiagnosed, or the indiscriminate performance of numerous tests, causing unnecessary discomfort to children and their parents, as well as causing unjustified health expenses.

In short, this new CODEPEH Recommendations Document 2015 aims to provide guidelines to support professionals in decision-making during the process of aetiological diagnosis, also aimed at preventing, as far as possible, the variability in clinical action observed and documented in other countries (Rangan et al., 2012: 2: e001174).

1. DIAGNOSTIC SEQUENCE

Proper aetiological guidance requires the thorough collection of family and personal history, including risk factors and a detailed physical examination, as well as additional tests, where necessary and in relation to these sections.

1.1. MEDICAL HISTORY AND PHYSICAL EXAMINATION

1.1.1. Family history

In order to collect data on the family history of the index case, it would be appropriate to be able to determine the family tree, taking into account that several premises must be met in order for it to be valid (Alford et al., 2014: 16: 347-55):

- attempting to collect data from three generations, with particular emphasis on first-degree relatives (and any otologic and audiologic examinations performed on them should be recorded).
- taking into account factors such as the dynamism of family trees in terms of their periodic re-evaluation, as well as false paternities, adoptions, assisted reproduction techniques (egg/sperm donation) and/or the appearance of *de novo* mutations.
- collecting data on the pattern of inheritance, consanguinity, ethnicity and country of origin.

1.1.2. Personal history and risk factors

Data on the health of both the mother and the father should be collected in the clinical history. Information on pregnancy, childbirth and the neonatal period should be included.

• Perinatal and postnatal history

The collection of data on pregnancy in relation to exposure to medications, drugs and/or toxic substances should be emphasised (Dyer et al., 1998: 19: 671-8) (Takemori et al., 1976: 102: 425-7). It should also be borne in mind that one of the most common causes of deafness are pre- and perinatal infections (*Table 1*), which can be diagnosed in the mother, foetus or the newborn. Amongst these are some, listed below, which are studied and monitored during pregnancy, making it easier to suspect at birth and early diagnosis (Badia et al., 2014: 18: 356-66):

- **Toxoplasmosis:** this infection is asymptomatic in most pregnant women. The definitive diagnosis of maternal infection is the demonstration of immunoglobulin (Ig) G seroconversion during pregnancy. For the diagnosis of foetal infection, the polymerase chain reaction (PCR) of the suspected germ in amniotic fluid is determined.
- **Syphilis:** its diagnosis is serological, using non-treponemal and treponemal tests. *Treponema pallidum* can be detected in amniotic fluid for prenatal diagnosis of congenital infection.
- **Rubella:** the diagnosis of maternal infection consists of checking an increase in the IgG titre four times over its initial value, as well as the existence of rubella-specific IgM, or through the detection of the virus in urine or nasopharyngeal secretions by PCR. Virus culture has low sensitivity. Prenatal diagnosis is made by the detection of IgM in foetal blood (obtained after week 22), direct detection of the virus in chorionic villi, or PCR in amniotic fluid.

- **HIV:** screening can be performed using rapid techniques, such as chemiluminescence to detect the HIV 1-2 antigen-antibody, and positive or doubtful tests with Western Blot are confirmed in the newborn. In case of a positive result, the virus should be quantified by PCR in the blood.

There are other pre- and perinatal infections with a high incidence of deafness for which routine screening is not performed and, therefore, their suspicion depends on the symptoms presented by the foetus or newborn. This is the case for the following viruses:

- **Cytomegalovirus (CMV):** this virus is currently the most common cause of congenital infection and one of the causes of deafness that is sometimes postnatal and progressive. CMV is the cause of deafness in up to 10-20% of children with proven hearing loss, although in some studies this figure reaches 30% (Park et al., 2014: 124: 2624-9).

Most newborns are asymptomatic at birth. Approximately 10-15% of asymptomatic newborns will develop deafness. Some of them will have altered outcomes in the neonatal hearing screening process. Several studies identified up to 75% of children with congenital infection due to changes in the hearing screening process. A total of 9% had later-onset deafness (therefore they are not eligible for diagnosis within a neonatal screening programme), with this being progressive in 20% of cases throughout childhood (DemmlerHarrison, 2015; online) (Goderis et al., 2014: 134: 972-82).

In symptomatic cases, 30-50% will have deafness that can be detected at birth, but 18-30% will appear at a later stage, and it may be progressive in up to 63% of cases,

over the first 6 years of life, and becoming deep in 78% of them.

The risk of vertical transmission is much higher in the primo-infection than in recurrent infections (32% vs.1.4%), as is the severity of the symptoms.

CMV testing is indicated in breastfed babies with proven hearing loss. Its performance should also be assessed in asymptomatic cases with altered final results in the neonatal auditory screening process and referred to the otolaryngologist (ENT) for confirmation.

The deadline for safely diagnosing congenital infection is at 2-3 weeks of postnatal life. Within this time frame, performing a PCR of the germ in urine, saliva or blood is indicated. If the newborn is more than 2-3 weeks old, this PCR will not be decisive, so dried-paper PCR in the metabolic panel will have to be used to confirm this (Botet et al., 2015: 83: 69) (Escosa-García et al., 2015: 83: 70-1) (Gunkel et al., 2014: 61: 61-4) (Ross et al., 2015: 8: 903-5) (Cardoso et al., 2015: 48: 206-7) (Boppana et al., 2010: 303: 1375-82) (Koontz et al., 2015: 66: 95-9).

- **Herpes virus:** the diagnosis is made through viral culture and PCR determination of vesicles, conjunctiva, oropharynx, blood and CSF. Serology is of little value, although persistence of IgG for more than 6-12 months confirms neonatal infection. According to some studies, herpes can also cause deafness in the same way as CMV, although it appears to be more uncommon (Dahle and McCollister, 1988: 9: 256-8).

- **Neonatal chickenpox:** the diagnosis is clinical, but serological confirmation, IgG and IgM, with two samples, is recommended within 15 days. Specific PCR screening can also be performed on skin lesions. It rarely produces deafness.

- **Other germs:** it is worth remembering that mumps virus, West Nile virus, and many other germs can cause deafness in children (Cohen et al., 2014: 18: 1-17).

In addition to what has been described so far, **other risk history** must be considered, such as: head trauma, exposure to ototoxic and/or chemotherapy drugs, admission to intensive care (assisted ventilation, extracorporeal membrane ventilation, hyperbilirubinaemia with exchange transfusion, severe prematurity, perinatal hypoxia) other perinatal infections, including bacterial or viral meningitis, neurodegenerative diseases, craniofacial abnormalities and persistent otitis (Núñez et al., 2015: 3: 163-86).

- **Hearing evaluation**

Evaluation and classification of hearing loss according to the 2010 and 2014 CODEPEH Recommendations. (Trinidad et al., 2010: 61: 69-77) (Núñez et al., 2015:3: 163-86).

- **Alterations in other systems**

In addition to collecting the history and risk factors, it is also necessary to rule out the presence of other alterations such as the neurological, ophthalmological, vestibular, cardiological or other spheres, as well as data on psychomotor development.

1.1.3. Physical examination

Regarding the classification of hearing loss as syndromic or non-syndromic, there are several signs in the physical examination that should be recognised since they can point towards a certain type of syndrome, since it is estimated that up to 30% of hearing loss of genetic origin is syndromic (Alford et al., 2014: 16: 347-55).

Therefore, physical examination should focus on dysmorphic features and other clinical signs, such as the following (Pickett and Ahlstrom, 1999: 32: (1019-35):

- **General appearance** (*Table 2*)

Patient height, body physique, skin colouring, hair and skin lesions as well as craniofacial morphology should be collected.

- **Outer ear** (*Table 3*)

The size and morphology of the pinna, as well as the implantation site, should be examined. It is also important the existence of preauricular pits or appendages, in addition to aural atresia.

- **Eyes** (*Table 4*)

It is important to highlight in the physical examination the disposition of the palpebral fissures, the intercanthal distance, the morphology and colour of the iris and cornea, as well as visual acuity, without forgetting the ocular motor muscle (or musculature).

- **Mouth** (*Table 5*)

The existence of cleft lip or cleft palate are characteristics related to hearing loss.

- **Facies** (*Table 6*)

Many syndromes involve facial abnormalities associated with hearing loss, so data should be collected on facial morphology, bone and/or muscle development of the face, as well as nasal morphology.

- **Neck and limbs** (*Table 7*)

Data must be collected on the morphology and length of the neck, as well as its

mobility and the existence of masses. On the other hand, limb morphology and size are important.

1.2.ADDITIONAL TESTS

1.2.1. Genetic tests

Most congenital sensorineural hearing loss is nonsyndromic and has a genetic aetiology (Kochhar et al., 2007: 9: 393-408) (Vona et al., 2015), genetic testing is therefore the diagnostic test that has been shown to have the best performance (Lin et al., 2011: 32: 259-64) (Robin et al., 2005: 17: 709-12).

The aetiological diagnosis of genetic hearing loss is very complex and there are no standardised protocols (Lin et al., 2011: 32: 259-64).

