BIAP Recommendation 12/7 :

“Which tests, what are the goals, at which age?”

AETIOLOGICAL ASSESSMENT AFTER THE DIAGNOSIS OF A PERMANENT HEARING LOSS

including genetic causes and associated illnesses (syndromes)

General foreword

This document presents a Recommendation by the International Bureau for Audiophonology BIAP. A BIAP Recommendation provides a reference standard for the conduct of an audiological or phonological intervention that represents, to the best knowledge of BIAP, the evidence base and good practice concerning the stated methodology and scope of the document at the time of publication.

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Introduction

In the case of a child diagnosed with a hearing loss the literature provides diverse lists of examinations which are recommended for (its) aetiological assessment. Yet most of these lists are kept quite general and do not specify for example:

- the details that should be requested when ordering a certain examination
- at what age the examination should be performed
- whether the examination must be repeated at certain intervals
- which kind of hearing loss requires which examinations
- how the medical history and already existing test results affect the selection of additional examinations ...

To ensure that the necessary examinations are performed at the right time and that unnecessary examinations can be prevented this recommendation tries to give guidelines to the questions**: Which tests, what are the goals, at which age?**

Recommendation

The BIAP recommends that the examinations necessary for an aetiological assessment should be proposed to the parents of all children with a permanent hearing loss at the beginning of the rehabilitation process:

- Aetiological assessments should be carried out parallel and without delaying the further multidisciplinary assessment of the hearing loss itself.
- The choice of tests has to depend on the prior clinical examination and the case history.
- The goals for this completive assessment after the diagnosis of the hearing loss are:
    - to supplement and specify the auditory diagnosis
    - to initiate certain risk preventive actions (e.g.: vaccination against haemophilus influenzae and pneumococcus in the case of a malformation of the internal ear, which increases the risk of a meningitis as a complication of an ear infection)
    - to adjust and complete the information given to the parents in respect to the diagnosis, the therapeutic proposals and the follow-up.
- Any aetiological assessment needs an informed consent of the parents.

Elements of the aetiological assessment

Searching for a clue that may lead to a possible cause of the deafness:

- Looking for risk factors according to the list of the JCIH
- Reconsidering the family history including parents and relatives of 3 generations (using a questionnaire with specific questions is helpful)
- All hearing impaired children need a careful pediatric examination including a pediatric neurology evaluation and a ENT clinical examination especially searching for signs like:
    - a white wick, unpigmented cutaneous spots, different eye colors or blue crystal eyes in combination with a bilateral sensorineural hearing loss would point to the diagnosis of a Waardenburg syndrome;
    - Cervical fistulas and pits with ear deformities suggesting branchio-oto-renal BOR. syndrome;
    - Cleft lip/palate, down-slanting eyes, coloboma, low- set small external ears, and mandible and maxillary hypoplasia in association with a conductive type of hearing loss that would possibly indicate Treacher Collins syndrome;
    - Palatal and lip clefts in association with choanal atresia, external ear deformity, and facial paralysis that might raise the suspicion for CHARGE association or similar syndromes;
    - Cleft palate, velopharyngeal dysfunction, congenital heart defects (often already detected by prenatal sonography) may suggest a microdeletion 22q11.2 syndrom (DGS, VCFS)
    - Microcephaly that might be seen in association with perinatal CMV or rubella infection or other events such as birth asphyxia or brain underdevelopment;

For reducing the strain for the families the recommended examinations should be combined as far as possible to keep the number of appointments low.

The timetable and the list of recommended examinations are not a strict and automatically followed rule but a proposal that must be adapted to the special situation of every child and its family.

