Guidelines for aetiological investigation into progressive 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 progressive hearing loss [1]:

1. To answer the questions parents may have, "Why is my child's hearing loss getting worse?"
2. Identification of conditions where timely treatment will prevent progression of the hearing loss e.g. congenital CMV, congenital cholesteatoma.
3. Investigation of progressive hearing loss may uncover conditions requiring medical management e.g. space occupying lesions, congenital toxoplasmosis, autoimmune disease.
4. To detect inner ear dysplasia in order to give appropriate advice: e.g. 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. Usher 3, possibility of syndrome with additional medical problems [mitochondrial disease]
6. To prioritise children requiring cochlear implants e.g. bacterial meningitis
7. 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.
8. To manage associated medical conditions e.g. thyroid dysfunction in Pendred syndrome, renal disease in Alport syndrome, autoimmune disease etc.

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 followed in conjunction with those for unilateral, mild /moderate and severe to profound 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 propose an evidence based approach to the investigation of the cause of progressive PCHI. 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:

Children with progressive PCHI may have previously had aetiological investigations. These should be reviewed if there is a progressive hearing loss, particularly as there may be a possibility for treatment. The importance of early investigation should be stressed to the family and, if appropriate to the child/young person. Appropriate counselling should be given with written information where possible, so that they can make a well informed choice about having investigations.

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).

Subjects

These guidelines apply to children with unilateral or bilateral progressive permanent childhood hearing impairment. The definition of progressive hearing loss is not universally agreed and several considerations are essential.

- Temporary middle ear dysfunction e.g. glue ear will need to be excluded as a cause of drop in hearing thresholds. Progression of hearing loss can also be due to middle ear pathology causing irreversible damage e.g. ossicular erosion, and this will be included as a cause of progressive hearing loss [5].
- Children with auditory neuropathy may have fluctuations in their hearing and are outside the scope of this document.
- Clinicians should be alert to the possibility of non-organic hearing loss presenting as a progressive loss in both normal hearing children and children with identified PCHI [6, 7]
- Due consideration should be given to the variation of hearing levels when comparing results of objective hearing tests [e.g. ABR] with behavioral hearing thresholds
- Hearing assessment should be performed by staff trained in Paediatric Audiology
- Some definitions of progressive hearing loss currently do not consider a time window for confirmation of progression in their definition. This may be left to the discretion of the clinician, based on the level of concern.
- Both air and bone conduction testing must be done when considering progression, and the definition may be applied to either.

The definitions of progressive hearing loss for the purpose of this document are any one of the following

- A decrease of hearing level of ≥20dB in the 3 frequencies pure-tone average (0.5, 1, and 2kHz) [8]
- A decrease of hearing level of ≥10dB at two or more adjacent frequencies between 0.5 and 4kHz [9]
- A decrease in ≥15dB at one octave frequency between 0.5 and 4kHz [9]
- A decrease of at least ≥15dB in either the pure-tone average [of 0.5, 1, 2 &4kHz] or the high frequency pure-tone average [of 4, 6 and 8kHz] with a minimum audiometric follow-up of 3 months. [10]

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 librarians 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 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 articles published from 1966 till 15/02/2017. 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 the members of the guideline group [A-E]. Full texts of all these relevant articles were obtained. Members of the guideline group [A-E] reviewed the full texts of the articles. The literature search was rerun in March 2017 by one member of the guideline group [B] to ensure inclusion of all articles published in 2017. The articles relevant to the guideline were graded for evidence level by members of the guideline group [A-E].

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

- Timeframe (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 [11]:

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: [12-14] [Recommendation D]
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. ototoxic medication, head injury, intracranial tumors. 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.

Onset, duration and progression of hearing loss
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

Timing of assessment: As soon as progressive deafness is suspected or confirmed

2) <u>Clinical examination:</u> [12-14] [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: rash, hypo- or hyper-pigmentation
➢ Spine: skeletal anomalies
➢ Hands, Limbs, Nails: hypoplasia
➢ Abdomen: hepatosplenomagaly
➢ Chest: heart murmur in syndromes
➢ Neurological assessment: focal deficits
Developmental assessment
Clinical vestibular examination
Eye examination
Examination of parents

Timing of assessment: As soon as progressive deafness is suspected or confirmed

3) MRI of Internal Auditory Meati and brain or CT scan of Petrous Temporal: [Recommendation C] [14, 15-23]

- Most children with PCHI will have had imaging prior to their progression of hearing loss. Consideration must be given to review the earlier imaging by a Radiologist with the relevant expertise

- There is insufficient evidence for repeating MRI/CT with progression of hearing loss. The decision to repeat imaging may be considered depending on the trigger for progression, and the extent, type and duration of progression and the following guidance may be used: [Recommendation D]

    - If there is change in type of hearing loss e.g. a purely sensorineural or conductive hearing loss becomes mixed without apparent explanation

    - If new unexplained symptoms of concern appear [e.g. unexplained increasing headaches, imbalance/dizziness] or the clinical course cannot be explained by current diagnosis.