Traditionally, genetic diagnosis has been based on Sanger sequencing, developed in 1975 and based on PCR (Sanger and Coulson, 1975: 94: 441-8). This highly sensitive and specific technique is the gold standard for analysing one or few genes, but its costs and timing make it impracticable to sequence dozens of genes simultaneously (Shearer et al., 2013: 50: 627-34). The technological development in recent years in the field of genomic sequencing has radically changed the genetic diagnosis of polygenic hereditary diseases, such as hearing loss.

This development, unprecedented in the history of molecular biology, makes possible today what was less than ten years ago a utopia: to sequence as many genes as you want (from a few dozen to the whole genome), in times and costs compatible with the care routine (Rehm, 2013: 14: 295300). This set of technologies, called Next Generation Sequencing (NGS), allows for three approaches to the diagnosis of hereditary diseases (Jamuar and Tan, 2015: 9: 10) (Atik et al., 2015: 97: e4): a)

whole genome (whole genome sequencing); b) exome (sequencing of the protein synthesis-coding portion of the genome, the exons); and c) gene panel (sequencing a set of genes associated with a specific disease).

Currently, in clinical practice, gene panels are considered the most appropriate methodology for the genetic diagnosis of deafness (Alford et al., 2014: 6: 347-55) (Shearer and Smith, 2015: 153: 175-82). The expected diagnostic yield of these panels is around 50% (Schrauwen et al., 2013: 161A: 145-52) (Shearer et al., 2013: 50: 627-34). This figure is highly variable, ranging from 13% to 100%, a difference conditioned by the methodology used and the population analysed (Gu et al., 2015: 87: 588-93) (Brownstein et al., 2011: 12: r89).

In the coming years, diagnostic rates are expected to increase as new genes are linked to the development of hereditary hearing loss (Atik et al., 2015: 97: e4).

When a diagnosis cannot be made by means of a panel, and an underlying genetic cause is still suspected, exomes are the appropriate tool to identify new genes involved in deafness (Vona et al., 2015) (Cabanillas et al., 2011: 155A: 2617-25). Today, exomes must be reserved for research because they are more expensive than panels, more difficult to interpret, and the results take longer to process (Shearer et al., 2013: 0: 627-34) (Jamuar and Tan, 2015: 9: 10). Another drawback of exomes is the fact that, as part of the analysis, variants can be detected in genes involved in diseases other than deafness (e.g. neurodegenerative diseases, hereditary heart diseases, etc.), generating difficulties in the genetic counselling of these patients (Green et al., 2013: 15: 565-74).

• Practical implications

If the history, examination and tests requested do not lead to the conclusion that hearing loss is acquired, or there is no clinical evidence to suspect it, confirmation of the genetic aetiology should be sought. This requires referring the patient to a genetic counselling consultation, according to the algorithm in *Figure 1* (Kochhar et al., 2007: 9: 393-408) (Robin et al., 2005: 17: 709-12) (Cabanillas and Cadiñanos, 2012: 63: 218-29).

In Spain, the law establishes the need for a genetic counselling process before and after any genetic test is performed, as well as the need for specific informed consent. In this situation, which must be part of the multidisciplinary team responsible for the care of the patient with deafness (Cabanillas and Cadiñanos, 2012: 63: 218-29), the characterisation of the hearing loss must be deepened to the extent possible. In cases where clinical evaluation suggests the possibility that a particular gene or set of genes may be responsible for the phenotype, a targeted genetic test may be requested (e.g., mitochondrial mutations in a compatible inheritance pattern and a history of aminoglycoside ototoxicity). Sometimes, when a syndrome is suspected that may be caused by several genes (e.g., Usher syndrome), it may be more cost-effective, in time and cost, to directly request NGS sequencing of a panel, including the genes of interest.

In most cases, it will not be possible to identify a candidate gene from the phenotype. Fortunately, at present, the advances in sequencing techniques, in the bioinformatic interpretation and the reduction in costs of the different steps make it possible to achieve a genetic diagnosis, independent of the phenotype, quickly, without the need for additional confirmatory testing (Rehm et al., 2013: 15: 733-47).

At this point, in order to minimise process costs, the recommended first step is to analyse the presence of mutations in the GJB2 gene and deletions in GJB6, given their high prevalence in our setting (Kenneson et al., 2002: 4: 258-74) (Schrauwen et al., 2013: 161A: 145 -52).

If it is not possible to identify the cause of deafness after analysis of these genes, the next step should be sequencing an appropriately selected panel of genes, using NGS (Alford et al., 2014: 16: 347-55) (Shearer and Smith, 2015: 153: 175 -82). When selecting the panel, attention should be paid to the genes included, their sensitivity and specificity, and their ability to detect variations in the number of copies.

It is important to keep in mind that a negative result only indicates that no mutation was found in the genes analysed, but it does not rule out the possibility that the cause of the deafness is genetic. It is essential that this information be properly conveyed to the patient and/or their family members (for example, it would not eliminate the risk of having more children with deafness).

Additionally, in cases where, after the appropriate diagnostic process, no cause of deafness has been identified, the patient and his/her relatives should be offered participation in research projects aimed at identifying new genes involved in hereditary hearing loss, by sequencing their exome. Likewise, periodic reviews (e.g., every 3 years) should be scheduled with the genetic counselling specialist. In this way, it will be possible to identify newly emerging syndromic features, which may not be evident at the time of the initial assessment. These reviews also offer the patient the possibility of performing new genetic tests or reinterpreting the results of those already performed, as knowledge advances.

1.2.2. Imaging tests

In the study of the aetiology of neonatal hearing loss, it is important radiological studies using computerised tomography (CT) and/or magnetic resonance imaging (MRI) (Lemmerling and De Foer, 2015), each of which provides different features for the study of the different pathological anatomical alterations in the outer, middle and inner ears, as well as in the central auditory pathways.

The temporal bone develops from the first and second branchial arch, giving way to the outer and middle ear. The inner ear will form from the auditory vesicle, which means that malformations of the two do not necessarily need to occur at the same time. In addition, malformations of the internal auditory canal (IAC) are not necessarily always related to malformations of the inner ear, although they can all be associated.

According to the references, 39% of children with hearing loss have some kind of malformation in the ear visible by CT scan, and between 21% and 33% are in the inner ear (Mafong et al., 2002: 112: 1-7).

- **Malformations** (*Figure 2*)

- **Outer Ear Malformations:** have an incidence of approximately 0.7 to 2.3 per 10,000 births. They are often unilateral and associated with various middle ear malformations, as well as multiple syndromes.
- **Middle Ear Malformations:** isolated malformations of the ear ossicles and the structure of the ear walls are most often associated with alterations of the external auditory canal (EAC), such as stenosis or atresia, and are uncommonly found alone. The ossicles with the most alterations are the anvil and the stirrup, with the hammer being the least frequent.

There is a condition called “late disappearance”, which occurs at 25 months of age, at which point the bone marrow is transformed into bone. In this case, the marrow is reabsorbed and gives rise to a large medullary cavity in the anvil and hammer. This usually occurs in Treacher-Collins syndrome and trisomy 13 (Sando et al., 1998: 16 (1): 1-22). Changes in the ossicular chain can be associated with changes in the facial nerve, mainly related to its position, being more frequently located across the oval window and fixed to the abutment stirrup or together with congenital absence of the oval window, although isolated atresia may occur.

Congenital cholesteatomas can also be found.

- **Inner Ear Malformations:**

- *Vestibular aqueduct abnormalities*

The vestibular aqueduct is one of the last structures to develop in the inner ear. It is the most common cause of inner ear malformations in children, accounting for 42.9% of cases (Deklerck et al., 2015: 79: 216-22).

It is considered dilated when it measures more than 1.5 mm, which occurs when it is larger than the diameter of a normal posterior semicircular duct (*Figure 3*). Since the inception of high-resolution CT, it has been shown that it very commonly coexists with other cochlear alterations, in up to 100% of cases according to different series (Casselmann et al., 1996: 38 (3): 278-86).

- *Cochlear aqueduct anomalies*

They are very rare.

■ *Cochlear anomalies*

Classically they were classified as Michel aplasia, Bing Siebenmann Aplasia, Mondini Aplasia, Scheibe Aplasia and Alexander Aplasia (Valvassori et al., 1969: 78: 929-38). Some authors think that they can be reduced to those of Scheibe and Mondini, but there are numerous alterations that do not fit into any of these dysplasias.

Scheibe dysplasia is the most common amongst those of the inner ear. Lesions are found in the saccule and cochlea, with atrophy of the stria vascularis, deformation of the tectory membrane and poor differentiation of the Organ of Corti, collapsing the Reissner's membrane.

The Mondini alteration consists of the absence of development of one of the turns, hypoplasia of the modiolus and absence of the interstellar septum. It occurs due to an embryo developmental arrest in the seventh week of gestation.

■ *Bony or membranous labyrinth anomalies*

Malformation of the horizontal semicircular duct is the most frequent alteration within this group. That of the other isolated ducts is rare without association with that of the horizontal semicircular duct.

