Guidelines for aetiological investigation into severe to profound bilateral permanent childhood hearing impairment

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INDEX

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Background:

There are several reasons why it is important to establish the cause of hearing loss [1]:

1. To answer the questions parents may have, "Why is my child deaf" and "Is the hearing loss likely to get worse?"

2. To identify syndromes and manage associated medical conditions e.g. long QT interval in Jervell and Lange-Nielsen syndrome, thyroid dysfunction in Pendred syndrome, renal disease in Alport syndrome, etc.

3. Investigation of hearing loss may uncover conditions requiring medical management e.g. congenital toxoplasmosis, space occupying lesions, syphilis, etc.

4. Identification of conditions where timely treatment will prevent progression of the hearing loss e.g. congenital CMV, congenital cholesteatoma. Early diagnosis of congenital CMV infection means that the child will be eligible for treatment [currently recommended for infants less than four weeks of age] to prevent further loss of hearing.

5. To detect inner ear dysplasia in order to give appropriate advice: e.g.

- on the risk of recurrent meningitis
- on risk associated with head injury in EVA
- on whether hearing aids and cochlear implantation are appropriate, for example, if there is severe inner ear and/or eighth nerve hypoplasia

6. To identify genetic causes and to inform genetic counselling e.g. recurrence of deafness in a future child, GJB mutation.

7. To prioritise children requiring cochlear implants e.g. bacterial meningitis and Usher syndrome type 1.

8. To conserve hearing in patients and to help counsel other family members e.g. in hearing loss due to mitochondrial mutations and aminoglycoside induced deafness.

9. To counsel families on the effects of balance disorder if significant vestibular hypofunction is detected.

10. The information from investigation of childhood deafness informs epidemiological research, helps healthcare planning and may improve future healthcare delivery. It is likely to be helpful in the future in correlating cochlear implant outcomes with aetiology.

Hearing loss may initially start as unilateral or mild/moderate and progress to severe/profound. Several investigations are common to all types of PCHI. These guidelines should be read in conjunction with those for unilateral and mild/moderate PCHI. It may sometimes be difficult to pinpoint the aetiology of hearing loss despite investigations, and occasionally more than one aetiology may be identified for the hearing loss. The test results, hence should be interpreted in a clinical context.

Aim and Scope:

The aim of these guidelines is to update the evidence based approach to the investigation of the cause of bilateral severe to profound PCHI. This is an update to the guidelines on aetiological investigation into severe to profound permanent hearing loss in children produced by BAAP/BAPA (2009). These guidelines were produced in line with the procedure detailed in the BAAP manual for producing guidelines [2].

These guidelines are for use in the United Kingdom but could be applied worldwide depending on local clinical expertise, test facilities and resources. The intended users of these guidelines are health practitioners with a special interest in Audiovestibular Medicine. The guidelines:

- Provide up to date advice on effective clinical practice
- Support staff in improving and benchmarking Audiovestibular Medicine services
- Identify audit measures for performance and review
- Promote patient safety and implementation of clinical governance

These guidelines are evidence-based and link their concluding recommendations to the evidence identified through a literature search [3]. They are not intended to restrict clinical freedom, but practitioners are expected to use the recommendations as a basis for their practice. Areas lacking in evidence may form the basis for future research.

Timing of investigations:

This will depend on the time window for the test, the family's readiness to proceed and how well the child can cooperate with the tests. The process of aetiological investigations is an ongoing one and it is important to revisit this periodically because
[1] New medical information and new tests may become available
[2] New symptoms may develop e.g. reduced night vision, goitre
[3] New information relating to family history may become available e.g. hearing loss, renal failure.
[4] There may be progression of hearing loss
[5] Parents or young deaf people may request this

Who can undertake aetiological investigations?

A medical practitioner with the appropriate knowledge and skills can undertake aetiological investigations. Children should be referred appropriately when this service is not available locally [4]. It is the responsibility of the doctor providing the aetiology service to provide accurate and unbiased information to parents (or carers) and children if applicable about the investigations (pros/cons, outcomes and details of procedure etc). This should be done as soon as the hearing loss is confirmed so that they can make a well informed decision to have or not to have each investigation.