    - If the child has had bacterial meningitis

    - If earlier imaging has artefact, e.g. due to movement or dental braces

    - If the drop in hearing is triggered by head injury and temporal bone /ossicular involvement is suspected

- 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. Specific modalities may be used e.g. multidetector CT /cone beam CT if particular conditions are suspected e.g. otosclerosis [16,17]

- Both CT and MRI are indicated in bacterial meningitis [as either imaging modality alone is inadequate in detecting changes suggestive of fibrosis and ossification].

- Due consideration should be given when requesting CT scan to the requirements of IRMER 2000 [Ionising Radiation (Medical Exposure) Regulations] with regards to justifying exposure to radiation [24]

Timing of investigation: Soon after progressive hearing loss is confirmed

4) CMV testing: [14, 25-35] [Recommendation B]
Children with progressive hearing loss often present after one year of age although presentation during infancy is also seen. CMV testing should be carried out for all children with progressive hearing loss.

<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. 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 CMVIgG/IgM. If both are negative, congenital CMV infection is excluded. This may sometimes be used to avoid venepuncture in the child. 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/confirming the diagnosis of progressive 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 to older children in the next few years [34]. It may hence be helpful to seek advice from an Infectious Disease Consultant , on a case by case basis, even if the child is beyond the treatment window.

5) Family audiograms: [14, 36,37] [Recommendation D]
Parents and siblings should have their hearing checked and should have a clinical examination to detect familial conditions e.g. branchi-oto-renal syndrome and mitochondrial hearing loss. Audiograms may be helpful in interpreting genetic test results.

Timing of assessment: Early, before the genetics referral.

6) Ophthalmic assessment: [Recommendation B]

20-60% of children with PCHI have ophthalmic abnormalities which can remain undetected and impact on the child's communication [14, 38-41]. Ophthalmic assessment is guided by the Vision care document by NDCS/SENSE [42]. All children with confirmed progression of sensorineural hearing loss should have a full ophthalmic assessment to look for manifestations of syndromic and non syndromic conditions e.g. optic atrophy, retinitis pigmentosa, anterior lenticonus, high myopia in Stickler, Alstrom, Alport, Usher 3, DIDMOAD, CMV, Cogan etc. [43-49]

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 if:

- There is evidence of vestibular hypofunction or motor milestones are delayed [unless there is an adequate explanation i.e. vestibular malformation] to detect retinitis pigmentosa [50-52].
- There are symptoms suggestive of Usher syndrome e.g. night blindness, visual field loss.
- There are symptoms and signs suggestive of optic atrophy

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

Timing: As soon as feasible after confirmation of progressive hearing loss. Many children will have had this as part of their aetiological evaluation.

7) Urine examination (labstix) for microscopic haematuria and proteinuria: [53-55] [Recommendation D]

All children with progressive HL 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. Urinary abnormalities may be detected in Branchiootorenal syndrome. [56]

Timing: As soon as feasible after confirmation of progressive hearing loss.

8) Genetic tests: Blood test for GJB2/GJB6 [Connexin 26/30] [14, 57-63] **and for mitochondrial hearing loss [m.1555A>G]** [64-67]: [Recommendation B]

- These tests are advisable in all cases of bilateral progressive hearing loss, if not already done, where aetiology has not been determined.
- A history of aminoglycoside use should be specifically asked for
- Informed consent should be taken from parents prior to genetic testing. Parents should be informed that DNA is stored in the laboratory after testing. Permission should be taken to share results with other family members/professionals.
- 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. Guidelines for further genetic testing are likely to evolve over the next few years.

9) Serology for other infections [14, 68-75] [Recommendation C/D]
Mothers may be screened for some of these infections in pregnancy [e.g. syphilis] and these results should be checked. Many of the affected babies can be asymptomatic at birth. It is hence best to investigate the baby if the testing or immune status of the mother is unknown. These tests may also be done on maternal stored (booking) serum if available.

Congenital toxoplasmosis: [68, 69] Can cause a progressive hearing loss. Testing depends on age of the child
<u>If child is less than 1 year of age testing should include:</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.

Congenital Rubella [70] Progressive hearing loss is only occasionally reported. Testing of the child depends on age.

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

Congenital Syphilis: [71-73]
Can cause a progressive hearing loss. 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.

Congenital HIV: [74, 75]
Although HIV is a known to be associated with an increased risk of conductive and sensorineural hearing loss, there are no robust evident from longitudinal studies to indicate that it is a cause of progressive hearing loss in children. Testing may 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 team.

10) Investigation into autoimmune diseases:[76-83] [Recommendation C/D]
Progressive hearing loss can occur as a part of multisystem autoimmune conditions e.g. SLE, Cogans syndrome or it could be the only presenting feature of an immune-mediated inner-ear disorder. Given the potential for treatment and importance of early intervention, blood tests for autoimmune /immunological conditions should be offered to children with a progressive sensorineural hearing loss. Tests may include antinuclear antibodies, antineutrophil cytoplasmic antibodies, DsDNA, RA factor, antiphospholipid, anticardiolipin, antithyroid antibody, antibodies to Sm, C3 and C4. General inflammatory markers i.e. ESR and CRP and FBC may be useful. Tissue specific antibodies such as hsp70 (68kd) have been tested but there is not enough evidence for its routine use.

