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Main topic

Diagnosis and treatment of auditory synaptopathy/neuropathy

T. Moser (✉) - N. Strenzke - A. Meyer - A. Lesinski-Schiedat - T. Lenarz - D. Beutner - A. Foerst - R. Lang-Roth - H. von Wedel - M. Walger - M. Gross - A. Keilmann - A. Limberger - T. Steffens - J. Strutz

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T. Moser - N. Strenzke - A. Meyer
ENT University Clinic Göttingen, Robert-Koch-Straße 40, 37075 Göttingen

A. Lesinski-Schiedat - T. Lenarz
ENT Clinic, Hanover Medical School

D. Beutner - A. Foerst - R. Lang-Roth - H. von Wedel - M.
Walger ENT University Hospital Cologne

M. Large
Clinic for Audiology and Phoniatrics, Charité - Universitätsmedizin Berlin

A. Keilmann - A. Limberger
University Clinic for Communication Disorders Mainz

T. Steffens - J. Strutz
ENT University Clinic Regensburg
✉ E-mail: tmoser@gwdg.de

Summary

The audiological constellation of pathological early auditory evoked potentials (absent, increased threshold and disturbed waveform) despite detectable otoacoustic emissions is often accompanied by hearing loss or deafness characterised by poor speech comprehension. This heterogeneous group of diseases, first described as auditory neuropathy, includes peripheral auditory disorders of synaptic sound coding by inner hair cells (synaptopathy) and/or excitation formation and transmission in the auditory nerve (neuropathy). This consensus paper provides up-to-date background information and recommendations for diagnosis and treatment in German-speaking countries. It refers to current international statements.

Keywords

Consensus paper - Synaptopathy - Neuropathy - Deafness - Speech comprehension

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Diagnosis and therapy of auditory synaptopathy/neuropathy

Abstract

The audiological constellation of pathologic early acoustic evoked potentials (lacking, elevated threshold and disturbed form of curve) despite demonstrable otoacoustic emissions is often accompanied by impaired hearing characterised by poor understanding of speech, or even deafness. This heterogeneous group of illnesses first reported as auditory neuropathy includes peripheral auditory impairments of the synaptic sound coding by internal hair cells (synaptopathy) and/or of stimulus formation and conduction in the auditory nerve (neuropathy). This consensus paper gives up-to-date background information and recommendations on diagnosis and treatment for the German-speaking world, also referring to current international statements.

Keywords

Consensus paper - Synaptopathy - Neuropathy - Deafness - Understanding of speech

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Terms and definition

Auditory synaptopathy/neuropathy is a subgroup of sensorineural hearing loss that severely restricts speech comprehension, whereby the threshold hearing varies greatly from patient to patient. The hearing impairment leads to pathological changes or loss of early auditory evoked potentials (FAEP) despite at least initially preserved cochlear amplification[1] . The clinical spectrum of auditory synaptopathy/neuropathy ranges from disorders of temporal processing (hence the term "auditory dys-synchrony" [3a], which emphasises the disturbed synchronisation of the spiral ganglion neurons) to a complete block of coding or excitation conduction. Auditory synaptopathy/neuropathy can be part of a generalised neuropathy [41]. In recent years, however, isolated

[1] Diagnostic criteria: detectable otoacoustic emissions (OAE) and/or cochlear microphone potentials at levels <80 dB HL (CM); threshold of early acoustic evoked potentials (FAEP) worse than 80 dB HL with poor reproducibility of the curves.

Disorders of the inner hair cells or their synapses are suspected as a possible site of pathology (perisynaptic audiopathy [21]).

As it is currently not possible to clinically and audiologically differentiate the exact localisation of the disorder, the overarching term auditory synaptopathy/neuropathy appears to be helpful. Auditory synaptopathy/neuropathy can be regarded as an auditory processing disorder, but should be differentiated from central auditory processing and perception disorders (AVWS), which require normal peripheral auditory function .

Aetiology and pathophysiology

This is caused by the loss or dysfunction of the inner hair cells (IHZ) and their synapses (disturbance of synaptic sound coding: auditory synaptopathy) or the spiral ganglion neurones (SGN) (auditory neuropathy). Pathophysiologically, the audiological constellation of findings can be understood as a disturbed or abolished synchronisation of the excitation of the spiral ganglion neurons.