The most severe malformations of the semicircular ducts are usually associated with a dilated vestibular aqueduct and result in a semicircular ductal cavity with the utricle and saccule, absorbing one or all of the semicircular ducts. These alterations may be unilateral or bilateral and, if they exist, they do not always give rise to hearing loss, and may cause asymmetric hearing loss.

Superior canal dehiscence can also be found.

Isolated lesions of the utricle, saccule and vestibule are rare.

In addition to the different classifications of the cochlea, there are other classifications that cannot be classified, such as dwarf or hypoplastic cochlea with normal number of turns. There may be complete aplasia, a common cavity, or hypoplasia associated or not with semicircular alterations.

■ *Internal auditory canal anomalies*

An IAC calibre of less than 2 mm is considered pathological, and may be stenotic, atresic or divided by bony septae. IAC disorders may also be associated with aplasias, hypoplasias, or duplication of the facial nerve.

Acquired lesions may include tumour lesions such as neurofibromatosis type 2.

Cochlear nerve aplasia is the most common cause in unilateral sensorineural hearing loss in children, with tumour lesions occurring infrequently (Laury et al., 2009: 417-27) (Bockmühl et al., 2001: 574-81).

Central lesions alone or associated with lesions of the cochlear and facial vestibular nerve are rare and identifiable by MRI (Singh et al., 2015: 1038-43).

• **Techniques**

We mainly have two imaging techniques for the study of congenital infant hearing loss, such as CT and MRI, though other techniques should be considered, such as positron emission tomography (PET), which provide us with functional images that, in certain cases, may be important when making therapeutic decisions.

CT is currently used primarily for the diagnosis of middle and outer ear malformations. Two types are available:

- Multi-slice CT (MSCT), for single-plane image acquisition.
- Cone Beam CT (CBCT), which can obtain 3D data and perform reconstructions on any plane. In recent years this type of CT has become the technique of choice, because the exposure time is shorter, it has higher spatial resolution and the radiation to which the child is exposed is lower. One inconvenience is its greater sensitivity to the patient's movement.

MRI is used for the diagnosis of the inner ear, the cerebellopontine angle and the brain, as well as for the diagnosis of cholesteatoma of the middle ear. There is no consensus to select the type of sequences for diagnosis of temporal bone lesions.

1.2.3. Laboratory tests

In the aetiological study of deafness, and always after a proper history and a complete physical examination is performed, laboratory testing can be used to confirm or support the hypotheses arising from the first aetiological approach.

In addition to the search for infectious agents described above, there are other laboratory examinations useful in the diagnosis of deafness, such as:

- in suspicious cases, thyroid metabolism should be measured in older children related to Pendred syndrome.
- it is important to check (if recorded in the history) the levels of ototoxic medications (e.g., aminoglycosides/vancomycin) in the cases of newborns treated with them.
- a urine test in older children may be useful in relation to Alport Syndrome.
- other tests, such as insulin resistance, related to Wolfram syndrome, or the study of renal and parathyroid function

in hypoparathyroidism and sensorineural deafness syndrome together with renal disease (HDR syndrome), amongst others, should be guided by clinical suspicion.

1.2.4. Other tests: cardiological evaluation

Related to long QT syndrome, Jervell and Lange-Nielsen Syndrome (JLNS) is an autosomal recessive variant of congenital long QT syndrome (SQT), characterised by severe-deep bilateral sensorineural hearing loss, long QT interval on electrocardiogram (ECG), and ventricular tachyarrhythmias.

The prevalence is unknown and varies according to the population studied (1:200,000-1:1,000,000). Almost 50% of patients become symptomatic before 3 years of age.

The typical presentation of JLNS is a deaf child with syncopal episodes during periods of stress, exercise or fear. Deafness is congenital, bilateral, deep and sensorineural. The QT interval in JLNS is markedly prolonged (>500 msec) and is associated with tachyarrhythmias that may cause syncope or sudden death. JLNS is caused by compound homozygous or heterozygous mutations in either the KCNQ1 gene (locus LQT1; 11p15.5) or the KCNE1 gene (locus LQT5; 21q22.1-q22.2), and is inherited in an autosomal recessive manner (Crotti et al., 2008: 3:18).

1.2.5. Ophthalmological evaluation

One third of children with hearing loss have changes in the ophthalmologic examination that may also contribute to the aetiological diagnosis of deafness, so this assessment should always be performed.

2. DISCUSSION

This document proposes a protocol designed as a guide to help and assist professionals in establishing the cause of confirmed hearing loss in children.

A sequential approach is proposed for the aetiological diagnosis of hearing loss according to the most prevalent causes. Figure 4 shows an inverted pyramid, with different blocks where the different diagnostic tests are found. The size of each block represents, on the one hand, the diagnostic yield of the test (meaning the proportion of relevant results) and, on the other hand, the volume of children to be studied using that method.

The approach begins with actions and tests in the **FIRST DIAGNOSTIC LEVEL**: clinical history and physical examination.

The family history and risk factors for hearing loss are assessed, for which an accurate medical history is essential, as well as the generation of a detailed family tree, whenever possible, and the physical examination of the patient in search of signs or stigmas suggesting different syndromes. Without doubt, the inclusion of data on perinatal and postnatal history (with special attention to risk factors for hearing loss) is essential to achieving, in this block, the highest diagnostic yield of the entire test sequence. The expected yield is 41% for family history, 65% for risk factors for hearing loss, and 21% for examination for craniofacial anomalies and stigmas of syndromes (Deklerck, 2015: 79: 216-22).

The **SECOND DIAGNOSTIC LEVEL** corresponds to the performance of different modalities of genetic tests. The extreme genetic heterogeneity of deafness has historically been a challenge in integrating genetic diagnosis into clinical practice. However, the benefits of obtaining an aetiological diagnosis are unquestionable, since it provides us with prognostic and reproductive information,

helps reduce anxiety in the patient and their relatives, allows us to rule out or predict potentially serious syndromic manifestations, avoids unnecessary diagnostic tests and is sometimes useful in making therapeutic decisions (Robin et al., 2005: 17: 709-12) (Cabanillas and Cadiñanos, 2012: 63: 218-29) (Palmer et al., 2009: 149A: 1169-82).

This latter point is increasingly relevant, both because of the influence that certain genetic alterations may have on the yield of the cochlear implants, and because genetic diagnosis is the first step in accessing future targeted pharmacological interventions to possible gene and cell therapy options (Muller and Barr-Gillespie, 2015: 14: 346-65) (Yu et al., 2014: 21: 71-80), options that have already borne fruit in hereditary blindness (MacLaren et al., 2014: 383: 1129-37) (Jacobson et al., 2015: 372: 1920-6).

More than 80 genes and more than 1,000 different mutations are known to cause non-syndromic sensorineural hearing loss (Shearer and Smith, 2015: 153: 175-82).

In our setting, mutations in the GJB2 gene and deletions in the GJB6 gene together constitute the most common cause of hereditary hearing loss (Gallo-Terán et al., 2005: 56: 463-8) (del Castillo et al., 2005: 42: 588-94).

Changes in these genes account for between 10% and 50% of cases of deafness of genetic origin, depending on the study population and the clinical characteristics of the patients evaluated (Kenneson et al., 2002: 4: 258-74) (Schrauwen et al., 2013: 161A: 145-52). Therefore, the analysis of the GJB2 and GJB6 genes is an essential element of the diagnostic process of infant hearing loss (Alford et al., 2014: 16: 347-55). The remaining cases are the result of mutations in dozens of different genes, each responsible for a small percentage of families (Schrauwen et al., 2013: 161A: 145-52) (Vona et al., 2014: 16: 945-53). These cases would be eligible for broader techniques such as gene panels conducted with next-generation sequencing (NGS) studies.

Specialists requesting NGS studies must necessarily be familiar with the limitations of this technology and therefore select the most appropriate methodology (Jamuar and Tan, 2015: 9: 10). The genes included, the sensitivity and specificity of the panel, and its ability to detect variations in the number of copies, are the variables that must be taken into account when requesting and evaluating the results of a particular panel (Shearer and Smith, 2015: 153: 175-82) (Rehm et al., 2013: 15: 733-47).

Knowing the genes that have been analysed in the requested panel is crucial to understanding the scope of a negative test. The design of a panel can range from a few dozen genes associated with non-syndromal sensorineural hearing loss, to hundreds of genes responsible for different syndromes, or even genes whose association with deafness in humans is still under study.

At this time, there is no consensus on which genes should be included in a panel for the diagnosis of hereditary hearing loss, or which syndromes should be part of it (Shearer and Smith, 2015: 153: 175-82). This causes the number of genes in the different panels to range from a few dozen to more than 200.