Level 2 investigations

These are for selected children depending on clinical features

1) Haematology and Biochemistry: where clinically indicated [14, 22,84, 85] [Recommendation D]

Haemoglobinopathies can be associated with a progressive hearing loss [e.g. sickle cell anaemia]. A sickle cell screen is a part of the UK newborn screening program. Consider doing FBC, peripheral smear and haemoglobinopathy screen if there is clinical indication or a family history.

Routine tests such as U & E and TFT have a low diagnostic yield. TFT 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.

2) Renal ultrasound: [14, 86, 87] [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

3) Metabolic Screen on blood and urine: [88-90] [Recommendation D]
Where clinically indicated e.g. epilepsy, neurodegeneration, developmental delay. These investigations should be preferably planned in liaison with a specialist Paediatric Neurology team.

4) Lyme disease serology: [91]. [Recommendation D]
Sudden sensorineural hearing loss due to Lyme disease is rarely reported in children. Positive serology to Borrelia has been reported in adults with a sudden sensorineural hearing loss. Diagnosis is by serology, although this is to be considered in context of the clinical symptoms and exposure to the tick. This test should be considered only in specific cases.

6) CGH microarray: [92, 93] [Recommendation D] Indicated if

- History of developmental delay
- Dysmorphic features

Parental bloods may be requested in order to fully interpret findings.

7) Further genetic testing: [94-99] [Recommendation C/D]
Testing for syndromic and non-syndromic forms of deafness has become more widely available. Specific circumstances include:

- Testing for SLC26A4 in children with EVA,
- Testing for EYA1/SIX1 if there is evidence of clinical features of BOR
- Testing for Usher type 3

Improving access to Next generation sequencing and development of 'deafness gene panels' and whole genome sequencing will increase the yield of genetic testing in PCHI.

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

- Parents are consanguineous,
- A syndrome is suspected,
- Child has multiple system 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: [100-103] [Recommendation C/D]
Vestibular dysfunction is seen in several conditions that cause a progressive hearing loss e.g. CMV, EVA, Usher 3, Cogan, meningitis. All children with progressive hearing loss should have a clinical vestibular examination and if feasible, vestibular investigations. Increasing use of VEMPs, video Frenzels glasses and vHIT testing can improve access to vestibular testing.

10) Referral to Paediatric Rheumatologist/Immunologist
This may be considered if

- There are systemic symptoms of autoimmune disease e.g. joint involvement, skin rash, fever, visual symptoms, vertigo
- Abnormalities are found on autoimmune blood investigations
- There is sudden sensorineural hearing loss to severe/ profound levels

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Appendix 1: Keywords

aetiological test/aetiology	Alport /Alstrom syndrome	autoimmune/immunological/antiphospholipid/anticardiolipin
blood test	biochemistry	BOR
Behcet	CGH array	child/children
chromosomal analysis	clinical examination	CMV/ Cytomegalovirus
connexin/GJB	CT	Cogan
ERG/electroretinogram	full blood count	genetic
Guthrie	haematology	history
HIV/Human Immunodeficiency Virus	IgG avidity	kidney /renal function/U & E/urea electrolytes
kidney/renal ultrasound	liver function	Lyme disease
metabolic screen	mitochondrial mutation	MRI
mumps	neonatal blood spot	neonatal/perinatal history

Non organic	ophthalmology/eye	parent/sibling/family audiogram
PCHI/permanent childhood hearing loss/hearing impairment	permanent conductive hearing loss	Pendred syndrome/ SLC26A4
rubella	sensorineural hearing loss, progressive	Serology
SLE/Sjogren	syphilis	thyroid function test
toxoplasma	Usher	VEMP
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
VEMP Vestibular Evoked Myogenic Potentials
vHIT Video Head impulse Testing

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",
- 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 in progressive hearing loss is thin. Areas of research that could help to support an evidence base include

- Standardising definitions of progressive hearing loss
- Yield of aetiological battery and individual aetiological tests/ assessments in children with progressive PCHI
- Yield of history and clinical examination using a prospective study
- Systematic review of studies on aetiological investigations

Appendix 6: Authorship and Acknowledgements

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Author:
Dr Waheeda Pagarkar, Consultant in Audiovestibular Medicine

Guideline group members:
Dr Chrysa Spyridakou [A], Consultant in Audiovestibular Medicine
Dr Waheeda Pagarkar [B], Consultant in Audiovestibular Medicine
Dr Anuradha Shetye [C], Consultant in Audiovestibular Medicine,
Dr Juan Mora [D], Consultant in Audiovestibular Medicine,
Dr Sudhira Ratnayake [E], Consultant in Audiovestibular Medicine,
Dr Alpana Kulkarni [F] Consultant in Audiovestibular Medicine
Dr Radha Narayan [G] Consultant in Audiovestibular Medicine

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

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