Subjects

These guidelines apply to children with bilateral permanent childhood hearing impairment and thresholds over 70 dBHL in the better ear averaged across 0.5, 1, 2 and 4 kHz.

Search Methodology:

The literature search covered databases including Pubmed, Medline, Embase, AMED, BNI, CINAHL, HMIC, PsychINFO and Cochrane Library Database. The keywords detailed in Appendix 1 were used. The search was carried out by the librarian and one member of the guideline group [B]. All relevant articles including randomised control trials, systematic reviews, meta-analyses, observational studies, case reports and expert opinion were reviewed. Unpublished data from the BAAP National Audit and from the Clinical Virology Network guidelines was included due to its extreme relevance to the topic. Some review articles were referenced but not included to support recommendations in the guidelines. Case reports and series were included as there was paucity of references with level of evidence 1 and 2. Articles not available in English or only available in abstract forms were excluded. Relevant guidelines and standards from other national and international organisations were included in this review.

The literature search covered a period from 01/01/2008 to 15/03/2014. The abstracts of the list of articles obtained following the literature review were scanned to produce a list of articles relevant to the guideline. This was done by a member of the guideline group [B]. Full texts of all these relevant articles were obtained with the help of the librarian. In addition, full texts of all the references quoted in the earlier version of this guideline were reviewed with their cross references. Members of the guideline group [A and C-E] reviewed the full texts of the articles. The articles relevant to the guideline were graded for evidence level by members of the guideline group [B-C].

Keywords:

The keywords were guided by questions using the PICOT format:

- **P**opulation to which the question applies
- **I**ntervention (e.g. or diagnostic test, exposure etc.) being considered in relation to this population
- **C**omparison(s) to be made between those receiving the intervention and those who do not receive the intervention
- **O**utcome(s) i.e. any effect caused by the intervention
- **T**imeframe (optional)

The keywords used are detailed in the Appendix 1:

Grade of evidence and recommendation

The evidence from the full text articles was graded according to the Scottish intercollegiate Guideline Network [SIGN] grading system as follows [5]:

Level of evidence	Definition
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

The strength of recommendations in this guideline is based on the SIGN grading of evidence as follows [5].

Recommendation A This recommendation is based on evidence rated as 1++ or 1+ directly applicable to the target population and demonstrating overall consistency of results

Recommendation B This recommendation is based on evidence rated as 2++ or based on extrapolated evidence from studies rated as 1++ or 1+ directly applicable to the target population and demonstrating overall consistency of results

Recommendation C This recommendation is based on evidence rated as 2+ or based on extrapolated evidence from studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results

Recommendation D This recommendation is based on evidence rated as level 3 or 4 or based on extrapolated evidence from studies rated as 2+

Guidelines for good practice

Aetiological investigations are categorized based on the available evidence, expected yield and considering the causes of PCHI in children. Level 1 investigations should be offered to all children and Level 2 investigations to children with specified indications.

Level 1 investigations include:

[1] Clinical history: [6-9] [Recommendation D]

Onset, duration and progress of symptoms
Speech and language: expressive , receptive, play skills
Balance, dizziness, tinnitus, hyperacusis
Antenatal History
➢ Alcohol, drugs including recreational drugs
➢ Diabetes, epilepsy
➢ Maternal health during pregnancy
➢ Results of antenatal scans and bloods
➢ Medications
➢ Radiation
➢ Infections
Birth history
Postnatal history
➢ Ventilation
➢ Sepsis
➢ NICU stay
➢ Jaundice
➢ Ototoxic medication
Developmental milestones
Family history
➢ Ethnicity and consanguinity
➢ Deafness
➢ Speech /language delay
➢ Thyroid/renal disease/ white forelock/heterochromia
➢ Inherited conditions
➢ Balance and visual difficulties
➢ Developmental delay
➢ Three generation family tree
Medical history
➢ Head injury
➢ Accidents
➢ Noise exposure
➢ Meningitis/ Infectious illness
➢ Immunisation
➢ Ear disease
➢ Ototoxic medication/radiation
➢ Old records, photos, discharge summaries, parental illness record

The history and examination are important not only for identifying aetiological factors in hearing loss but also for detection of conditions requiring medical management: e.g. cleft palate, cardiac lesions, skeletal anomalies. This is to be done with a problem solving approach rather than as a tick box exercise. A table of anamnesis for history and examination is given.

