BIAP Recommendation 12/9:

The assessment and management of auditory neuropathy spectrum disorders (ANSD) in babies after newborn hearing screening

General foreword

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

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Introduction

A specific type of sensorineural hearing loss was first described and named Auditory Neuropathy (AN) by Starr et al. in 1996. This new entity was observed owing to a diagnosis mismatch: the presence of otoacoustic emissions (OAE), suggesting a near normal hearing (normal cochlear function) and the abnormal or absent auditory brainstem responses (ABR), suggesting hearing loss.

Other terms describing the same condition are: auditory dys-synchrony, auditory mismatch, neural hearing loss, persistent outer hair cell function, auditory neuropathy/dys-synchrony or auditory synapthopathy.

Since 2008 this type of hearing loss has been defined as Auditory Neuropathy Spectrum Disorder (ANSD) describing a condition in which a patient's OAE are or were at one time present, and the ABR are abnormal or absent. Presently ANSD is diagnosed on the basis of the presence of cochlear microphonics (CM) and abnormal or absent ABR with or without abnormalities of OAE. Behavioural observation audiometry is an essential part of the ANSD diagnosis and must be performed before any intervention.

Prevalence and risk factors. ANSD may be present in newborns who are not at risk for hearing loss (between 0.006% and 0.03%), but the highest ever incidence reported in newborns at risk was 24%. The most common risk factors are: hyperbilirubinaemia/kernicterus requiring exchange transfusion, prematurity under 28 weeks of gestation, low birth weight under 1500 g, anoxia/hypoxia or respiratory distress, artificial ventilation, ototoxic medication, intensive care more than 7 days.

Recent studies show that ANSD may be present in 5–15% of infants with sensorineural hearing loss (SNHL). About 10–15% of newborns discharged from a neonatal intensive care unit (NICU), have a higher prevalence of SNHL, and particularly of ANSD. The prevalence of SNHL in the NICU-discharged population is around 1/50 compared with 1/1000 in full term newborns. Similarly, their ANSD prevalence is also higher than in full term infants, as ANSD accounts for up to 30% of all SNHL in NICU-discharged children.

Approximately 1.3 to 7.3% of patients diagnosed with ANSD present a unilateral type and approximately 2.4–4.7% of patients with unilateral deafness are diagnosed with unilateral auditory neuropathy (UAN).

***Lesion site*.** From audiological and electrophysiological measures, ANSD can be classified by the anatomical site of dysfunction. These divisions include:

- presynaptic or synaptic lesions - cochlear inner hair cell (IHC) dysfunction and/or loss of IHC ribbon synapses.
- postsynaptic lesions - axonal neuropathies, dendritic nerve terminals, auditory ganglion cell disorders, myelin disorders, hypoplasia of auditory nerve, auditory nerve conduction disorders.

***Aetiology and classification*.** ANSD can have multiple causes: genetic (certain types of syndromic or non-syndromic hereditary hearing losses), malformations (auditory nerve hypoplasia or aplasia, brain anomalies), neurodegenerative diseases (Charcot Marie Tooth disease, Friedreich's ataxia), metabolic diseases or mitochondrial disorders. Acquired ANSD includes infection during pregnancy, prematurity, hyperbilirubinaemia/kernicterus and perinatal hypoxia.
Genetic aetiology can be represented by: OTOF or DFNB9 gene mutations (autosomal recessive), responsible for the coding of the protein otoferlin; Pejvakin or DFNB59 gene mutations (autosomal recessive), coding the protein pejvakin; DIAPH3 or AUNA1 gene mutations, another protein coding gene, causing autosomal dominant non syndromic ANSD. Late onset ANSD is linked to ATP1A3, OPA1 or RFVT2 & RFVT3 gene mutations.