However, there is a consensus that, in order to maximise the diagnostic yield of panels, at least the most common variable expressive syndromes should be included (Alford et al., 2014: 16: 347-55) (Behar et al., 2014: 18: 123-6) (Lu et al., 2014: 59: 599-607). It should not be forgotten that approximately 30% of sensorineural hearing loss is syndromic in nature and, in some syndromes, non-audiological signs and symptoms can be very subtle, especially during the first years of life. Even mutations in genes associated with syndromes such as Usher, Wolfram, Stickler or Pendred may not have syndromic manifestations (Wei et al., 2012: 413: 1866-71) (Young et al., 2001: 10: 2509-14). Moreover, at times, genetic diagnosis may be the only indication of life-threatening syndromes, such as that of Jervell Lange-Nielsen, which, occasionally,

may present electrocardiographic readings of normal appearance (Tekin et al., 2014: 87: 190-1).

On the other hand, the selected panel should be subject to continuous review as 1 or 2 new genes are discovered each month, the mutations of which may cause perceptive deafness. In fact, over the past five years, more than 25% of the genes currently involved in sensorineural hearing loss were discovered using NGS technology (Atik et al., 2015: 97: e4).

It is necessary to take into account that there are different methodologies, both when isolating the genomic regions to be analysed and for their sequencing. While the sensitivity and specificity of Sanger sequencing is excellent and considered as a reference standard, NGS should be compared for each panel, with >99% being possible. Therefore, the panel selected should ensure values of sensitivity and specificity equivalent to those of sequencing (Schrauwen et al., 2013: 161A: 145-52) (Shearer et al., 2013: 50: 627-34) (Shearer et al., 2010: 107: 21,104-9).

Another variable that is becoming increasingly important is the ability of analysis to detect not only point mutations, but also variations in the number of copies of the genes studied. At least 15% of mutations capable of causing hearing loss are the result of large deletions or amplifications, variants that are not detected by Sanger sequencing and that require specific NGS techniques to be identified (Rehm et al., 2013: 15: 733-47) (Ji et al., 2014: 14: 9) (Shearer et al., 2014: 6: 37).

In the absence of mutations, after a suitable genetic testing, the possibility of requesting additional tests (imaging, electrocardiogram, ophthalmological evaluation, vestibular tests, microbiological and autoimmunity studies, etc.) should be considered.

Currently, given the low diagnostic yield of the additional tests, their possible disadvantages (pain, sedation, irradiation, use of contrast media...) and the efficiency of the

genetic tests, the indication for non-genetic tests should be assessed individually in each case and, unless a well-defined clinical suspicion is present, they should be postponed until the results of the genetic tests are obtained (Lin et al., 2011: 32: 259-64) (Alford et al., 2014: 16: 347-55) (Madden et al., 2007: 133: 162-8) (Chiang, 2004: 2: 222-34).

In this regard, and if no longer available, there is a recommendation to carry out, in combination with genetic tests, the study of cytomegalovirus (CMV) infection, since this virus is one of the most common causes of deafness, which is sometimes postnatal and progressive, and its detection is not included in the regular monitoring of pregnant women.

It should be noted that CMV infection does not necessarily rule out the possibility of simultaneous genetic alterations related to hearing loss, as some studies have shown (Karlton et al., 2012: 101: e357-62) (Lim et al., 2013: 22: 209-15) (Teek et al., 2013: 58: 419-28) (Schimmenti et al., 2011: 13: 1006-10).

As in congenital infection, the diagnosis of CMV infection is based on the isolation of the virus or the identification of its genome by PCR in various biological samples (Alarcón and Baquero-Artigao, 2011: 74: 52.e1-52.e13) (Badia, 2014: 18: 356-66) (De Vries et al., 2013: 56: 113-7).

The advantage of PCR is the small amount of sample required, as well as the short time required to obtain the results (24-48 h).

Simple urine amplification methods have even been developed, which take only one hour to obtain results, allowing for the immediate diagnosis of the patient and could be very useful in the study of newborns with alterations in their hearing screening, performed with evoked potentials (Kohda et al., 2014: 208: 160-5).

The diagnosis of CMV may be of particular interest in children who fail neonatal screening and are referred to the ENT for confirmation before 2-3 weeks of life, since most studies have concluded that the start of treatment

for CMV is effective if it is started before one month of life and lasts several months, at least between 6 and 12 months (Choi et al., 2009: 28: 1095-8).

Recently, data have been published showing that CMV screening in saliva targeting newborns with altered neonatal auditory screening is cost-effective, saving more than 50% of expenditure (Williams et al., 2015: 100: F501-6) (Williams et al., 2014: 99: F230-6) (Kadambari et al., 2013: 102: 928-33).

The recommendation for universal screening for CMV infection in urine (more accurate) or saliva (more feasible) is under discussion (Kadambari et al., 2015: online) (Barkai et al., 2014: 60: 361-6) (Cannon et al., 2014: 24: 291-307) (Botet et al., 2014: 81: 256.e1-4), based on the high prevalence of infection and the possibility of improving prognosis with appropriate management and treatment (Kimberlin et al., 2015: 372: 933-43).

Universal CMV screening would allow for the detection of newborns who are not susceptible to diagnosis because they are asymptomatic who have a normal first hearing screening and may have subsequent deafness (Toumpas et al., 2014; online).

Unlike congenital CMV infection, acquired infection in the newborn and breastfed baby does not appear to be associated with deafness or long-term neurodevelopmental alterations. Hence the importance of accurate identification of the time of infection with PCR detection in biological samples from the first three weeks of life or in the dry blood of the sample for the metabolic panel, although its sensitivity is lower (approximately 35%), meaning a positive result would confirm the infection, but a negative one would not completely rule it out (Demmler-Harrison, 2015: online) (Smiechura et al., 2014: 68: 303-7) (Nuñez-Ramos et al., 2013: 31: 93-6). Not all authors agree on the innocuousness of postnatal infection; therefore, prolonged follow-up of infected children at any age is recommended (Çelikel et al., 2015: 32: 259-64).

Although the pharmacological treatment is debated, the simple awareness of the infection allows for the adequate follow-up of these children and the possibility of early diagnosis of deafness, which optimally allows for the most appropriate audiological treatment.

Since CMV deafness occurs in symptomatic and asymptomatic children, and is fluctuating and often postnatal, these children should be monitored for at least 6 years with more frequent check-ups in those most affected.

Vaccines are being developed for CMV that could change the current situation of this disease (Wang and Fu, 2014: 6: 13-23) (Schleiss, 2013: 8: 1161-82).

The **THIRD DIAGNOSTIC LEVEL** corresponds to imaging tests.

It is becoming more common for children to undergo CT examinations for a variety of reasons, which increases their risk of developing cancer throughout their lives. The risk of developing cancer from exposure to head CT in a one-year-old child is estimated to be 0.07%. Although apparently low, an estimated 500 children die each year in the United States from radiation from CT scans performed before the age of 15. (Brenner et al., 2001: 176 (2): 289-96). (Thomas et al., 2006: 36: 823-32) (Lee et al., 2004: 231: 393-98).

It is very important to realise that when making a diagnosis in children, we must choose the imaging technique well to avoid side effects that, although uncommon, can cause mortality in a non-negligible number of cases (Lee et al., 2004: 231: 393-98).

It should be borne in mind that many of the children with hearing loss also have other additional pathologies that also require radiological studies. In these cases, an attempt should be made to improve coordination so that the different professionals caring for the child take advantage of this moment to perform them together, especially if they are to be performed in the same body area. In addition, the test that provides the most information

and the best quality CT scan should be determined to reduce radiation and the number of repetitions due to doubts on the diagnosis.

It should be stressed that if a test is performed it must be to guide a diagnosis, a prognosis and, above all, a treatment, so the appropriate age must also be chosen in relation to the objectives, causing the least harm to the patient.

The older the child, the lower the risks due to radiation, so for middle and outer ear malformations, the CT should ideally be postponed until 3 or 4 years of age. And, in sensorineural hearing loss, always start the study with an MRI.

It should also not be forgotten that young children need sedation for these tests, with the risks and discomforts involved (American Academy of Pediatrics, 2006: 118: 2587-602).

The **FOURTH DIAGNOSTIC LEVEL** consists of laboratory testing and other additional examinations.

These include laboratory tests to confirm clinical suspicions and associated syndromes, as well as electrocardiogram (ECG) in patients with arrhythmias or syncope.

In addition to the above, and given its relevance, it is important to highlight the need for adequate and complete ophthalmological examination in all cases, since one third of children with hearing loss have alterations in this examination that, on the other hand, can guide the aetiology of deafness.

3. 2015 CODEPEH RECOMMENDATIONS

The recommended sequence for the aetiological diagnosis of child deafness (*Figure 4*), according to the different levels of diagnostic cost-effectiveness, from the highest to lowest, is as follows:

FIRST DIAGNOSTIC LEVEL. MEDICAL HISTORY AND PHYSICAL EXAMINATION

- Formulate a detailed family tree using family history.
- Collect data on risk factors for hearing loss.
- Take into account, within the complete physical examination, data on the stigmas related to syndromic hearing loss.