Timetable

Type of Hearing Loss		Sensorineural (SNHL)						conductive	
Degree of Hearing Loss		Profound		Other degrees progressive		Other degrees stable			
	Examination	1st test	Test-Repetition	1st test	Test-Repetition	1st test	Test-Repetition	1st test	Test-Repetition
1.	CMV screening	a.s.a.p.		a.s.a.p.		a.s.a.p.		-	-
2.	Genetic	See remark							
3.	MRI	< 12m		a.s.a.p.	-	When possible without sedation		-	-
4.	CT scan	< 12m	-	-	-	-	-	When possible without sedation or before surgery	-
5.	Ophtalmological examination	6m	every year	6m	every year	6m	every year	6m	every year
6.	Searching for pre- and perinatal infections	< 12m a.s.a.p.	-	< 12m a.s.a.p.	-	< 12m a.s.a.p.	-		-
7.	Hématurie/ Protéinurie screening + echo kidney	If malfor-mation of external or middle ear	-	If malfor-mation of external or middle ear		If malfor-mation of external or middle ear		a.s.a.p.	-
8.	ECG	< 6m	Once at ~ 18m	-	-	-	-	if CHARGE-S. in CT	-
9.	ERG	>9M See remark	-	if clinical RP-signs	-	-	-	-	-
10.	Vestibular tests	< 6m	if first abnormal and pre and post CI	a.s.a.p.	if motor delay	< 12m	if motor delay	if hypotonia or if CHARGE-S.	if hypotonia or if CHARGE

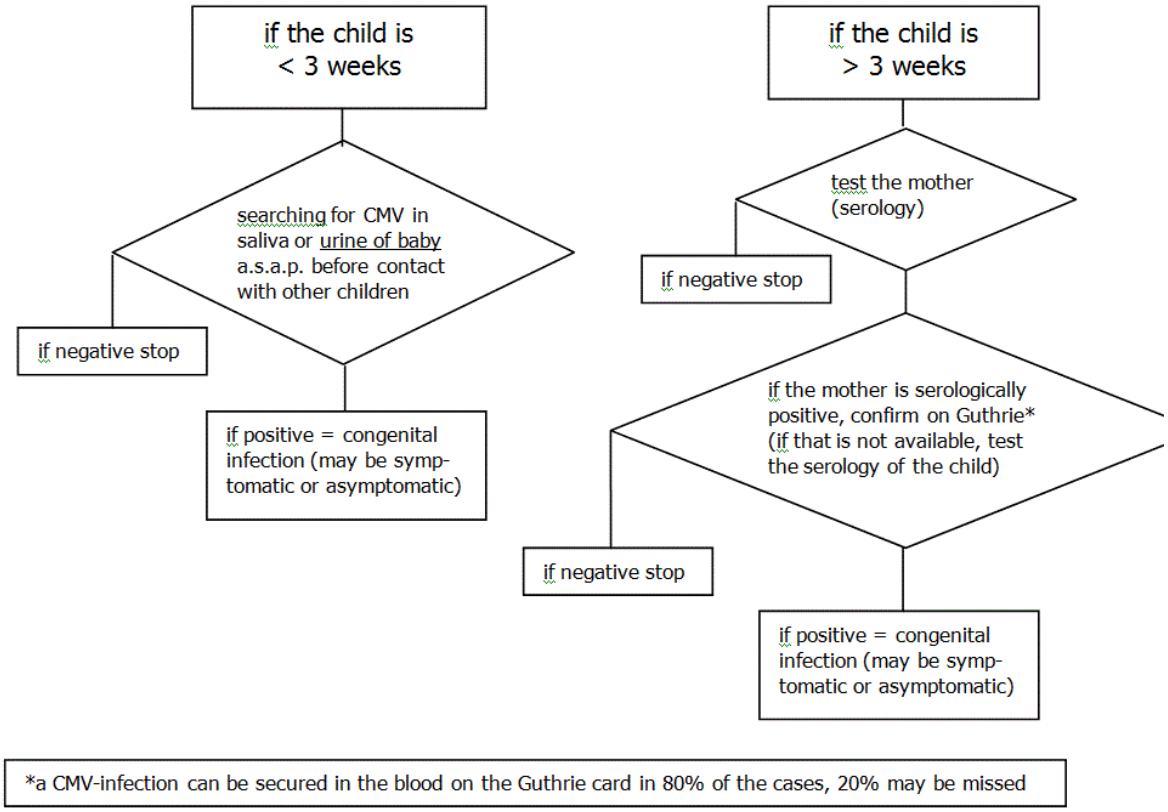
NB : In case of a mixed hearing loss the CT-scan should be done < 12m. If this CT-scan shows an inner ear malformation follow the recommendation for the "SNHL- other degrees stable".