Genetic aetiology of ANSD related to the lesion site (ANNEX 1)

***Degree of hearing loss and severity of hearing dysfunction*.** The degree of hearing loss, as assessed by pure tone audiometry (PTA), found in patients with ANSD ranges from essentially subnormal hearing sensitivity to a profound hearing loss. From the functional point of view, perceptual deficits can accompany ANSD, such as problems with sound audibility, complex auditory signal processing (cochlear or neural processing) and speech perception in quiet and in noise (temporal resolution including gap detection, intensity and frequency resolution, adaptation, spatial streaming). ANSD intervention presents a particular challenge for professionals because of the large differences in ANSD patients' outcomes. Objective auditory thresholds are poorly correlated with behavioural outcomes.

The degree of hearing loss should be estimated from behavioural audiometry, nevertheless the severity of auditory dysfunction in a patient with ANSD may not be strictly related to the degree of hearing loss. ANSD may affect both ears or just one.

Over time, the degree of hearing loss may have different types of evolution (stable, progressive, fluctuating) or the hearing may normalise.

Scope

This document is a recommendation for practical issues in diagnostic assessment of ANSD in babies after newborn hearing screening.

There are currently different approaches to universal neonatal hearing screening in different countries. Cases of ANSD occurring in the well-baby population, screened only by OAE, may remain undetected until some problems are observed by the parents or professional staff.

For the early diagnosis of ANSD it is necessary to perform a cochlear-sensitive auditory test (OAE) as well as ABR.

Recommendation

Audiological assessment

The main purpose of the audiological assessment in ANSD is to determine the degree of hearing impairment and the site of the lesion, on which depends both the indication of therapeutic intervention and the predictions of outcomes.

1. ***Anamnesis and clinical otologic evaluation***

***Anamnesis/History*.** The anamnesis must include the following data:

Outcomes from the newborn hearing screening program (OAE and/or AABR/ASSR)

- General medical history: head injury, history of recurrent infections (e.g. otitis media, sinusitis), sepsis/meningitis, use of ototoxic medication.
- Birth history: gestational age, hypoxia/asphyxia, neonatal sepsis/meningitis, (degree of) hyperbilirubinaemia, exposure to aminoglycoside antibiotics or neurotoxic risk factors.
- Developmental history, if available: speech, language, vision, muscle tonus, gross and fine motor development.
- Family history: parental consanguinity, SNHL (e.g. ANSD) and outcomes with hearing devices, neurological conditions, visual impairment, speech delay, attention-deficit/hyperactivity disorder (ADHD), social communication disorder, special educational needs.

***Clinical otologic evaluation*.** Inspection of outer ear, external ear canal and middle ear otoscopy/micro-otoscopy/video-otoscopy.

2. ***Middle ear measurements - Tympanometry and stapedial reflex***

High frequency tympanometry should be carried out for babies under the age of 6–9 months. Wideband tympanometry is ideal for all ages.

Stapedial reflexes (SR) are an important part of the evaluation. SR appear to be absent in ANSD, but sometimes may be present with elevated thresholds, in principal due to the auditory nerve dysfunction.

3. ***Clinical TEOAE and/or DPOAE – (see BIAP Recommendation 12-8.1.3)***

(https://www.biap.org/en/recommandations/recommendations/tc-12-newborn-hearing-screening-unhs/367-rec-12-8-1-3-en-audiometric-procedures-in-the-first-year-of-life-otoacoustic-emissions/file)

- A clear transient evoked OAE (TEOAE) and/or distortion product OAE (DPOAE) response with abnormal or absent ABR is indicative of ANSD. In order to identify an ANSD both OAE and ABR must be assessed. – (BIAP Recommendation 12-8.1.3).
- The lack of TEOAE and/or DPOAE does not exclude an ANSD. If TEOAE and/or DPOAE are absent, ANSD needs to be confirmed by the presence of the cochlear microphonic (CM) by measuring a click-ABR or electrocochleography. - (BIAP Recommendation 12-8.1.3)

4. ***Auditory brainstem responses (ABR) – (see BIAP Recommendation 12-8.1.4)***

(https://www.biap.org/en/recommandations/recommendations/tc-12-newborn-hearing-screening-unhs/396-rec-12-8-1-4-en/file)

- To rule out ANSD it is highly recommended to use click-evoked ABR systematically. Both condensation and rarefaction single-polarity clicks are required to determine if a CM is present (with abnormal or absent ABR) and so identify ANSD. The CM is produced by the outer hair cells and can therefore still be present in cases of ANSD. The CM waveforms elicited by the condensation and rarefaction clicks exactly mirror

each other (whereas the typical ABR neural potentials appear in the same direction in both waveforms).