Timing of assessment: When diagnosis of deafness is confirmed, at first visit

2) Clinical examination: [6, 7, 9] [Recommendation D]

Anthropometry: height, weight and head circumference including centile range
Clinical examination of craniofacial region
➢ Dysmorphism
➢ Ears: e.g. ear pits, tags
➢ Neck: e.g. skin tag, sinus, webbing, goitre, scars
➢ Oral cavity, palate, teeth
➢ Nose examination
➢ Otoscopy
➢ Skull
Systemic examination
➢ Skin: hypo- or hyper-pigmentation
➢ Spine
➢ Hands, Limbs, Nails: hypoplasia
➢ Abdomen:
➢ Chest: heart murmur
➢ Neurological assessment
Developmental assessment
Clinical vestibular examination
Eye examination
Examination of parents

Timing of assessment: When diagnosis of deafness is confirmed, at first visit, as soon as opportunity provides.

3) Family audiograms: [9 -11] [Recommendation D]

Parents and siblings should have their hearing checked. This may be particularly helpful in interpreting genetic test results. (i.e. [a] if parents' genotype indicates they may be mildly affected, this can be confirmed, or [b] normal parental hearing confirms a likely de novo pathogenic mutation in a child).

Timing of assessment: Early, before the genetics referral.

4) Electrocardiography (ECG) for QTc: [12 -15] [Recommendation D]

Twelve lead ECG for prolongation of the corrected QT interval. This is essential in children with evidence of vestibular hypofunction which may manifest as delayed motor milestones [e.g. head lag, delayed sitting without support, delayed walking] or be apparent on clinical examination [absent VOR]. The QTc should be calculated manually rather than relying on the printed value in the report. The clinician requesting this investigation should be appropriately trained to review the results in the clinical context. If such expertise is not available, liaison with local Paediatric Cardiology department should be considered. QTc of more than 460ms in girls and 450 ms in boys is considered as abnormal.

Timing of assessment: when diagnosis of deafness is confirmed, as soon as opportunity provides

5) Ophthalmic assessment: [Recommendation B/C]

20-60% of children with PCHI have ophthalmic abnormalities which can remain undetected and impact on the child's communication [9, 16-19]. Ophthalmic assessment is guided by the Vision care document by NDCS/SENSE [20].

The child should be referred for a full ophthalmic assessment following the diagnosis of PCHI and at any time if parents or the education service have concerns. In addition, an ophthalmic assessment should be done at the following times:

- 1-3 years of age
- 4-5 years of age [vision screening by an orthoptist, which is usually done at school]
- 7-9 years of age [where the cause of the deafness is unknown, an ophthalmologist assessment for signs of Usher syndrome. A normal result at this age may not exclude Usher Type II or Usher Type III syndrome].
- At referral for cochlear implantation and other complex interventions
- Transition to secondary school

The ophthalmic examination should include formal testing and recording of visual acuity, functional assessment of vision, refraction, visual field assessment, assessment of ocular alignment and eye movements, fundoscopy and assessment of binocular vision depending on the feasibility and age of the child. Discuss performing ERG with the ophthalmologist to detect retinitis pigmentosa if

- There is evidence of vestibular hypofunction or motor milestones are delayed [unless there is an adequate explanation i.e. vestibular malformation] [21-23].
- There are symptoms suggestive of Usher syndrome e.g. night blindness, visual field loss.

Further ophthalmic monitoring will be determined by the underlying diagnosis e.g. Stickler syndrome, Congenital CMV

6) Urine examination (labstix) for microscopic haematuria and proteinuria: [24-27] [Recommendation D]

All children should have urine tested for haematuria and proteinuria particularly with a family history of renal disease. This should be repeated at least on one occasion as abnormalities may be missed with a single sample. Hearing loss due to Alport syndrome is not usually manifest until school age and is an unlikely diagnosis in a deaf infant. Urinary abnormalities may be detected in Branchiootorenal syndrome.

Timing: As soon as feasible, but depends on condition suspected.