The order of the recommended examinations refers to a very efficient proposal of E.M.R De Leenheer[1]. This proposal heavily relies on an early genetic evaluation. As this may not be accepted by all patients, the concept was not fully endorsed by the BIAP, but the proposed flow chart can be found in an annex of this recommendation.

[1] E.M.R. De Leenheer et al, Etiological diagnosis in the hearing impaired newborn: Proposal of a flow chart, Int. J. Pediatr. Otorhinolaryngol. (210), doi:10.1016/j.ijporl.21010.05.040

Specifications for the diagnostic procedures named in the timetable above:

1. Exam: congenital CMV - examination algorithm:



2. The chances and the limits of the genetic testing must be discussed with the parents. The parents must be informed of the potential likelihoods of heredity transmission, but also that the results of the genetic assessment might concern not only the deaf child but also other members of his family. The testing is only allowed with the parent`s permission. The counseling of the parents should be done by a geneticist specialized in hearing disorders (or a hearing specialist specially trained in genetic counseling). For the genetic testing its necessary to have as far as possible the complete medical history, a clinical pediatric examination and the results of the above recommended aetiological assessment including the audiometric results of the family members.

   In case of an isolated cochlear SNHL it is recommended to search for a mutation in connexin 26 and 30 genes first, because it is the most frequent cause in this case.
   In case of a motor developmental delay and vestibular problems it is recommended to search for an Usher Syndrome, provided that there are no additional clinical signs, e.g. pointing to CHARGE or other syndromic conditions with a developmental delay, vestibular and hearing problems.

   The decision which kind of genetic test should be used will depend on whether you are looking for a syndromic (Waardenburg, Pendred, Jervell, Alport ….) or an isolated non-syndromic cause of the hearing loss.
   In case of a non-syndromic hearing loss the selection of genetic tests will be influenced by the preceding diagnostic findings of a:

- conductive or sensorineural
- AN or auditory dyssynchrony spectrum (otoferlin)
- Inner ear malformation or not
- Outer ear or middle ear malformation
- Genetic transmission mode shown by the family history (mitochondrial type ?, X-linked ?, dominant ?, recessive ?)

High throughput next generation sequencing (NGS) allows parallel screening of large panels of hearing related genes with high accuracy, in a short time, at a cost lower than conventional Sanger sequencing. This can be achieved either by targeted capture of several dozens of genes, or by direct sequencing of all exons present in the genome (so called “whole exome sequencing” or WES). Targeted NGS screening would only detect genome variations in genes known to be involved in hearing loss. WES theorically xould uncover all DNA sequences variations, but laboratories that offer such WES may decide to filter the data and consider only pertinent genes (giving nevertheless the possibility go back to the raw data and to analyze further genes if necessary). Obviously, obly targeted sequencing is convenient in a diagnostic setting. The strategy followed by the laboratory to which samples are send must thus be clearly defined. At this point, the use of non filtered WES data is limited to research. Parents must be informed before the examination whether the NGS screening will be in a diagnostic setting (i.e. focused on known hearing loss-causing genes) or whether the investigation is wider and may uncover unexpected negative findings, such as harmful mutations in genes predisposing to late onset disorders. Genetic diagnosis and genetic counseling using these new technologies requires a close connection between clinicians and audiologists, clinical geneticists (or genetic counselors) and molecular biologists, to avoid improper interpretation and cross validation between genotype and phenotype: even targeted NGS discloses a vast amount of DNA sequence variations whose significance may be unknown, or dubious. Genetic counseling based on NGS data may thus involve a number of ethical risks and questions that are not satisfactorily answered neither politically, juristically and by civil societies themselves.