- In case of ANSD (without post-synaptic neural potentials, which could cover the CM) the CM becomes visible as a potential starting within 1 ms after a click stimulus at intensities above 70 dBnHL. The CM shows a variable duration of 3 to 5 or 6 msec in ANSD.
- Electrocochleography (EcoG) is a gold standard for the study of the CM, SP and CAP, and may have a role in detecting the site of the lesion in ANSD and thereby in predicting the outcomes of ANSD patients with cochlear implants. However, for the most clinical teams, EcoG is not a routine procedure.

5. Auditory Steady State Responses (ASSR)

(https://www.biap.org/en/recommandations/recommendations/tc-12-newborn-hearing-screening-unhs/396-rec-12-8-1-4-en/file)

The Auditory Steady State Responses (ASSR) by themselves are not sufficient for the diagnosis of ANSD, none of the studies until now showing strong correlations between behavioural and ASSR thresholds.

ASSR may be present in ANSD subjects, produced by phase-locking to microphonic and/or neurophonic responses, but do not match the real hearing thresholds.

6. Behavioural audiological measurements (BAM)

(https://www.biap.org/fr/recommandations/recommendations/tc-12-newborn-hearing-screening-unhs/418-rec-12-08-2-en-audiometric-procedures-in-the-first-year-of-life-visual-reinforcement-audiometry-vra/file)

Behavioural audiological responses (BAM) are the most important and mandatory tool for the estimation of the minimum response levels/hearing thresholds necessary in the planning of therapeutic intervention, and should be the only base for the fitting of hearing aids.

Along with the ongoing diagnostic process and also within the child‘s follow-up process BAM are mandatory in order to reveal auditory fluctuations, temporary or progressive hearing loss or normalisation of hearing thresholds.

7. Cortical auditory evoked potentials (CAEP)

Measurement of the cortical auditory evoked potentials (CAEP) (non-invasive physiological testing of the central auditory pathway) can be used as a biomarker for the hearing threshold and auditory cortical development and as a clinical tool to guide the intervention choices, to provide prognoses, to make adjustments to treatments and to monitor treatment effectiveness and rehabilitation outcomes in children with ANSD.

The P1 CAEP responses show three developmental patterns: *normal* (present and normal P1 CAEP responses), *delayed* (present P1 CAEP responses of delayed latency and reduced amplitudes) and *abnormal* (abnormal or absent P1 CAEP responses). These patterns reflect an increasing severity (respectively) in the degree of neural dys-synchrony in the ascending input affecting cortical maturation.

8. Vestibular assessment

Some ANSD patients show abnormalities of oVEMP and cVEMP (ocular and cervical vestibular evoked myogenic potentials), indicating vestibular involvement.

The vestibulo-ocular reflex (VOR) gain is reduced in individuals with ANSD, but they can develop compensatory mechanisms. ANSD patients with neuro-sensorial vestibular disturbance are better described as having ‘‘auditory-vestibular neuropathy”.

The association of vestibular dysfunction in ANSD is part of ongoing research.

Multi-disciplinary approach

The management of a child with ANSD requires a multi-disciplinary team approach, working in partnership with the family. The team should include a paediatric audiologist, a medical professional (audiological physician, ENT consultant and paediatrician), a speech-language therapist, an early interventionist, an ophthalmologist and a neurologist.

