Guidelines for aetiological investigation into unilateral permanent childhood hearing impairment

April 2015

Produced by
British Association of Audiovestibular Physicians

INDEX

Background:

There are several reasons why it is important to establish the cause of unilateral 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. Investigation of hearing loss may uncover conditions requiring medical management e.g. space occupying lesions, etc.

3. 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.

4. 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

5. To identify genetic causes and to inform genetic counselling e.g. recurrence of deafness in a future child e.g. in mutation of EYA1 gene.

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

7. The information from investigation of childhood deafness informs epidemiological research, helps healthcare planning and may improve future healthcare delivery.

Hearing loss may initially start as unilateral and progress to bilateral. Several investigations are common to unilateral and bilateral of PCHI. These guidelines should be read in conjunction with those for severe/profound and mild/moderate PCHI. It may sometimes be difficult to pinpoint the aetiology of hearing loss despite comprehensive 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 unilateral permanent childhood hearing impairment. This is an update to the guidelines on aetiological investigation into permanent unilateral hearing loss in children produced by BAAP/BAPA in August 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 availability of 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 base 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 are highlighted and may form a 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 when:

[1] New medical information and new tests become available
[2] New symptoms develop e.g. neurological difficulties,
[3] New information relating to family history becomes available e.g. hearing loss
[4] There is progression of hearing loss, hearing deteriorates in the normal hearing ear
[5] Parents or young deaf people request this

Who can undertake aetiological investigations?

A medical practitioner with the appropriate knowledge, skills and competencies 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) 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 unilateral permanent sensorineural and conductive hearing loss of pre-lingual or late onset. There is insufficient good quality evidence regarding the outcome of aetiological investigations as related to the severity of the unilateral hearing loss and clinical judgement is advised.

Search Methodology:

The literature search covered databases including PubMed, Medline, Embase, AMED, BNI, CINAHL, HMIC, PsychINFO and Cochrane Library Database. The keywords detailed below 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 till 30/08/2014. 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-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: [Appendix 1]

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)

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 studies or High quality case control or cohort studies with a very low risk of confounding bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding 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 undertaken in all children and Level 2 investigations to children with specified indications.

Level 1 investigations include:

[1] Clinical history [6-11] [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
➢ Course 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 if available

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, and skeletal anomalies. This should be done with a problem solving approach rather than as a tick box exercise. Given below is a table of detailed anamnesis for history and examination

Timing of assessment: History should be taken when diagnosis of deafness is confirmed, at first visit.

2) **Clinical examination:** [6-12] [Recommendation D]

Anthropometry: height, weight, head circumference, including centile range
Clinical examination of craniofacial region
➢ Dysmorphism
➢ Ears: e.g. ear pits, tags, sinus
➢ Neck: skin tags, sinus, webbing, 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 according to findings above e.g. for ear pits, dysmorphism

Timing of assessment: Examination should be done when diagnosis of deafness is confirmed, at first visit, as soon as opportunity provides.

3) **Family audiograms:** [9, 11, 13-15] [Recommendation D]

Parents and siblings should have their hearing checked, particularly as unilateral hearing loss can be missed.

Timing of assessment: Early, before the genetics referral.

4) **CMV testing:** (sensorineural hearing loss) [9, 12, 16-24, 25] [Recommendation B/C]

If the child is less than one year of age

- 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 name at time of birth
- Mother's address at the time of 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.

<u>At any age,</u>

Consider testing mother's CMV IgG. If negative this excludes congenital CMV infection. This may sometimes be used to avoid venepuncture in the child.[28]
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 including the Audiologists, doctors and the testing laboratory to facilitate a timely diagnosis. Guidelines on antiviral therapy for congenital CMV may evolve in the next few years.

5) MRI of Internal Auditory Meatus or CT scan of Petrous Temporal

[9, 10, 12, 26-39] **:** [Recommendation C]

- Diagnostic radiologic imaging is the highest yielding test for evaluating children with SNHL. The choice of imaging will depend on the clinical picture and the type of permanent hearing loss.
- MRI of Internal Auditory Meatus is the preferred investigation for SNHL due to the advantage of visualisation of the cochleo vestibular nerve, its

cochlear branch and the posterior fossa. The fluid in the cochlea, fibrosis, and interscalar defects are often only visible on MRI. MRI of the brain should included in the study to look at the auditory pathways and cortex.