3./4. Imaging should be performed by a specialist for pediatric radiology:

The decision whether to use a CT or a MRI first will be influenced whether one is searching for bony or soft tissue deficiencies.

CT and temporal MRI scan, general considerations:

- in case of a profound deafness
- before the end of the first year of life
- for a CT a low radiation scanner should be used (e.g. cone beam scanner)
- a CT needs radiation but can be done so quick that it can be performed in natural sleep (especially with very young children) or in sedation
- a MRI has no radiation but takes much longer and therefore normally needs a general anesthesia

Aim of temporal MRI: searching for a malformation of the

- vestibular aqueduct dilatation
- cochlear or vestibular fibrosis
- internal auditory canal
- the auditory, vestibular and facial nerve
- Central auditory pathways
- Brain lesions

Aim of CT: searching for a malformation of the

- ear (outer, middle and inner ear) and the vestibular organ,
- internal auditory canal
- vestibular aqueduct dilatation

5. Exam: ophthalmological (incl. ocular motricity study and funduscopy) done by a specialist experienced in examining young children
Aim: searching for any impaired vision that might enhance the sensory deficit of the child and specifically for any signs of an “oculo-auditory syndrome”: coloboma, optical nerve abnormalities, oculomotor anomalies, refraction disorders, inflammation of the cornea or the retina, cataract.
(The early funduscopy does not rule out an “Usher syndrome I”, because the specific signs of a retinitis pigmentosa occur later in childhood!)
For the indication of an electroretinogram see top 8.

6. As with some infections as CMV, Toxoplasmosis and Rubella neither the mother nor the child might show obvious clinical signs of the infection, one should search for the following prenatal and perinatal infections also in cases of an isolated, idiopathic hearing loss:

   a. CMV (see above)
   b. Toxoplamosis:
      Determination of antibodies (IgM and IgG) against Toxoplasma gondii in the hearing impaired newborn should be performed, except in cases where the mother was known to be immune before pregnancy.
   c. Rubella:
      If either maternal rubella immunization by vaccination has not been performed, or the maternal status is unknown, this diagnosis should be considered, and maternal and neonatal rubella-specific IgM and IgG should be determined.
      As asymptomatic congenital infections of Syphilis and Herpes are very unlikely, routine serological screenings for these infections are not necessary in otherwise healthy hearing impaired children.

Particular situations are an indication for complementary testing:

6. Exam: urine stick
Aim: searching for a haematuriae and/or proteinuriae
(a non-invasive procedure, but strong evidence to recommend this examination as a general screening is missing. If any clinical signs for a kidney malfunction occur, a thorough examination of the kidneys is necessary)

   Exam: Kidney sonography, if there are even minor malformations of the ear or a history urinary and renal symptoms
Aim: searching for malformations of the kidney and urinary tract

7. Exam: The ECG should be done by a pediatric cardiologist
Aim: searching for a prolongation of the QT interval in case of bilateral deafness (Jervell syndrome et Lange-Nielsen syndrome).

8. (see also top 5)
   Exam: An electroretinogram should be done in profoundly deaf children showing hypotonia and/or vestibular areflexia (not before the age of 9 month).
   Aim: Searching for “Usher syndrome type I”. But an abnormal ERG does not prove the Usher diagnosis in all cases; therefore a genetic assessment is additionally necessary. The diagnosis of an Usher-Syndrome should be communicated with the parents only by a clinician with specific experience in the management of patients with Usher syndrome.

9. A vestibular examination should include otolithic functions and the semicircular canal functions

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