SECOND DIAGNOSTIC LEVEL. GENETIC TESTS AND CYTOMEGALOVIRUS

- If the first diagnostic level does not provide conclusive information on the aetiology of the hearing loss or there is no clinical evidence to suspect it, the genetic aetiology must be sought, according to the algorithm in Figure 1.
- Refer the patient to a genetic counselling consultation.
- In order to minimise process costs, the recommended first step is to test for the presence of mutations in the GJB2 gene and deletions in GJB6.
- If the cause of deafness cannot be identified after testing these genes, the next step should be sequencing a panel of genes.
- Offer the patient and their relatives access to exome sequencing, aimed at identifying new genes involved in hereditary hearing loss, in cases where, after the appropriate diagnostic process, no cause of deafness has been identified.
- Do not forget that a negative result only indicates that no mutation has been detected in the genes analysed, and does not exclude the possibility that the cause of deafness is genetic.
- Check the patient's history for previous CMV-positive PCR tests within the first three weeks of life, which would define the presence of congenital infection.
- The blood collected for the genetic test can be used for the PCR test for CMV infection as well, if this has not been able to be determined previously, being mindful that from 2-3 weeks of life a positive result for the presence of the virus has an uncertain value for the diagnosis of congenital infection.
- In cases of positive detection, the study of congenital infection due to CMV should be completed by PCR in stored biological samples from the first three weeks of life or in the dried blood sample from the newborn metabolic panel test, if available.
- The usefulness of initiating treatment with Valganciclovir should be considered in such cases.

If confirmation of congenital infection is not possible, the diagnosis will be presumed and will be based on additional compatible clinical signs (eye, brain, haematological problems...) in the opinion of the physician, who will decide the approach to follow.
- Follow-up congenital CMV-infected children for at least 6 years with more frequent check-ups of those most affected, since congenital CMV deafness, which occurs in both symptomatic and asymptomatic children, is fluctuating and often postnatal.

THIRD DIAGNOSTIC LEVEL. IMAGING TESTS

- Both CT and MRI are appropriate and, in different situations, complementary methods for the aetiological diagnosis of infant hearing loss.
- Consider the technique that involves minimal radiation for the patient when choosing the type of test to be applied in the diagnostic process.
- Take into account the age of the patient and the best time to perform the tests.

In malformative pathology of the outer ear and middle ear, the technique of choice is CT. It is advisable to wait until 3 years of age as long as it is not required for another reason. Cone Beam CT is the best choice as it emits minimal radiation and is very efficient for diagnosis.
- MRI is the technique of choice in the malformations of the inner ear, IAC and brain. Considering that inner ear lesions are the most common cause of infant sensorineural hearing loss, MRI should be the first imaging test.

FOURTH DIAGNOSTIC LEVEL. LABORATORY TESTING AND OTHER TESTS

- Evaluate the use of a thyroid hormone test, urinalysis, or other laboratory testing designed to detect specific syndromes, as clinically suspected.
- Assess ECG in deaf children with syncope or other manifestations suggestive of cardiac disease.

OPHTHALMOLOGICAL EXAMINATION

Additional ophthalmological examination is always necessary, which can also explain specific infections or syndromes associated with deafness.

4. FIGURES AND TABLES

Figure 1. Proposed algorithm for the Genetic Diagnosis of Infant Sensorineural Hearing Loss. (NGS, next generation sequencing)