- CT is preferred in children with a permanent conductive component to their hearing loss. [It is useful to remember that EVA can cause a conductive component and MRI is the preferred scan].
- 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 is useful to distinguish fibrosis from calcification

Timing of investigation: Soon after diagnosis, best within 3 months age in natural sleep if diagnosis follows newborn hearing screen [to avoid the need for sedation]. If the child is older sedation or GA may be required and this risk should be weighed with the benefit of early imaging. Imaging may be delayed until it can be performed with the cooperation of the child unless clinical features imply that earlier diagnosis is likely to improve outcome or prevent complications.

6) Ophthalmic assessment: [26, 27, 40-42] [Recommendation C]

20-60% of children with PCHI have ophthalmic abnormalities which can impact on the child's communication, but the evidence about eye abnormalities in unilateral hearing loss is sparse. Ophthalmic assessment in unilateral hearing loss is currently guided by the Vision care document by NDCS/SENSE until further evidence is available. The child should be referred for a full ophthalmic assessment at the following times:

- Following the diagnosis of PCHI
- At any time if parents or the education service have concerns
- At one to three years of age
- At four to five years of age [vision screening by an orthoptist, which is usually done at school and will include an assessment of visual acuity]
- At seven to nine years of age
- Transition to secondary school

The ophthalmic examination should include formal testing and recording of visual acuity, functional assessment of vision, refraction, visual field assessment, diagnosis of strabismus and eye movement anomalies, fundoscopy and assessment of binocular vision depending on the feasibility and age of the child. Further ophthalmic monitoring will be determined by the underlying diagnosis e.g. Congenital CMV

Level 2 investigations

Level 2 investigations will be indicated based on history and clinical findings.

1) Serology: To exclude congenital infection: (for sensorineural hearing loss) [25, 26, 39, 43-48] [Recommendation C]

Mothers may be screened for these infections in pregnancy and it is useful to know these results. As many of the babies affected by congenital infections can be asymptomatic at birth, if the results or immune status of the mother are 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:

If child is less than 1 year of age:

- Toxoplasma IgM: if persists more than one month age is indicative of congenital infection. If both Toxoplasma IgG and IgM are negative, congenital toxoplasmosis can be excluded
- 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 child is over 1 year of age:

- Child Toxoplasma IgG
- Consider doing maternal Toxoplasma IgG

If either 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) Genetic testing [specific genes/chromosomes/CGH microarray]:

Informed consent should be taken from parents prior to genetic testing. Parents should be informed that DNA is stored in lab after testing and that genetic testing can take a long time. Permission should be taken to share results with other family members/professionals [49]. Consider genetic testing in cases where a syndrome is suspected e.g.

- Waardenburg [50, 51],
- BOR [52] ,
- Hemifacial microsomia [53] or
- Testing for SLC26A4 in children with EVA[54].

Testing for syndromic forms of deafness is likely to become more widely available.

There is no convincing evidence to support a GJB2 test [Connexin 26] in a unilateral Sensorineural hearing loss, although some cases have been reported. [39, 55-59] 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. [60]

Chromosomal studies/CGH microarray is indicated if the child has

- History of developmental delay
- Dysmorphic features

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

3) Renal ultrasound [61]: [Recommendation D] Indicated if the child has

- Preauricular pits or sinuses, deformity of ear[microtia, anotia, 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

4) Haematology and Biochemistry where clinically indicated [10, 59, 62, 63]: [Recommendation D]

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

- Family history of thyroid disease
- Goitre, clinical symptoms/signs of thyroid disease
- 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.

5) Investigation into autoimmune diseases [64,65]: [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, gastric and others as indicated.

6) Metabolic Screen on blood and urine:

Where clinically indicated e.g. epilepsy, neuroregression. There is little evidence to support this recommendation.

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

- Family history of hearing loss, parental consanguinity
- A syndrome is suspected,
- Child has multiple abnormalities,
- Parental request

8) Vestibular investigations: [66-67] [Recommendation D]

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

- Motor milestones are delayed
- Progressive deafness
- Conditions known to be associated with vestibular dysfunction e.g. post-meningitis
- Vertigo/dizziness
- Vestibular malformations

References

[1] MacArdle B, Bitner-Glindzicz M. Investigation of the child with permanent hearing impairment. Arch Dis Child Educ Pract Ed 2010;95:14–23. [Review]

[2] British Association of Audiovestibular Physicians manual for producing guidelines, Clinical Standards Subcommittee BAAP, 2013.