For the diagnostic and intervention in ANSD and for parental counselling, the audiological assessment should be followed by different medical evaluations:

- Clinical genetic referral and genetic tests: screening for Otoferlin, Pejvakin, Connexine 26 and m.1555AG.
- Pediatric referral: to exclude developmental delays and other co-morbidities depending on the etiology of ANSD.
- Imaging of VIIIth cranial nerve: MRI can reveal morphological abnormalities of the 8th nerve (hypoplasia or aplasia), which is important in the choice of further management options.
- Neurological evaluation: to assess the condition of the cranial nerves in order to exclude other peripheral neuropathies.
- Ophtalmological evaluation: to identify visual impairment which would impact rehabilitative strategies in ANSD. Liaising with the ophthalmologist to rule out optic neuropathy in case of a visual concern.
- Congenital cytomegalovirus infection (cCMV) testing: ANSD can be present in infants with cCMV infection without any other symptoms.

Intervention

The intervention should start as soon as possible on the basis of results of both audiological and multidisciplinary assessment.

The treatment modality should be chosen following intensive counselling and the patient's family must be informed regarding the eventual outcome limits in the case of postsynaptic or associated central nervous system lesions.

All children with ANSD, no matter the degree of their hearing loss, should start with early intervention by auditory stimulation in order to activate the maturation of the auditory pathways and to prevent sensory deprivation. Hearing aids should always be the first intervention step no matter the age of the child.

Hearing aids are used to amplify the acoustic signal and improve speech audibility for listeners with ANSD. In some cases, hearing aids may not be helpful, as making sounds louder does not improve the speech intelligibility. https://www.biap.org/fr/recommandations/recommendations/tc-06-hearing-aids/516-rec-06-17-en-hearing-aid-fitting-in-children-with-auditory-neuropathy-spectrum-disorder-ansd/file

Children with ANSD with hearing thresholds in the severe or profound range meet the criteria for a cochlear implantation, solely based on the degree of hearing loss. For these children, cochlear implantation should be offered unless there are medical or radiological contra-indications.

For patients with ANSD fitted with hearing aids who do not show a good and stable progress in the development of speech, language and communication, a cochlear implant can be the next step in the intervention. This decision takes more time for children with this type of sensorineural hearing loss than those with ANSD (REC TC 24-01): https://www.biap.org/en/recommandations/recommendations/tc-24-early-screening-for-

children-s-language-disoders/263-rec-24-01-en-language-development-in-children-aged-0-to-3-years/file

For ANSD cases with unclear development there may be a need for more time and more information based on multidisciplinary observations, to recommend the best intervention.

In cases with unilateral ANSD the indication for treatment remains particularly difficult. The child can develop normally owing to the healthy ear, with the possible known losses similar to unilateral hypoacusis. Many aspects can be discussed: whether the impact of amplification or cochlear implant stimulation of the pathological ear would be beneficial, or whether these solutions could have an unfavourable effect in the presence of a normal ear, especially considering that many of the unilateral ANSD are due to anomalies of the cochlear nerve. The current information regarding the results in such situations refer most often only to isolated cases and cannot constitute evidence for good practice.

Favourable CI outcomes can be anticipated in patients with certain aetiologies of ANSD, particularly in those with OTOF, WFS1 and OPA1 variants, while patients with cochlear nerve deficiency may have suboptimal outcomes. For children with a history and clear genetic aetiology suggestive of limited progress, the CI will be considered as early as possible.

Recommendations on treatment options include hearing assistive technology (HAT). https://www.biap.org/fr/recommandations/recommendations/tc-06-hearing-aids/228-rec-06-16-07-7-en-management-of-hearing-assistive-technology/file

Follow-up, outcomes and prognoses

The audiological results in children with ANSD may fluctuate during the follow-up and some evidence of ANSD could disappear. It is essential to follow-up the child with routine audiological tests.

The improvement of cochlear nerve maturation can be a good indicator of development of the auditory pathway, monitoring the pattern of the waves of ABR potentials and cochlear microphonics under sound stimulation. This non-invasive and reproducible test can be repeated periodically before and after the fitting the hearing aids. Considering the importance of the age-related management recommendation for the best auditory and speech development evolution of the child, as well as the possible neural maturation time, the ABR should be repeated not later than the age of 12 month and afterwards up to 18 months.