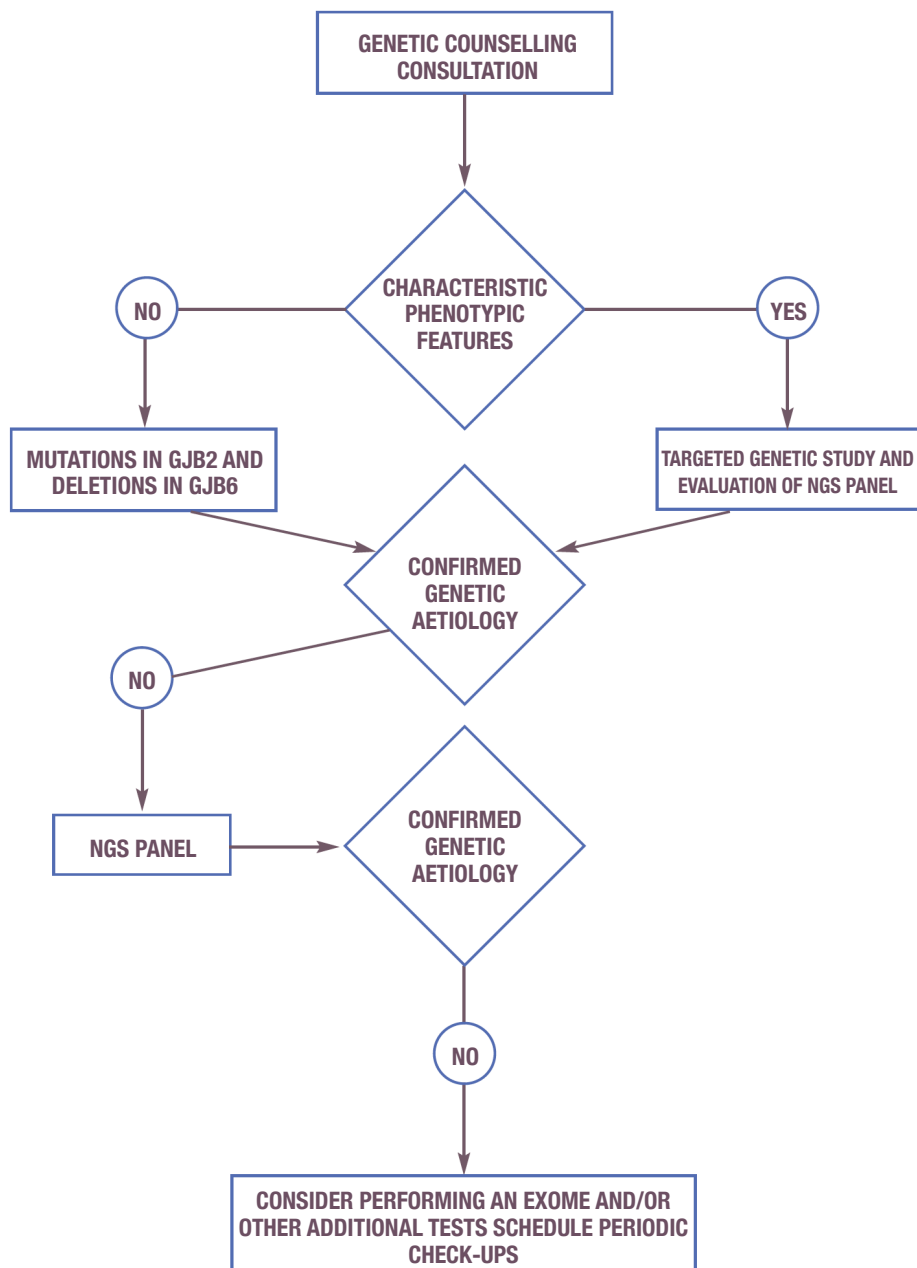


Figure 2. Diagnostic Imaging Flow Chart

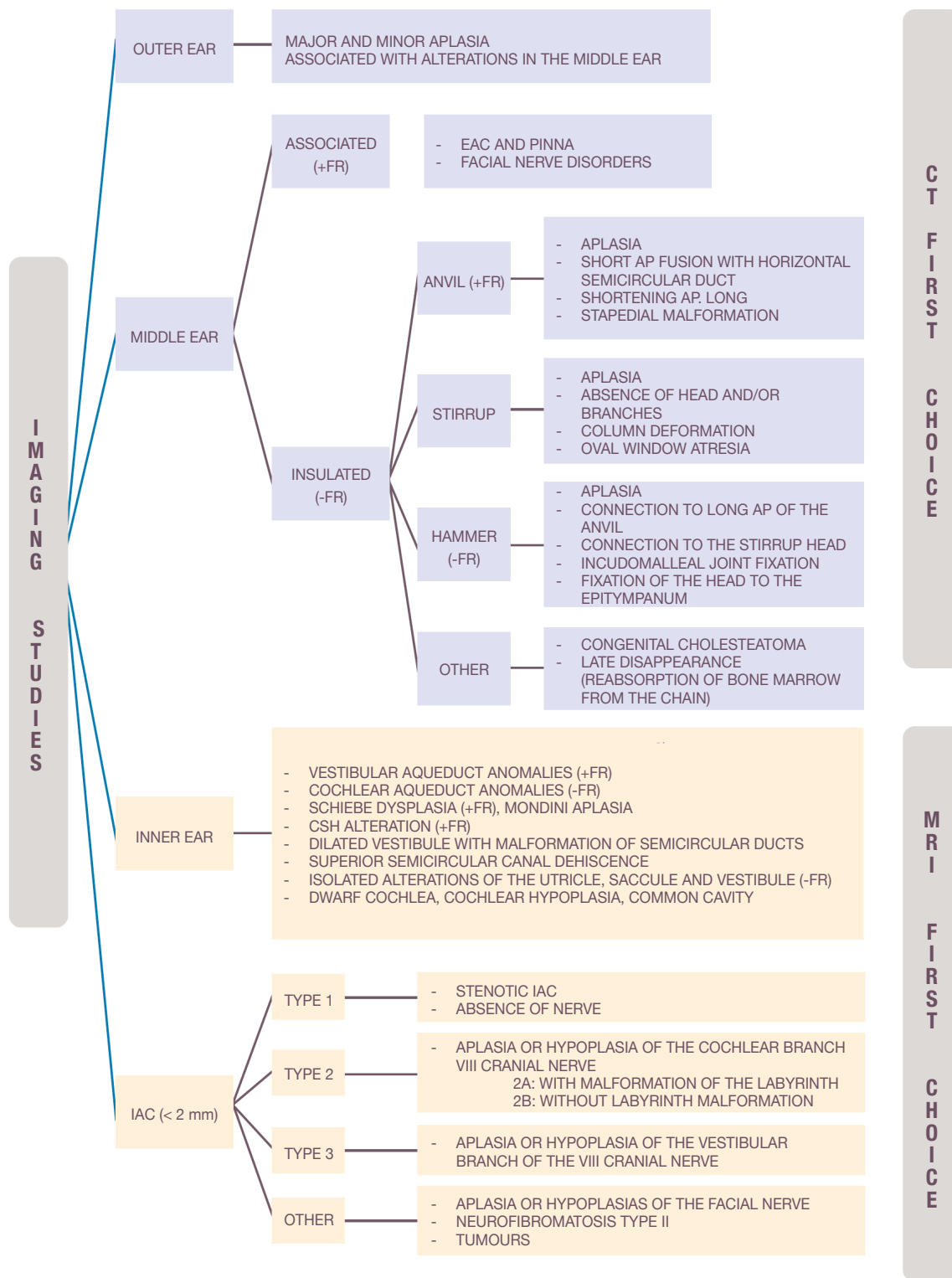


Figure 3. Dilated Vestibular Aqueduct



Figure 4. CODEPEH-recommended sequence for Aetiological Diagnosis (Diagnostic cost-effectiveness levels, ordered from highest to lowest)

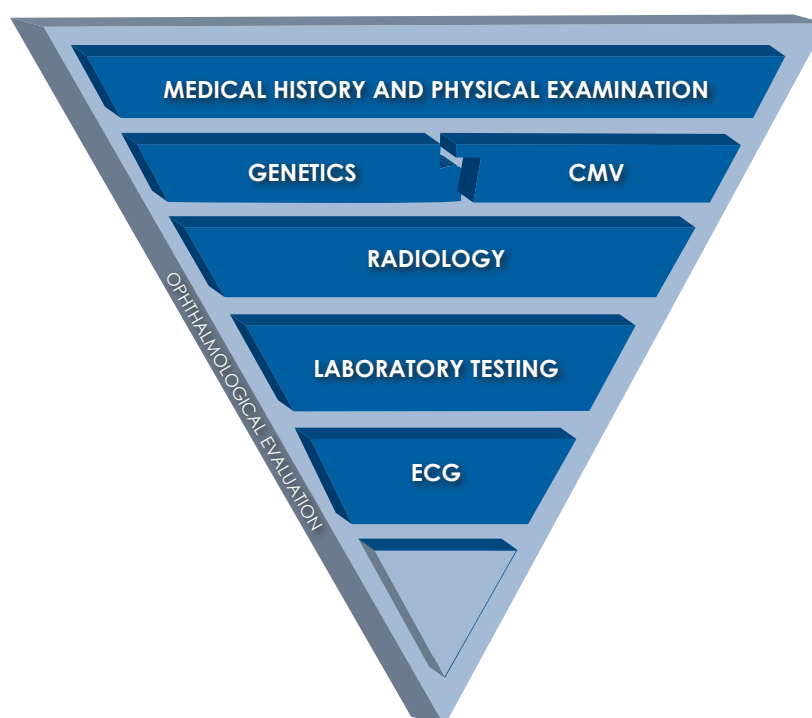


Table 1. Viruses related to infections causing deafness

Congenital virus infection	Deafness Type	Side	Grade	Incidence	Prevention	Treatment	Recovery
Cytomegalovirus	Sensorineural	bilateral	Severe	6-23% asymptomatic 22-65% symptomatic	No	Valganciclovir	With treatment
Lymphocytic choriomeningitis	Sensorineural	bilateral	Severe	7.4%	Isolation	Ribavirin Favipiravir	No
Rubella	Sensorineural	bilateral	Moderate-Severe	12-19%	Vaccine	No	No
HIV	Sensorineural Conductive	bilateral unilateral	Moderate-Severe	27.5-33.5%	Post-exposure treatment	HIV treatment	Variable
Herpes simplex	Sensorineural	bilateral unilateral	Moderate-Severe	<33%	No	Acyclovir	No

Acquired infection	Deafness Type	Side	Grade	Incidence	Prevention	Treatment	Recovery
Measles	Sensorineural	bilateral	Severe	0.1-3.4%	Vaccine, Ig	No	No
Varicella_zoster	Sensorineural	unilateral	Mild-Moderate	7-85%	Vaccine	Acyclovir	Variable
Mumps	Sensorineural	unilateral	Variable	<4%	Vaccine	No	Yes
Nile virus	Sensorineural	bilateral	Moderate-Severe	Very rare	Vaccine	No	Yes

(Modified from: Cohen et al., (2014): "Viral causes of hearing loss: a review for hearing health professionals". Trends Hear. 29;18).

Table 2. General appearance

Physical appearance	Pointing towards:	Type of Hearing Loss
Short stature	Mucopolysaccharidoses Achondroplasia	Transmissive
Asthenic physique	Marfan Sd.	Mixed
Skin and hair	Albinism Lentigo: Leopard Sd.	Sensorineural
	Cafe-au-lait macules: von Recklinghausen Sd.	
	Patch of white hair: Waardenburg Sd.	
Anomalous craniofacial morphology	Anomalous Apert Sd. Crouzon disease	Transmissive

Table 3. Ears

Size and morphology	Pointing towards:	Type of Hearing Loss
Microtia	Treacher-Collins Goldenhar Sd.	Transmissive
	Möbius Sd.	
	Branchiootorenal Sd.	
Low implantation	Down Sd	Transmissive
	Apert Sd.	
Pits or preauricular appendages	May indicate middle ear pathology	Transmissive
Aural atresia	Isolated defect	Transmissive
	Treacher-Collins Sd.	
	Goldenhar Sd.	
	Klippel-Feil Sd.	

Table 4. Eyes

Eye alteration	Pointing towards:	Type of Hearing Loss
Palpebral fissures oblique and downslanting	Treacher-Collins Sd.	Transmissive
Increase in intercanthal distance and iris heterochromia	Waardenburg Sd.	Sensorineural
Coloboma	CHARGE Sd.	Sensorineural
Strabismus	Duane Sd.	Transmissive
Ocular paralysis	Möbius Sd.	Transmissive
Corneal opacification	Congenital syphilis	Sensorineural
Cataracts	Congenital rubella	Sensorineural
Loss of visual acuity	Usher Sd. Refsum Sd.	Sensorineural
Blindness	Stickler Sd. Cockayne Sd. Marshall Sd.	Sensorineural

Table 5. Mouth

Alteration	Pointing towards:	Type of Hearing Loss
	Isolated cleft lip or cleft palate	
Cleft lip and palate	Orofaciodigital Sd. Oropalatodigital Sd. Pierre-Robin Sd.	Transmissive

Table 6. *Facies*

Associated alterations	Pointing towards:	Type of Hearing Loss
Oculus-auricular-vertebral Aberrant development of the 1st and 2nd brachial arches 22% Facial nerve dysfunction	Goldenhar Sd.	75% Transmissive 11% Sensorineural
Mandibulofacial dysostosis: flattened cheeks, narrow face, mandibular hypoplasia	Treacher-Collins Sd.	Transmissive
Prominent frontal bone, coarse facies	Hurler Sd.	Transmissive
Frontal Protuberance	Oto-palato-digital Sd.	Transmissive
Micrognathia	Apert Sd. Pierre-Robin Sd.	Transmissive
Nasal anomalies	Waarneburg Sd.	Sensorineural
Saddle nose	Congenital syphilis	Sensorineural
Parrot beak nose	Crouzon Sd.	Transmissive

Table 7. Neck and Limbs

Associated alterations	Pointing towards:	Type of Hearing Loss
Outer, middle or inner ear anomalies	Klippel-Feil Sd.	Mixed
Short, wide neck with reduced mobility		Transmissive Sensorineural
Long and thin neck	Marfan Sd.	Mixed Transmissive Sensorineural
Cervical masses anterior to sternocleidomastoid muscle (brachial cysts)	Branchiootorenal Sd.	Transmissive
Mid cervical mass (goiter)	Pendred Sd.	Sensorineural
Syndactyly	Apert Sd.	Transmissive
Contractures in finger flexion	Hurler Sd.	Sensorineural
Lobster claw deformities	Cockayne Sd.	Sensorineural