[3] Quality Standards in the NHS Newborn Hearing Screening Programme 2010. http://hearing.screening.nhs.uk/standardsandprotocols#fileid10752

[4] Woolf S, Grol R, Hutchinson A, et al. Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines. BMJ 1999;318(7182):527-530.

[5] Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. BMJ 2001;323:334-336.

[6]General Medical Council (2013) Good Medical Practice London GMC. http://www.gmc-uk.org/guidance/good_medical_practice.asp

[7] Hampton J, Harrison M, Mitchell J, et al. Relative Contributions of History-taking, Physical Examination, and Laboratory Investigation to Diagnosis and Management of Medical Outpatients. BMJ 1975; 2:486-489. [Level3]

[8]Paley L, Zornitski T, Cohen J et al. Utility of Clinical Examination in the Diagnosis of Emergency Department Patients Admitted to the Department of Medicine of an Academic Hospital Arch Intern Med. 2011;171(15):1393-1400. [level 3]

[9]Yield of investigations from the BAAP National Audit, 2013. Unpublished data, BAAP. [Level 3]

[10] Mafong D, Shin E, Lalwani A. Use of Laboratory and Radiologic Imaging in the Diagnostic Evaluation of Children with Sensorineural Hearing Loss. Laryngoscope 2002;112(1):1-7. [Level 3]

[11] Yelverton J, Dominguez L, Chapman D et al. Risk factors associated with unilateral hearing loss. JAMA Otolaryngol Head Neck Surg 2013; 139(1):59-63 [Level 2++]

[12] Ratnayake S, Mac Ardle B, Harrop-Griffiths K. Permanent unilateral deafness identified by newborn hearing screening: Yield of aetiological medical investigations and the association with risk factors, audiological profile and stability of hearing loss. Arch Dis Child 2011; 96(A33):0003-9888 [Level 2++]

[13] Stephens D. Audiometric investigation of first- degree relatives. In: Martini A, Mazzoli M, Stephens, D, Read A, eds. Definitions, Protocols & Guidelines in Genetic Hearing Impairment. London: Whurr Publishers 2001: 32-33.

[14] Stephens D, Meredith R, Sirimanna T, et al. Application of the Audioscan in the detection of carriers of genetic hearing loss. Audiology. 1995;34(2):91-7. [Level 2-]

[15] Lina-Granade G, Collet L, Morgon A Physiopathological investigations in a family with a history of unilateral hereditary deafness. Acta Otolaryngol 1995;115 (2) :196 – 201 [Level 2-]

[16]Boppana S, Ross S, Shimamura M, et al. Saliva Polymerase-Chain-Reaction Assay for Cytomegalovirus Screening in Newborns. N Engl J Med 2011;364(22):2111-2118. [Level 2+/2++]

[17]Boppana S, Ross S, Novak Z, et al. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection. JAMA 2010;303(14):1375–1382. [Level 2+/2++]

[18] Barbi M ,Binda S, Primache V, et al. Cytomegalovirus DNA detection in Guthrie cards: a powerful tool for diagnosing congenital infection. J Clin Virol 2000;17(3):159-65. [Level 2+/++]

[19]Williams E, Kadambari S, Berrington J, et al. Feasibility and acceptability of targeted screening for congenital CMV-related hearing loss. Arch Dis Child Fetal Neonatal Ed. 2014: F1-7. [Level 2+/++]

[20]de Vries J, van der Eijk A, Wolthers K, et al. Real time PCR versus viral culture on urine as a gold standard in the diagnosis of congenital cytomegalovirus infection. J Clin Virol 2012(2):167-70. [Level 2-]

[21]Atkinson C, Walter S, Sharland M, et al. Use of stored dried blood spots for retrospective diagnosis of congenital CMV. J Med Virol 2009;81:1394–8. [Level 2-]

[22] Tagawa M, Tanaka H, Moriuchi M, et al. Retrospective diagnosis of congenital cytomegalovirus infection at a school for deaf by using preserved dried umbilical cord. J Paediatrics 2009:155(5):749-751. [Level 2-]

[23]Enders G, Daiminger A, Bäder U, et al. The value of CMV IgG avidity and immunoblot for timing the onset of primary CMV infection in pregnancy. J Clin Virol 2013;56(2):102-7. [Level 2+]