7) CMV testing: [9, 28-36] [Recommendation B/C]

<u>If the child is less than one year of age:</u>

- Urine x 2 samples or saliva swab x 2 samples are sent for CMV DNA PCR
- Urine samples can be collected using a bag, a pad or balls of cotton wool. Saliva swabs should be left in the mouth until soaked [approximately one minute]. Precautions for avoiding breast feeding for the preceding 60 minutes must be taken to avoid the possibility of false positive results due to shedding of CMV in breast milk.
- Saliva swabs are comparable in sensitivity and specificity to the urine samples and have a practical advantage.
- If the infant is less than 3 weeks old at the time of the test, a positive test on either of saliva or urine sample can be taken as evidence of congenital CMV infection. If the infant is more than 3 weeks of age, the neonatal dried blood spot must be requested [with parental consent] for CMV DNA testing to confirm the diagnosis of congenital CMV infection.

<u>If the child is more than one year of age:</u>

- CMV IgG +/- Urine CMV DNA PCR
- If either is positive, request neonatal dried blood spot for CMV DNA testing. Checking the child's IgG is necessary to exclude congenital CMV.

<u>Details required while requesting neonatal dried blood spot</u>

- Signed parental consent form is required.
- Infant's name at the time of birth
- Mother's name and address at the time of the infant's birth
- Newborn screening laboratory address

Request that the dried blood spot is sent direct to virology laboratory, not the clinician. A positive result for CMV DNA PCR on the dried blood spot taken in the first 3 weeks of life confirms the diagnosis of congenital CMV, but a negative result cannot reliably exclude congenital CMV. It is best to check the sensitivity figures with virology laboratory used when interpreting the test result. Dried umbilical cord can also be used instead of

the dried blood spot to confirm a diagnosis of congenital CMV. CMV DNA PCR may not be available worldwide but CMV urine culture or antigen testing may be used as alternative tests.

At any age:
Consider testing mother's CMVIgG. If negative, congenital CMV infection is excluded. This may sometimes be used to avoid venepuncture in the child. [36] If mother's antenatal sample is available, consider mother's IgG avidity studies. A low avidity is indicative of recent CMV infection.

Timing of investigation: As soon as possible on suspecting the diagnosis of sensorineural hearing loss. The timing of this investigation is crucial given the implications of missing the window of opportunity for treatment, which is currently before the age of four weeks. A fast and reliable pathway should be developed locally to include the audiologists, doctors and the testing laboratory in order to facilitate a timely diagnosis. Guidelines on antiviral therapy for congenital CMV may evolve in the next few years.

8) Blood test for GJB2 [Connexin 26] mutations including deletions involving GJB6 [Connexin 30] [9, 37-42]**:** [Recommendation C]

- This is advisable in all cases of bilateral hearing loss, which is congenital in origin and where aetiology has not been determined.
- Informed consent should be taken from parents prior to genetic testing. Parents should be informed that DNA is stored in the laboratory after testing and that genetic testing can take a long time. Permission should be taken to share results with other family members/professionals (see guidelines for consent for genetic testing
- Most laboratories will test for deletions involving Connexin30 when a request for Connexin26 is made and a separate request is unnecessary [43].This will be evident from the test report.
- More widespread genetic testing for deafness will become available with the advent of Next Generation (Massively Parallel) sequencing where large numbers of genes can be sequenced rapidly and cost-effectively. In the case of non-syndromic deafness many genes can be tested simultaneously, without regard to phenotype but this will make interpretation of multiple novel or rare genetic variants more difficult initially. Guidelines for further genetic testing are likely to evolve over the next few years.

9) MRI of Internal Auditory Meati and brain or CT scan of Petrous Temporal [9, 44-52]**:** [Recommendation C]

- Diagnostic radiological imaging is the highest yielding test for evaluating children with SNHL. The choice of imaging will depend on the type of permanent hearing loss, local availability and need for sedation or anaesthesia.
- MRI is the preferred investigation for SNHL due to the advantage of visualisation of the cochlea-vestibular nerve and its cochlear branch. The fluid in the cochlea, fibrosis, and interscalar defects are often only visible on MRI. The auditory

pathways and cortex are only visible on MRI.