Cochlear-implanted children with profound hearing loss due to ANSD can be evaluated by electric ABR to study the stage and the dynamics of neural dys-synchrony/maturation after the implantation.

Language and communication development should be assessed periodically, the results of this monitoring being the leading factor for the management options.

Because speech perception skills are age-dependent and influenced by a child's vocabulary and language levels, speech perception tests or questionnaires must be selected in relation to the development stage: Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS), LittlEARS Auditory Questionnaire, LittlEARS Early Speech Production Questionnaire, Early Speech Perception Test (ESP), Glendonald Auditory Screening Procedure (GASP) words and sentences. In many children with ANSD, speech testing scores improve with initial hearing aid use, and over time with extended hearing aid use and with the education level.

Some children with ANSD who initially demonstrate a profound hearing loss may show a spontaneous improvement in hearing between 1 to 15 months after initial diagnosis with a mean improvement of 5.8 months. Owing to a possible significant variability in hearing over

time, repeated audiometric testing is imperative in this unique population and necessary for successful rehabilitation.

Speech testing, such as speech detection thresholds (SDT) or speech recognition thresholds (SRT) in the neuropathic ear, typically yields poor results and even poorer responses occur in the presence of background noise.

The majority of ANSD patients demonstrate a gradual decrease in pure tone thresholds over time. More specifically, a hearing loss pattern over time has been observed in ANSD with low-frequency deficits occurring in the early stages of the disorder, followed by high frequency hearing losses and ultimately mid-frequency reductions at later test dates.

Some patients, with ANSD stemming from reversible causes (e.g. hyperbilirubinaemia, extreme prematurity), improve over time, whereas patients who do not improve continue to have audiometric deficiencies.

Present data show that the hearing, speech and language development outcomes in children with ANSD are very heterogeneous, depending on associated disorders. Until now, there is no literature available on long-term results of children with ANSD, but treatment outcomes seem to be correlated closely with the underlying aetiologies.

In some children with ANSD, speech test scores can improve with initial hearing aid use and also over time with extended hearing aid use.

Patients with poor improvements with hearing aids are candidates for CI and rehabilitation.

The observed efficacy of CI seems to be closely related to the locus of the lesion. In presynaptic ANSD, outcomes are invariably good, with audiological results similar to those of patients with cochlear sensorial hearing loss. CI outcomes in postsynaptic ANSD have been reported as much more variable. This is partially explained by the wide area of aetiologies classified as postsynaptic ANSD, compounded by their relative rarity and limited published data.

ANNEX 1. Genetic aetiology related to the lesion site.

GENETIC LESIONS TO THE SYNAPSE

Presynaptic Synaptopathies

- OTOF gene encoding for Otoferlin
- CACNA1D gene codes for a subunit of Cav1.3 a Ca^{2+} channel
- CABP2 gene
- SLC17A8 gene codes for the vesicular glutamate transporter type 3 (VGluT3)

Postsynaptic Synaptopathies

- OPA1 gene – cause dominant optic atrophy (DOA) or syndromic dominant optic atrophy (DOA+) - optic atrophy as well as AN presenting with moderate to severe hearing loss due to degeneration of the terminal axons of the spiral ganglion neurons
- ROR1 gene - the receptor tyrosine kinase-like orphan receptor 1
- ATP1A3 gene
- DIAPH3 gene