[24] Misono S, Sie K ,Weiss N et al. Congenital cytomegalovirus infection in pediatric hearing loss. Arch *Otolaryngol Head Neck* Surg 2011; 137(1): 47-53 [Level 2++]

[25] Clinical Virology Network Guidelines. Unpublished data [Guideline]

[26] Declau F, Boudewyns A, Van den Ende J et al. Etiologic and audiologic evaluations after universal neonatal hearing screening: analysis of 170 referred neonates. Pediatrics, 2008; 121(6):1119-26[Level 2+]

[27] Wiley S, Arjmand E, Jareenmeinzen-Derr, et al. Findings from multidisciplinary evaluation of children with permanent hearing loss. Int J Pediatr Otorhinolaryngol. 2011 Aug;75(8):1040-4. . [Level 3]

[28] Haffey T, Fowler N, Anne S . Evaluation of unilateral sensorineural hearing loss in the pediatric patient. Int J Pediatr Otorhinolaryngol. 2013 Jun;77(6):955-8. [Level 3]

[29] Bamiou DA, Savy L, O'Mahoney C , Phelps P, Sirimanna T . Unilateral sensorineural hearing loss and its aetiology in childhood: the contribution of computerised tomography in aetiological diagnosis and management International Journal of Pediatric Otorhinolaryngology 51 (1999) 91–99 [Level 3]

[30] Licameli G, Kenna M. Is Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) More Useful in the Evaluation of Pediatric Sensorineural Hearing Loss? Laryngoscope 2010; 120: [Level 2+]

[31] Holman M, Schmitt W, Carlson M, et al. Pediatric cerebellopontine angle and internal auditory canal tumors: clinical article.. J Neurosurg Pediatr. 2013;12(4):317-24. [Level 2+]

[32] Vrabec J, Lin J. Inner ear anomalies in congenital aural atresia. Otol Neurotol 2010; 31(9):1421-1426. [Level 2+]

[33] Yang J.,Li Y. Constitute, imaging and auditory characteristics of pediatric patients with congenital malformations of inner ear in sensorineural hearing loss. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2011;25(1):1-5. [Level 2+]

[34] Song J, Choi H, Oh S et al. Unilateral sensorineural hearing loss in children: The importance of temporal bone computed tomography and audiometric follow-up. Otol Neurotol 2009; 30(5):604-608. [Level 2+]

[35] McClay J, Booth T, Parry D, et al. Evaluation of pediatric sensorineural hearing loss with magnetic resonance imaging. Arch *Otolaryngol Head Neck* Surg 2008; 134(9): 945-952 [Level 2++/2+]

[36] Laury A, Casey S, McKay S, et al . Etiology of unilateral neural hearing loss in children. Int J Pediatr Otorhinolaryngol 2009; 73(3):417-427 [Level 2+]

[37] Taiji H, Morimoto N, Matsunaga T. Unilateral cochlear nerve hypoplasia in children with mild to moderate hearing loss. Acta Otolaryngol 2012; 132(11): 1160-1167 [Level 3]

[38] Simons J,Ruscetta M,Chi D. Sensorineural hearing impairment in children with Chiari I malformation. Ann Otol Rhinol Laryngol 2008; 117(6): 443-447 [Level 2+]

[39] Ghogomu N, Umansky A, Lieu J Epidemiology of Unilateral Sensorineural Hearing Loss With Universal Newborn Hearing Screening. Laryngoscope, 2014; 124(1):295-300

[40]Nikolopoulos P, Lioumi D, Stamataki S, et al. Evidence-based overview of ophthalmic disorders in deaf children: a literature update. Otology and Neurotology 2006. 27:S1-S24 [level 2++]

[41] Sharma A, Ruscetta M, Chi D. Opthalmologic findings in children with sensorinerual hearing loss. Archives of otolaryngology Head Neck Surgery 2009;135(2):119-123. .[Level 2+]

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

[43] Brown E, Chau J, Atashband S, et al. A systematic review of neonatal toxoplasmosis exposure and sensorineural hearing loss. Int J Pediatr Otorhinolaryngol. 2009;73(5):707-11. [Level 2++]

[44] de Jong E, Vossen A, Walther F, How to use...neonatal TORCH testing. Arch Dis Child. Education and practice edition 2013;98(3):93-8 [Review]