5. REFERENCES

- Alarcón, A. and Baquero-Artigao, F. (2011): "Revisión y recomendaciones sobre la prevención, diagnóstico y tratamiento de la infección posnatal por citomegalovirus". *An Pediatr (Barc)*; 74: 52.e1-52.e13.
- Alford, RL. et al. (2014): "ACMG Working Group on Update of Genetics Evaluation Guidelines for the Etiologic Diagnosis of Congenital Hearing Loss; Professional Practice and Guidelines Committee. American College of Medical Genetics and Genomics guideline for the clinical evaluation and etiologic diagnosis of hearing loss". *Genet Med*; 16: 347-55.
- American Academy of Pediatrics et al. (2006): "Guidelines for Monitoring and Management of Pediatric Patients During and After Sedation for Diagnostic and Therapeutic Procedures". *Pediatrics*; 118(6): 2587-602. Reaffirmed March 2011.
- Atik, T. et al. (2015): "M. Whole-exome sequencing and its impact in hereditary hearing loss". *Genet Res (Camb)*; 97: e4.
- Badia, J. et al. (2014): "Infecciones congénitas". *Pediatr Integral*; 18: 356-66.
- Barkai, G. et al. (2014): "Universal neonatal cytomegalovirus screening using saliva report of clinical experience". *J Clin Virol*; 60: 361-6.
- Behar, DM. et al. (2014): "The many faces of sensorineural hearing loss: one founder and two novel mutations affecting one family of mixed Jewish ancestry". *Genet Test Mol Biomarkers*; 18: 123-6.
- Botet, F. et al. (2015): "Cribado universal de infección por citomegalovirus en prematuros de menos de 1.500 g". *An Pediatr*; 83: 69.
- Botet, F. et al. (2014): "Cribado universal de infección por citomegalovirus en prematuros de menos de 1.500 g". *An Pediatr*; 81: 256.e1-4.
- Bockmühl, U. et al. (2001): "Visualization of inner ear displasias in patients with sensorineural hearing loss". *Acta Radiológica*; 42: 574-81.
- Boppana, SB. et al. (2010): "Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection". *JAMA*; 303: 1375-82.
- Brenner, DJ. et al. (2001): "Estimated Risk of radiation Induced Fatal Cancer from Pediatric CT AJR". *American Journal of Roentgenology*; 176(2): 289-96.
- Brownstein, Z. et al. (2011): "Targeted genomic capture and massively parallel sequencing to identify genes for hereditary hearing loss in Middle Eastern families". *Genome Biol.*; 12: R89.
- Cabanillas, R. and Cadiñanos, J. (2012): "Hipoacusias hereditarias: asesoramiento genético". *Acta Otorrinolaringol Esp.*; 63: 218-29.
- Cabanillas, R. et al. (2011): "Nestor-Guillermo progeria syndrome: a novel premature aging condition with early onset and chronic development caused by BDNF1 mutations". *Am J Med Genet A*; 155A: 2617-25.
- Cannon, MJ. et al. (2014): "Universal newborn screening for congenital CMV infection: what is the evidence of potential benefit?". *Rev Med Virol*; 24: 291-307.
- Cardoso, ES. et al. (2015): "The use of saliva as a practical and feasible alternative to urine in large-scale screening for congenital cytomegalovirus infection increases inclusion and detection rates". *Rev. Soc. Bras. Med. Trop*; 48: 206-7.
- Casselman, JW. et al. (1996): "Inner ear malformations in patients with sensorineural hearing loss: detection with gradient-echo (3DFT-CISS) MRI". *Neuroradiology*; 38(3): 278-86.
- del Castillo, FJ. et al. (2005): "A novel deletion involving the connexin-30 gene, del (GJB6d13s1854), found in trans with mutations in the GJB2 gene (connexin-26) in subjects with DFNB1 non-syndromic hearing impairment". *J Med Genet.*; 42: 588-94.
- Chiang, CE. (2004): "Congenital and acquired long QT syndrome. Current concepts and management". *Cardiol Rev.*; 12: 222-34.
- Choi, BY. et al. (2013): "Diagnostic application of targeted resequencing for familial nonsyndromic hearing loss". *PLoS One.*; 8: e68692.
- Choi, BY. et al. (2009): "Detection of cytomegalovirus DNA in dried blood spots of Minnesota infants who do not pass newborn hearing screening". *Pediatr Infect Dis J*; 28: 1095-8.
- Cohen, BE. et al. (2014): "Viral causes of hearing loss: a review for hearing health professionals". *Trends Hear*; 18: 1-17.
- Crotti et al. (2008): "Congenital long QT syndrome". *Orphanet Journal of Rare Diseases*; 3:18.
- Çelikel, E. et al. (2015): "Evaluation of 98 immunocompetent children with cytomegalovirus infection: importance of neurodevelopmental follow-up". *Eur J Pediatr*. DOI 10. 1007/s00431-015-2513-9.
- Dahle, AJ. and McCollister, FP. (1988): "Audiological findings in children with neonatal herpes". *Ear Hear*; 9: 256-8.
- Declau, F. et al. (2008): "Etiologic and audiologic evaluations after universal neonatal hearing screening: analysis of 170 referred neonates". *Pediatrics*; 121: 1119-26.
- Deklerck, AN. et al. (2015): "Etiological approach in patients with unidentified hearing loss". *Int J Pediatr Otorhinolaryngol*. 79: 216-22.
- Demmler-Harrison, G. (2015): *Congenital cytomegalovirus infection: Clinical features and diagnosis*. In: Up To Date, Post TW (Ed), Up To Date, Waltham, MA. (online): features-and-diagnosis, access July 7, 2015.
- De Vries, JJ. et al. (2013): "Cytomegalovirus DNA detection in dried blood spots and perilymphatic fluids from pediatric and adult cochlear implant recipients with prelingual deafness". *J Clin Virol*; 56: 113-7.
- Dyer JJ. et al. (1988): "Teratogenic hearing loss: a clinical perspective". *Am J Otol.*; 19: 671-8.
- Escosa-García, L. et al. (2015): "Cribado de citomegalovirus en prematuros menores de 1.500 g. Comité Científico del Registro Estatal de Infección Congénita por Citomegalovirus". *An Pediatr*; 83: 70-1.
- Estivill, X. et al. (1998): "Connexin-26 mutations in sporadic and inherited sensorineural deafness". *Lancet.*; 351: 394-8.
- Gallo-Terán, J. et al. (2005): "Prevalence of the 35delG mutation in the GJB2 gene, del (GJB6-D13S1830) in the GJB6 gene, Q829X in the OTOF gene and A1555G in the mitochondrial 12S rRNA gene in subjects with non-syndromic sensorineural hearing impairment of congenital/childhood onset". *Acta Otorrinolaringol Esp.*; 56: 463-8.
- Goderis, J. et al. (2014): "Hearing loss and congenital CMV infection: a systematic review". *Pediatrics*; 134: 972-82.
- Green, RC. et al. (2013): "ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing". *Genet Med.*; 15: 565-74.
- Gu, X. et al. (2013): "Genetic testing for sporadic hearing loss using targeted massively parallel sequencing identifies 10 novel mutations". *Clin Genet.*; 87: 588-93.
- Gunkel, J. et al. (2014): "Urine is superior to saliva when screening for postnatal CMV infections in preterm infants". *J Clin Virol*; 61: 61-4.
- Jacobson, SG. et al. (2015): "Improvement and decline in vision with gene therapy in childhood blindness". *N Engl J Med.*; 372: 1920-6.
- Jamar, SS. and Tan, EC. (2015): "Clinical application of next-generation sequencing for Mendelian diseases". *Hum Genomics.*; 9: 10.
- Ji, H. et al. (2014): "Combined examination of sequence and copy number variations in human deafness genes improves diagnosis for cases of genetic deafness". *BMC Ear Nose Throat Disord.*; 14 :9.
- Joint Committee on Infant Hearing (2007): "Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs". *Pediatrics*; 120: 898-921.
- Kadambari, S. et al. (2015): "Evaluating the feasibility of integrating salivary testing for congenital CMV into the Newborn Hearing Screening Programme in the UK". *Eur J Pediatr.*; doi.org/10.1007/s00431-015-2506-8.
- Kadambari, S. et al. (2013): "Clinically targeted screening for congenital CMV potential for integration into the National Hearing Screening Programme". *Acta Pediatr*; 102: 928-33.
- Karltorp, E. et al. (2012): "Congenital cytomegalovirus infection a common cause of hearing loss of unknown aetiology". *Acta Pediatr*; 101: e357-62.
- Kenneson, A. et al. (2002): "GJB2 (connexin 26) variants and non-syndromic sensorineural hearing loss: a HuGE review". *Genet Med.*; 4: 258-74.
- Kimberlin, DW. et al. (2015): "Valganciclovir for symptomatic congenital cytomegalovirus disease". *N Engl J Med*; 372: 933-43.