- CT is preferred in children with a permanent conductive component to their hearing loss.
- Both CT and MRI are indicated in bacterial meningitis [as either imaging modality alone is inadequate in detecting changes suggestive of fibrosis and ossification]. CT and MRI both may be required for children undergoing cochlear implantation. CT is useful to distinguish fibrosis from calcification and to give the surgeon a road map (e.g. to determine the normal position of the facial nerve and the jugular bulb)
- MRI of the brain should be performed in children with severe to profound hearing loss given the incidence of abnormalities along with the MRI Internal Auditory Meati [45].

Timing of investigation: Soon after diagnosis, best within 3months age in natural sleep if diagnosis follows newborn hearing screen [to avoid the need for sedation]

Level 2 investigations

Level 2 investigations will be indicated from the history and clinical findings.

1) Serology: For congenital infection [9, 36, 53-57] [Recommendation C]

Mothers may be screened for these infections in pregnancy and hence these tests should be carried out in 'at risk' babies. As many of these babies can be asymptomatic at birth, if the testing or immune status of the mother is unknown it is best to investigate the neonate. These tests may also be done on maternal stored (booking) serum if available.

Syphilis: IgM-positive neonatal serum should be considered as evidence of congenital infection. TPHA and FTA-ABS tests [IgG] can be used to exclude congenital syphilis if the tests are non-reactive before the age of one year in an infant who has not received treatment.

HIV: is a known cause of sensorineural hearing loss in children and testing should be considered in 'at risk' pregnancies when the maternal HIV status is unknown. Testing may be done with adequate counselling in conjunction with an infectious disease unit.

Rubella

Up to 6 months of age: Child Rubella IgM

- If negative – Congenital rubella is unlikely. Consider confirming with a rubella IgG test at one year (but before MMR). Before this age detectable IgG may be of maternal origin.
- If positive – sample must be sent for further confirmatory testing [as positive predictive value of a single IgM test is poor]

Over 6 months of age: Child Rubella IgG at one year of age (before MMR vaccination only)

- If negative-excludes congenital rubella infection

- If positive – Rubella can be considered as a potential diagnosis

Toxoplasma:

<u>If child is less than 1 year of age:</u>

- Maternal toxoplasma IgG: If negative – excludes congenital Toxoplasma infection. If positive – congenital toxoplasma cannot be excluded, consider further specialist investigation of child's and maternal blood (and antenatal maternal blood if available).
- If Toxoplasma IgM in the child is positive, this is indicative of congenital infection. If both Toxoplasma IgG and IgM are negative, congenital toxoplasmosis can be excluded

<u>If child is over 1 year of age:</u>

- Child Toxoplasma IgG
- Consider doing maternal Toxoplasma IgG

If either is negative – excludes congenital Toxoplasma infection. If both positive – further specialist investigation of child's and maternal blood (and antenatal maternal blood if available) may be indicated.

2) Haematology and Biochemistry: where clinically indicated [9, 49, 58, 59] [Recommendation D]

Routine laboratory evaluation with FBC, ESR, U & E, TFT should not be done considering its low diagnostic yield. Thyroid Function tests are indicated if there is:

- Family history of thyroid disease
- Goitre
- EVA or Mondini deformity of cochlea . The onset of thyroid dysfunction in Pendred syndrome is usually in late childhood or early puberty and the tests should be timed accordingly.

3) Investigation into autoimmune diseases: [60, 61] [Recommendation D]

Where clinically indicated i.e. where there is evidence of systemic involvement [fever, joint symptoms, skin rash, ocular inflammation] or evidence of progressive hearing loss. Tests may include antinuclear antibodies, antineutrophil cytoplasmic antibodies, DsDNA, RA factor, antiphospholipid, anticardiolipin, antithyroid antibody, antibodies to Sm, ESR, CRP and others as indicated.

4) Metabolic Screen on blood and urine: [45] [Recommendation D]

Where clinically indicated e.g. epilepsy, neurodegeneration.