[45]Sánchez P, Wendel G, Norgard M. Congenital syphilis associated with negative results of maternal serologic tests at delivery. Am J Dis Child 1991; 145:967–969. [Review]

[46] Rawstron S, Mehta S, Bromberg K. Evaluation of a Treponema pallidum-specific IgM enzyme immunoassay and Treponema pallidum western blot antibody detection in the diagnosis of maternal and congenital syphilis. Sex Transm Dis 2004; 31:123–126[Level 3]

[47] Torre P, Zeldow B, Hoffman H, et al. Hearing loss in perinatally HIV-infected and HIV-exposed but uninfected children and adolescents. Pediatric HIVAIDS Cohort Study. Pediatr Infect Dis J. 2012;31(8): 835-841 [Level2-?]

[48] Palacios G, Montalvo M, Fraire M et al. Audiologic and vestibular findings in a sample of Human Immunodeficiency Virus type-1-infected Mexican children under Highly Active Antiretroviral Therapy. Int J Pediatr Otorhinolaryngol 2008; 72(11):1671-1681 [Level 2+]

[49] Lucassen A, Hall A. Consent and confidentiality in clinical genetic practice: guidance on genetic testing and sharing genetic information. A report of the Joint Committee on Medical Genetics. Clin Med. 2012 Feb;12(1):5-6 [Guideline]

[50] Lalwani A, Mhatre A, San Agustin T et al Genotype-phenotype correlations in type 1 Waardenburg syndrome. Laryngoscope. 1996;106(7):895-902.[Level 3]

[51] Tuysuz B,Collin A,Arapoglu M et al. Clinical variability of Waardenburg-Shah syndrome in patients with proximal 13q deletion syndrome including the endothelin-B receptor locus. Am J Med Genet 2009;149A(10): 2290-5

[52] Lindau, T ; Cardoso, A ; Rossi, N et al. Anatomical changes and audiological profile in Branchio-oto-renal syndrome: a literature review. Int Arch Otorhinolaryngol 2014;18(01):068-076

[53] Ear abnormalities in patients with oculo-auriculo vertebral spectrum (Goldenhar syndrome). Rosa, R ; Silvia A ; Goetze, T et al Brazilian journal of otorhinolaryngology, 2011, Vol.77(4), 455-6

[54] Chattaraj P, Reimold F, Muskett J, et al. Use of SLC26A4 mutation testing for unilateral enlargement of the vestibular aqueduct. JAMA Otolaryngol Head Neck Surg. 2013 ;139(9):907-13. [Level 2+]

[55]Kenna M, Feldman H, Neault M, et al. Audiologic phenotype and progression in GJB2 (Connexin 26) hearing loss. Arch Otolaryngol Head Neck Surg. 2010;136(1):81-7. [Level 2+]

[56] Ballana E, Ventayol M, Rabionet R et al. Connexins and deafness Homepage. World wide web URL: http://www.crg.es/deafness

[57] Kessell D, Dunlop J, Lench N, et al. Connexin 26 mutations in hereditary non-syndromic, sensorineural hearing deafness. Nature 1997;387: 80- 83. [Level 3]

[58]] Dodson K, Georgolios A, Barr N et al. Etiology of unilateral hearing loss in a national hereditary deafness repository. Am J Otolaryngol 2012; 33(5):590-4.

[59] Preciado D, Lawson L, Madden C at al. Improved diagnostic effectiveness with a sequential diagnostic paradigm in idiopathic pediatric Sensorineural hearing loss. Otol Neurotol 2005;26(4):610-5 [Level 2+]

[60] Shearer A, DeLuca A, Hildebrand M, et al. Comprehensive genetic testing for hereditary hearing loss using massively parallel sequencing. Proc Natl Acad Sci U S A. 2010. 7;107(49):21104-9 [Level 3]

[61] Wang R, Earl D et al.Syndromic ear anomalies and renal ultrasounds Pediatrics. 2001; 108(2):E32. [Level 2-]

[62]Bogazzi F, Russo D, Raggi F, et al. Mutations in the SLC26A4 (pendrin) gene in patients with sensorineural deafness and enlarged vestibular aqueduct. J Endocrinol Invest.2004, 27(5):430-5.[Level 2-]

[63] Iwasaki S, Tsukamoto K, Usami S, et al Association of SLC26A4 mutations with clinical features and thyroid function in deaf infants with enlarged vestibular aqueduct. J Hum Genet. 2006;51(9):805-10. [Level 2-?]