- Kochhar, A. et ál. (2007): "Clinical aspects of hereditary hearing loss". *Genet Med.*; 9: 393-408.
- Kohda, C. et ál. (2014): "A simple smart amplification assay for the rapid detection of human cytomegalovirus in the urine of neonates". *J Virol Methods*; 208: 160-5.
- Koontz, D. et ál. (2015): "Evaluation of DNA extraction methods for the detection of Cytomegalovirus in dried blood spots". *J Clin Virol.*; 66: 95-9.
- Laury et ál. (2009): "Etiology of unilateral neural hearing loss in children". *Intenational Journal of Pediatric Otorhinolaryngology*; 73: 417-27.
- Lee, Cl. et ál. (2004): "Diagnostic CT Scans: Assessment of Patient, Physician, and Radiologist Awareness of Radiation Dose and Possible Risks". *Radiology*; 231: 393-98.
- Lemmerling, M. y Foer, B. (2015): "Temporal Bone Imaging. Berlin": eBooks. Springer-Verlag.
- Lim, BG. et ál. (2013): "Utility of genetic testing for the detection of late-onset hearing loss in neonates". *Am J Audiol*; 22: 209-15.
- Lin, JW. et ál. (2011): "Comprehensive diagnostic battery for evaluating sensorineural hearing loss in children". *Otol Neurotol.*; 32: 259-64.
- Lu, Y. et ál. (2014): "Resolving the genetic heterogeneity of prelingual hearing loss within one family: Performance comparison and application of two targeted next generation sequencing approaches". *J Hum Genet.*; 59: 599-607.
- MacLaren, RE. et ál. (2014): "Retinal gene therapy in patients with choroideremia: initial findings from a phase 1/2 clinical trial". *Lancet.*; 383: 1129-37.
- Madden, C. et ál. (2007): "The influence of mutations in the SLC26A4 gene on the temporal bone in a population with enlarged vestibular aqueduct". *Arch Otolaryngol Head Neck Surg.*; 133: 162-8.
- Mafong, DD. et ál. (2002): "Use of laboratory evaluation and radiologic imaging in the diagnostic evaluation of children with sensorineural hearing loss". *Laryngoscope*; 112: 1-7.
- Muller, U. and Barr-Gillespie, PG. (2015): "New treatment options for hearing loss". *Nat Rev Drug Discov.*; 14: 346-65.
- Núñez, F. et ál. (2015): "Recomendaciones CODEPEH 2014", *Revista Española de Discapacidad*; 3 (1): 163-86.
- Nuñez-Ramos, R. et ál. (2013): "Early diagnosis of congenital cytomegalovirus infection: lost opportunities". *Enferm Infecc Microbiol Clin*; 31: 93-6.
- Palmer, CG. et ál. (2009): "A prospective, longitudinal study of the impact of GJB2/GJB6 genetic testing on the beliefs and attitudes of parents of deaf and hard-of-hearing infants". *Am J Med Genet A.*; 149A: 1169-82.
- Park, AH. et ál. (2014): "A diagnostic paradigm including cytomegalovirus testing for idiopathic pediatric sensorineural hearing loss". *Laryngoscope*; 124: 2624-9.
- Preciado, DA. et ál. (2005): "Improved diagnostic effectiveness with a sequential diagnostic paradigm in idiopathic pediatric sensorineural hearing loss". *Otol Neurotol*; 26: 610-5.
- Pickett, BP. and Ahlstrom, K. (1999) "Clinical evaluation of the hearing-impaired infant". *Otolaryngol Clin North Am.*; 32: 1019-35.
- Rangan, S. et ál. (2012): "Deafness in children: a national survey of aetiological investigations". *BMJ Open*; 2: e001174.
- Rehm, HL. (2013). "Disease-targeted sequencing: a cornerstone in the clinic". *Nat Rev Genet.*; 14: 295-300.
- Rehm, HL. et ál. (2013): "ACMG clinical laboratory standards for next-generation sequencing". *Genet Med.*; 15: 733-47.
- Robin, NH. et ál. (2015): "The use of genetic testing in the evaluation of hearing impairment in a child". *Curr Opin Pediatr.*; 17: 709-12.
- Ross, S. et ál. (2015): "Urine Collection Method for the Diagnosis of Congenital Cytomegalovirus Infection". *Pediatr Infect Dis J.*; 34: 903-5.
- Sando, I. et ál. (1998): "Frequency and localization of congenital anomalies of the middle and inner ears: a human temporal bone histopathological study". *Int J Pediatric Otorhinolaryngol.*; 16(1): 1-22.
- Sanger, F. and Coulson, AR. (1975): "A rapid method for determining sequences in DNA by primed synthesis with DNA polymerase". *J Mol Biol.*; 94: 441-8.
- Schrauwen, I. et ál. (2013): "A sensitive and specific diagnostic test for hearing loss using a microdroplet PCR-based approach and next generation sequencing". *Am J Med Genet A.*; 161A: 145-52.
- Schimmenti, LA. et ál. (2011): "Evaluation of newborn screening bloodspot-based genetic testing as second tier screen for bedside newborn hearing screening". *Genet Med*; 13: 1006-10.
- Schleiss, MR. (2013): "Developing a Vaccine against Congenital Cytomegalovirus (CMV) Infection: What Have We Learned from Animal Models? Where Should We Go Next?". *Future Virol*; 8: 1161-82.
- Shearer, AE. and Smith, RJ. (2015): "Massively Parallel Sequencing for Genetic Diagnosis of Hearing Loss: The New Standard of Care". *Otolaryngol Head Neck Surg.*; 153: 175-82.
- Shearer, AE. et ál. (2014): "Copy number variants are a common cause of non-syndromic hearing loss". *Genome Med.*; 6: 37.
- Shearer, AE. et ál. (2013): "Advancing genetic testing for deafness with genomic technology". *J Med Genet.*; 50: 627-34.
- Shearer, AE. et ál. (2010): "Comprehensive genetic testing for hereditary hearing loss using massively parallel sequencing". *Proc Natl Acad Sci U S A.*; 107: 21.104-9.
- Singh, D. et ál. (2015): "MR Evaluation of vestibulocochlear Neuropathy". *J Neuroimaging*; 1.038-430.
- Smiechura, M. et ál. (2014): "Congenital and acquired cytomegalovirus infection and hearing evaluation in children". *Otolaryngol Pol*; 68: 303-7.
- Takemori, S. et ál. (1976): "Thalidomide anomalies of the ear". *Arch Otolaryngol*; 102: 425-7.
- Teek, R. et ál. (2013): "Hearing impairment in Estonia: an algorithm to investigate genetic causes in pediatric patients". *Adv Med Sci*; 58: 419-28.
- Tekin, D. et ál. (2014): "Comprehensive genetic testing can save lives in hereditary hearing loss". *Clin Genet.*; 87: 190-1.
- Thomas, KE. et ál. (2006): "Assessment of radiation dose awareness among pediatricians". *Pediatr Radiol.*; 36: 823-32.
- Toumpas, CJ. et ál. (2014): "Congenital cytomegalovirus infection is a significant cause of moderate to profound sensorineural hearing loss in Queensland children". *J Pediatr Child Health*; doi: 10.1111/jpc.12776. (online).
- Trinidad, G. et al. (2010): "Recomendaciones de la Comisión para la Detección Precoz de la Hipoacusia (CODEPEH) para 2010". *Acta Otorinolaringol. Esp*; 61: 69-77.
- Valvassori, GE. et ál. (1969): "Inner ear anomalies: clinical and histopathological considerations". *Ann Otol Rhinol Laryngol.*; (5): 929-38.
- Vona, B. et ál. (2015): "Non-syndromic hearing loss gene identification: A brief history and glimpse into the future". *Mol Cell Probes*.
- Vona, B. et ál. (2014): "Targeted next-generation sequencing of deafness genes in hearingimpaired individuals uncovers informative mutations". *Genet Med.*; 16: 945-53.
- Wang, D. and Fu, TM. (2014): "Progress on human cytomegalovirus vaccines for prevention of congenital infection and disease". *Curr Opin Virol*; 6: 13-23.
- Wei, X. et ál. (2012): "Next-generation sequencing identifies a novel compound heterozygous mutation in MYO7A in a Chinese patient with Usher Syndrome 1B". *Clin Chim Acta.*; 413: 1.866-71.
- Williams, EJ. et ál. (2015): "First estimates of the potential cost and cost saving of protecting childhood hearing from damage caused by congenital CMV infection". *Arch Dis Child Fetal Neonatal*; doi: 10.1136/archdischild-2014-306756.
- Williams, EJ. et ál. (2014): "Feasibility and acceptability of targeted screening for congenital CMV-related hearing loss". *Arch Dis Child Fetal Neonatal*; 99: F230-6.
- Young, TL. et ál. (2001): "Nom syndromic progressive hearing loss DFNA38 is caused by heterozygous missense mutation in the Wolfram Syndrome gene WFS1". *Hum Mol Genet*; 10: 2509-14.
- Yu, Q. et ál. (2014): "Virally expressed connexin26 restores gap junction function in the cochlea of conditional Gjb2 knockout mice". *Gene Ther.*; 21: 71-80.



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