The objective audiological consequences of selective defects of these elements were investigated in detail in animal models. Hearing loss/deafness due to synaptic disorders of the IHZ (synaptopathy [30, 5, 10, 18, 35a]), disorders of excitation conduction in SGN (neuropathy: e.g. [47, 48, 28, 20]) and the combined loss of IHZ and SGN [9] were detected and characterised. In all these cases, the number of SGNs and brainstem neurones synchronously activated by sound was reduced for functional and/or structural reasons and the compound action potential (CAP) or FAEP was pathological or absent.

The CAP, which is also depicted as the first peak of the FAEP, is commonly thought to be generated in the peripheral part of the auditory nerve, while the second component of the FAEP is generated in the part of the auditory nerve close to the brainstem or in the cochlear nucleus. A disturbed temporal precision of synaptic sound coding or excitation conduction in the individual neuron can only be assumed indirectly from the disturbed population responses (CAP, FAEP). In fact, it is possible that the function of individual "information channels" to the CNS (IHZ, SGN) is preserved and that "central compensation" also occurs due to the divergent innervation of many brainstem neurones by an SGN (e.g. [18]). This could explain the residual hearing performance and better preserved late auditory evoked potentials in auditory synaptopathy/neuropathy.

However, the distortion products of otoacoustic emissions (when tested) as a sign of normal amplifier function of the outer hair cells (ÄHZ) were detectable (review in [43]). FAEP deficits range from discrete latency delays and pathological adaptation [20], to loss of brainstem potentials [28] and loss of CAP [30, 10]. By direct electrical stimulation of the spiral ganglion, FAEPs could be evoked in the mouse model for the human auditory synaptopathy DFNB9. This is consistent with clinical experience of successful cochlear implant treatment in auditory synaptopathy/neuropathy [21, 34, 25, 15, 16, 35]. In humans, this can be diagnosed using the subjective promontory test (in adults) and the recording of electrically evoked FAEP.
It may also be necessary to place the stimulation electrode intracochlearly in order to achieve sufficient stimulus propagation to the auditory nerves [21].

Human auditory synaptopathy/neuropathy is both hereditary and acquired. Hereditary forms include the autosomal recessive, prelingual hearing loss DFNB9 [45a, 26a, 26b, 44a, 44b], an autosomal dominant variant without general neurological symptoms [42], hereditary motor and sensory neuropathies (HMSN [36]) and syndromic diseases. Primary defects of the synapse of inner hair cells (DFNB9) are contrasted with primary disorders of the spiral ganglion neurons (HMSN, demyelination and/or axon loss), which in each case leave the amplification function of outer hair cells intact, at least initially. However, mixed forms can develop in the course of the disease (e.g. secondary loss of spiral ganglion neurones in the event of a synaptic defect) and global cochlear dysfunction can develop (loss of otoacoustic emissions; Fig. 1).

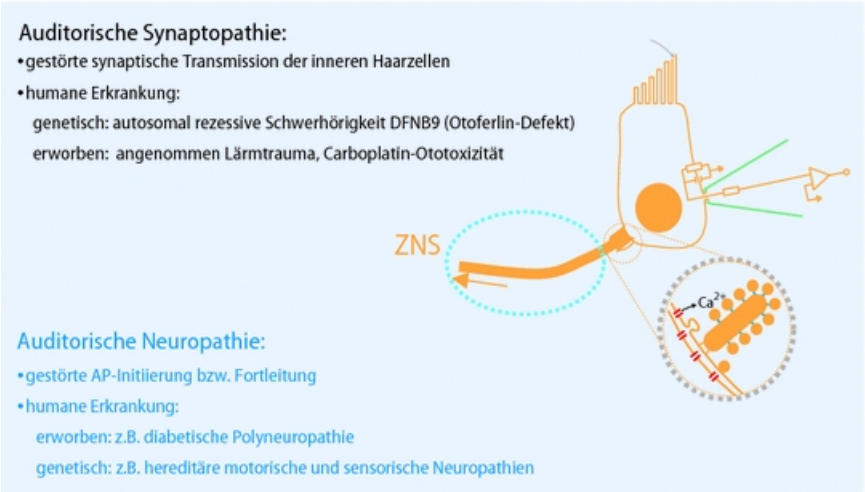

Fig. 1 Mechanisms of auditory synaptopathy/neuropathy. Schematic representation of the sites of damage in synaptopathy: IHZ and its ligament synapse (*magnification figure* active zone of the