[64]Reddy M, Satyanarayana V, Hemabindu L, et al. Immunological studies in children with hearing impairment. J Indian Med Assoc. 2005:103(10):520-1. [Level 2- to 3]

[65] Agrup C, Luxon L. Immune-mediated inner-ear disorders in neuro-otology Current Opinion in Neurology 2006;19:26–32. [Review article]

[66] Raglan E, Radomskij P et al An audio-vestibular study of 128 children presenting to a specialised paediatric audio-vestibular clinic: Should every child with hearing impairment have vestibular function assessed? Audiological Medicine. 2009; 7:143-147 [Level 2- to 3]

[67] De Kegel A, Maes L, Baetens T, et al. The influence of a vestibular dysfunction on the motor development of hearing-impaired children. Laryngoscope. 2012;122(12):2837-43. [Level 3]

Appendix 1 Keywords

aetiological test/aetiology	autoimmune/immunological	blood test
biochemistry	BOR	child/children
chromosomal analysis	clinical examination	CMV/ cytomegalovirus
craniofacial anomalies	connexin/GJB	CTscan
full blood count	genetic	Guthrie
haematology	herpes	history
HIV/Human immunodeficiency virus	IgG avidity	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	rubella	sensorineural hearing loss
serology	syndrome	syphilis
thyroid function test	toxoplasma	varicella
vestibular	Urine/saliva /mouth swab PCR	urine
U & E/urea electrolytes	unilateral hearing loss	

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 Acqueduct
PCHI Permanent Childhood Hearing Impairment
PCR Polymerase Chain Reaction
FBC Full Blood Count
ESR Erythrocyte Sedimentation rate
U & E Urea and electrolytes
TFT Thyroid function test

Appendix 3: Useful parent resources

- NDCS publication "Understanding your child's hearing tests"
- 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 BAAP national audit proforma can be used to benchmark practice. This is attached separately.

Appendix 5: Future Research

The evidence to support aetiological investigations of unilateral hearing loss 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 unilateral 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
- There are questions regarding the evidence base for the extent and frequency of Opthalmic assessment. There is an urgent need to assess the yield and the best regime for assessment.
- Indications and timing of thyroid function tests in PCHI
- Genetic test abnormalities in unilateral PCHI
- Cost benefit analysis of aetiological investigations

Appendix 6: Authorship and Acknowledgements

Acknowledgement: The authors are grateful to the librarians at the RNID library at Royal National Throat Nose and Ear Hospital for their help in procuring articles and for their help with the literature search. The authors would like to express their special thanks to Professor Maria Bitner-Glindzicz, Dr Jan Casselman, Miss Lucilla Butler, Dr Juan Kaski, Dr Simone Walter, Dr Susan Snashall and Professor Valerie Newton for their expert opinions and to Dr Katherine Harrop-Griffiths for allowing inclusion of the BAAP national audit proforma in this guideline. The authors acknowledge the help provided by colleagues who contributed to the consultation process and the advisory role of the BAAP executive committee in editing the document.

Authors:
Dr Anuradha Shetye, Consultant in Audiovestibular Medicine, East and North Herts NHS Trust, Lister Hospital, Stevenage
Dr Waheeda Pagarkar, Consultant in Audiovestibular Medicine, University College London Hospitals Foundation NHS Trust, London

Guideline group members:
Dr Alpana Kulkarni [A], Consultant in Audiovestibular Medicine, Hertfordshire Community NHS Ttrust

Dr Waheeda Pagarkar [B], Consultant in Audiovestibular Medicine, University College London Hospitals Foundation NHS Trust, London
Dr Anuradha Shetye [C], Consultant in Audiovestibular Medicine, East and North Herts NHS Trust, Lister Hospital, Stevenage
Dr S N Vijayanand [D], Consultant in Paediatric Audiovestibular Medicine, St Michael's Hospital, Oak Lane Clinic and Edgeware Community Hospital, Royal Free Hospitals NHS Trust, London
Dr Priya Somasegaram [E], Consultant in Audiovestibular Medicine, University College London Hospitals Foundation NHS Trust, London

Lay Members:
Ms Caroline Star [F], Parent of child with hearing loss, Chair of CMV Action
Mr Prashant Jain [G], Parent of child with hearing loss

Date of review: June 2019