GENETIC LESIONS AFFECTING THE SPIRAL GANGLION AND AUDITORY NERVE

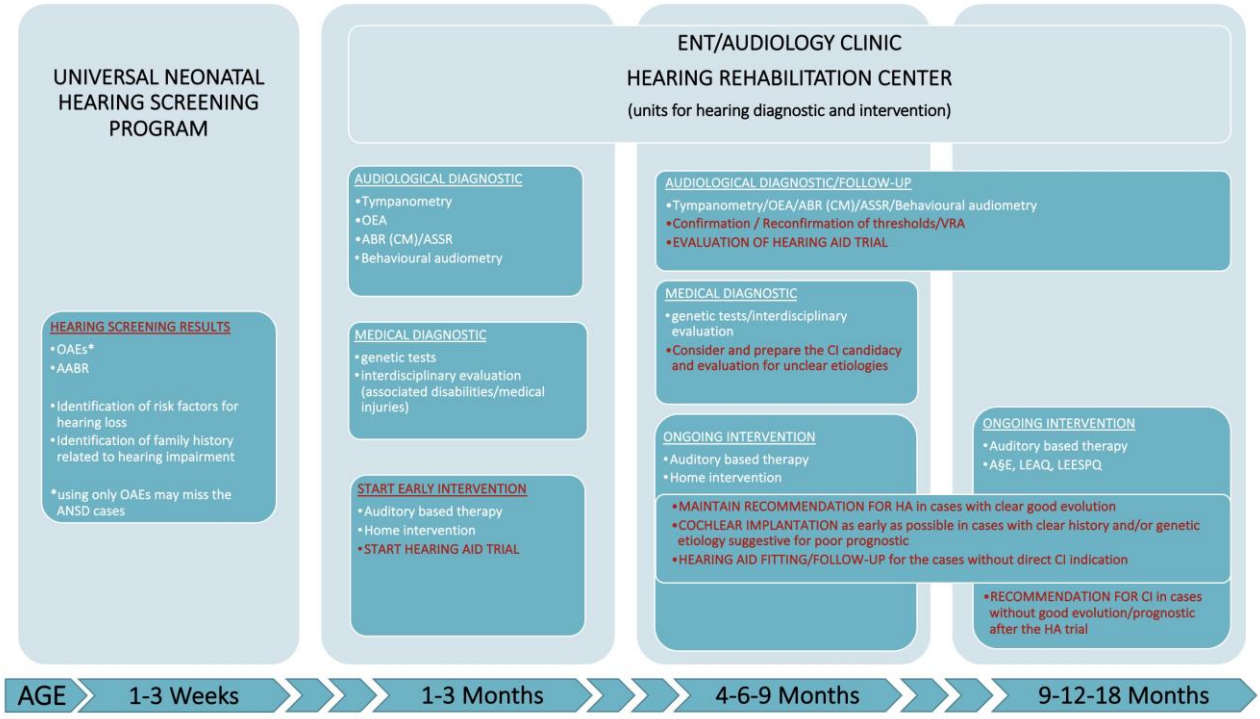
Auditory Neuropathy

- Hereditary Demyelinating Neuropathies – Charcot–Marie–Tooth disease (CMT) + Friedreich ataxia
- TIMM8A gene – deafness-dystonia-optic neuropathy (DDON or Mohr-Tranebjaerg syndrome)

- AIFM1 gene – Cowchock syndrome
- NARS2 – Leigh syndrome - the mitochondrial asparaginyl-tRNA synthetase (NARS2) mutation + variants of NARS2 due to homozygous missense mutation

GENES WITH POSSIBLE EFFECTS ON THE AUDITORY SYNAPSE OR SPIRAL GANGLION Synaptopathy and Neuropathy
- DFNB59 mutation-related deafness
- TMPRSS3 gene
- TBC1D24 gene

ANNEX 2. Early management recommendation for infants with ANSD.



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President of the commission 12: Sebastian Cozma (Romania)

Members of the commission 12: O. Bitere-Popa (Romania), E. Boéchat (Brazil), A. Bohnert (Germany), I. Caregnat (Italy), M. Chapchap (Brazil), N. Deggouj (Belgium), J.P. Demanez (Belgium), L. Demanez (Belgium), A. Enderle (Germany), C. van der Heyden (Belgium), K. Kerkhofs (Belgium), A. Kerouedan (France), G. Madeira (Belgium), M. Maggio (Spain), N. Matha (France), E. Muzzi (Italy), R. Olariu (Romania), I. Symann (Germany), H. Thai-Van (France), K. Tiede (Germany), P. Verheyden (Belgium), M. Willems (Belgium), Th. Wiesner (Germany), F. Zajicek (Austria)

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