IHZ with synaptic ribbon carrying synaptic vesicles; *red* presynaptic Ca^{2+} channels and postsynaptic glutamate receptors)

Acquired auditory synaptopathies/neuropathies occur in particular in preterm infants requiring intensive care (causally mainly hyperbilirubinaemia and hypoxia), but also in the context of metabolic polyneuropathies (e.g. in diabetes [8] and hypothyroidism [17]). In a histopathological analysis, cases with isolated loss of IHZ (3 of 12 cases) and combined loss of IHZ and ÄHZ (2 of 12) with a normal number of SGN were detected in premature infants with pathological FAEP screening [1]. This surprising observation suggests that the loss of IHZ may play an important pathogenetic role in hearing impairment in preterm infants . In another study, a loss of SGN was described [18a].

Risk factors for the occurrence of auditory synaptopathy/neuropathy

- Hyperbilirubinaemia,
- Anoxia/hypoxia/protracted ventilation requirement,
- extreme immaturity (birth before the 28th week of pregnancy),
- demyelinating and axonal neuropathies,
- genetic factors.

Clinical-audiological appearance

The clinical appearance of auditory synaptopathy/auditory neuropathy is characterised by objectively detectable and subjective pathological changes in hearing.

Objective criteria

- Pathological/missing FAEP with detection of OAE and/or CM,
- Stapedius reflexes not detectable or with a greatly increased threshold,
- lack of contralateral acoustic suppression of the OAE.

Subjective criteria

- Tone threshold audiogram: varying degrees of hearing loss for tones (from mild hearing loss to deafness), often fluctuating hearing ability,
- Poor speech intelligibility compared to the audiogram, especially in noise,
- poor performance in psychophysical tests of temporal auditory processing,
- little benefit from hearing aid provision,

Estimates of prevalence

The prevalence of the disease in the paediatric and adult hearing impaired populations is still quite unclear. An Australian study found a prevalence of auditory synaptopathy/neuropathy of ~11% in children with hearing loss [32]. In good agreement with this, Foerst et al [11] describe a prevalence of around 8% in children with profound hearing loss. Other authors have determined significantly lower prevalences [23]. These prevalence figures may be based on different patient populations, particularly with regard to the extent of the hearing loss detected and the accompanying risk factors.

The secondary loss of the OAE observed by several authors in the course of the disease poses a major problem for the identification of sensorineural hearing loss as auditory synaptopathy/neuropathy [41, 39, 34]. Therefore, early diagnosis (e.g. following a combined OAE-FAEP screening) promises information about the true prevalence, at least in childhood. However, a differentiation must be made from maturation delays of the auditory pathway, which are often still present in premature infants. Genetic investigations to detect causative genetic defects offer a further approach in selected patient populations. The Q829X mutation of the OTOF gene is the third most common mutation responsible for prelingual, profound hearing loss [26a].

To date, no data exist for adults with hearing loss. The significance of synaptopathic and/or neuropathic pathomechanisms in common forms of sensorineural hearing loss with a definite amplification defect, e.g. age-related hearing impairment or noise-induced hearing loss, cannot yet be assessed with certainty. Changes in hair cell synapses and SGN after noise trauma have been demonstrated in animal models [13]. These could be associated with excitotoxic damage to the SGN [31]. For human hearing loss, at least the secondary degeneration of the SGN

as a result of sensory defects is a known clinical problem that is also relevant for cochlear implant fitting. A loss of SGN dendrites has also been described several times in humans in connection with noise-induced hearing loss [40a, 40b, 33a].

Diagnostics

The recommended diagnostic procedure is described below, broken down by age group and divided into 2 stages. The first stage leads to a suspected diagnosis of auditory synaptopathy/neuropathy, which is then confirmed and, if necessary, differentiated by further diagnostics (Table 1).

[Tab. 1 is placed here, see end of document].