5) Renal ultrasound: [9, 47, 62] [Recommendation D]

Indicated if the child has

- Preauricular pits or sinuses, deformity of ear[microtia, cup/lop ear], branchial cleft or cysts
- Mondini defect or EVA on imaging.
- Permanent conductive or mixed hearing loss
- Features suggesting syndrome with kidney involvement e.g. CHARGE

6) Chromosomal studies/CGH microarray: Indicated if

- History of developmental delay
- Dysmorphic features

Chromosome analysis is being replaced by more detailed CGH microarray. Laboratories may request parental bloods in order to fully interpret findings.

7) Further genetic testing: Testing for syndromic forms of deafness is likely to become more widely available. Specific circumstances include:

- Testing for SLC26A4 in children with EVA,
- Testing for EYA if there is evidence of clinical features of BOR
- Testing in auditory neuropathy e.g. otoferlin
- Testing for m.1555A>G [63] if:
    1) Exposure to aminoglycoside antibiotics
    2) Progressive hearing loss
    3) Mother/sibling with sensorineural hearing loss
    4) High frequency sensorineural hearing loss

8) Referral to Clinical Geneticist: This may be considered if

- Parents are consanguineous,
- A syndrome is suspected,
- Child has multiple abnormalities,
- Parental request
- Opinion required on interpretation of genetic mutation testing
- Consider referral if after completion of investigations no cause has been identified.

9) Vestibular investigations: [64-66] [Recommendation D]

All children with PCHI should have a clinical vestibular examination. Consider further vestibular investigations if:

- Motor milestones are delayed
- Progressive deafness
- Conditions known to be associated with vestibular dysfunction e.g. Usher,

post-meningitis, Pendred
- Vertigo/dizziness
- Temporal bone malformations

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Appendix 1: Keywords

aetiological test/aetiology	Alport syndrome	autoimmune/immunological
blood test	biochemistry	BOR
child/children	chromosomal analysis	clinical examination
CMV/ Cytomegalovirus	connexin/GJB	CT
ECG/electrocardiogram	ERG/electroretinogram	full blood count
genetic	Guthrie	haematology
herpes	history	HIV/Human Immunodeficiency Virus
IgG avidity	Jervell Lange Nielsen syndrome/long QT	kidney /renal function/U & E/urea electrolytes
kidney/renal ultrasound	liver function	measles
metabolic screen	mitochondrial mutation	MRI
mumps	neonatal blood spot	neonatal/perinatal history
ophthalmology/eye	parent/sibling/family audiogram	PCHI/permanent childhood hearing loss/hearing impairment
permanent conductive hearing loss	Pendred syndrome	QTc interval
rubella	sensorineural hearing loss	serology
syndrome	syphilis	thyroid function test
toxoplasma	Usher	varicella
vestibular	Urine/saliva /mouth swab PCR	urine

Appendix 2: Abbreviations:

BAAP British Association of Audiovestibular Physicians
BAPA British Association of Paediatricians in Audiology
BOR Branchio oto renal syndrome
CMV Cytomegalovirus
EVA Enlarged Vestibular Aqueduct
PCHI Permanent Childhood Hearing Impairment
PCR Polymerase Chain Reaction
FBC Full Blood Count
ESR Erythrocyte Sedimentation rate
ERG Electro-retinography

U & E Urea and electrolytes
TFT Thyroid function test
VOR Vestibulo ocular reflex

Appendix 3: Useful parent resources

- NDCS publications: "Understanding your child's hearing tests", "Cytomegalovirus(CMV) and deafness", "Enlarged vestibular aqueduct syndrome", "Genetic counselling", "Meningitis and childhood deafness", "Waardenburg's syndrome"

- Quality Standards in Vision Care for Deaf Children and Young People. Guidelines for professionals. [NDCS and SENSE 2009].

- CMV action: cmvaction.org.uk

Appendix 4: Audit Measures

The proforma of the BAAP national audit can be used to benchmark practice. This is attached separately.

Appendix 5: Future Research

The evidence to support aetiological investigations is thin. Areas of research that could help to support an evidence base include

- Yield of aetiological battery and individual aetiological tests/ assessments in children with various degrees and types of PCHI: severe to profound/moderate / mild/unilateral hearing loss and ANSD
- Yield of history and clinical examination using a prospective study
- Systematic review of studies on aetiological investigations

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