Basic diagnostics

Auditory synaptopathy/neuropathy is suspected if the FAEPs are not detectable or only detectable at high levels (80 dB HL) despite the presence of OAEs. To reduce transducer artefacts, plug-in headphones are recommended and to rule out misinterpretation of artefacts as FAEP, both pressure and suction stimulation [3]. The click-evoked FAEPs should also be analysed at different stimulation rates. In premature infants, a result indicating auditory synaptopathy/neuropathy should be checked 2-3 months later. Due to the possibility of an auditory pathway maturation delay [14], a result indicating auditory synaptopathy/neuropathy should be checked 2-3 and 5-6 months later in the first year of life.

The absence of the stapedius reflex or a greatly increased reflex threshold supports the suspected diagnosis of auditory synaptopathy/neuropathy [4]. Whenever feasible, subjective audiometry is essential to assess the clinical picture of the hearing impairment. Experience has shown that speech comprehension is disproportionately severely impaired compared to threshold hearing. This is particularly true in noise, so that speech audiometry (Mainz, Göttingen, Oldenburg Children's Rhyme Test (OLKI) or Oldenburg Sentence Test (OLSA and OLKISA)) is recommended as soon as developmental age allows.

Further diagnostics

Electrocochleography is the central examination in further diagnostics [21, 33]. The detection of microphone potentials at low stimulus levels (less than 80 dB) and

If the summation potential is not intact, this indicates a functioning mechanoelectrical transduction of the outer or inner hair cells, even if this does not provide evidence of intact cochlear amplification. Since the primary synaptic or neuropathic damage can be accompanied by a secondary disturbance of the upstream inner ear function, the detection of microphone potentials, which is still possible in comparison to OAEs even with greater sensory hearing loss, is accepted as sufficient evidence for remaining hair cells. In fact, long-term observations have described the loss of primary OAEs in auditory synaptopathy/neuropathy [41, 39, 34].

The measurement of the compound action potential (CAP) is a more sensitive method for detecting the synchronised activity of the SGN compared to the FAEP. Whether the amplitude and latency of the CAP can contribute to the differentiation of synaptopathy and neuropathy must first be clarified in animal experiments and possibly in clearly defined patient groups (e.g. DFNB9 vs. HSMN). Initial studies show that the detection of a CAP does not rule out a synaptopathy [18]. The loss of contralateral acoustic suppression of the OAE has been described as a further feature of auditory neuropathy [2]. However, diagnostic value beyond a confirmatory statement still needs to be further investigated.

Mid and late auditory evoked potentials (MAEP, SAEP) as well as psychoacoustic examinations serve as further approaches to study the perception of acoustic stimuli by those affected. The subjectively stated threshold can often be reproduced in the cortically evoked potentials, although the FAEPs are not detectable or are only detectable at higher levels. The SAEP and FAEP, which are well preserved compared to speech comprehension and FAEP "mismatch negativity" [19, 26] could be interpreted to mean that the generation of SAEP requires less synchronisation than that of FAEP [14].

Psychoacoustic investigations in neuropathy patients can demonstrate a preferential disturbance in the processing of temporal characteristics of the sound stimulus, while the recognition of intensity differences does not appear to be impaired [46]. There are contradictory reports in the literature about the presence of vestibular deficits in auditory synaptopathy/neuropathy [12, 37, 45, 38]. Based on these indications and in order to be able to assess this aspect more reliably, vestibular function should be tested.

Diagnostic imaging is essential to detect malformations, the absence of or damage to the auditory nerve and morphological changes in the ascending auditory pathway.

In the absence of the auditory nerve, treatment with a cochlear implant is not possible and therefore treatment with an auditory brainstem implant should be discussed [7].

Supplementary diagnostics

Supplementary diagnostics endeavour to detect syndromic diseases or generalised neurological diseases, to uncover known mutations (DNFB9, HMSN) and to obtain morphological indications of functional and structural changes in the auditory pathway. The diagnosis of hearing, speech and communication development by speech therapists is also important with regard to the therapy and rehabilitation of patients (especially children),
Hearing-impaired pedagogues, if necessary with the help of an accompanying child neurological and developmental psychological diagnosis.

Counselling, rehabilitative care and follow-up

The aim is to provide those affected or their families with detailed information and counselling regarding treatment after diagnosis. If it is possible to specify the diagnosis and identify a genetic disease, for example, this provides more certainty for the patient's choice of treatment and allows genetic counselling. Table 2 lists general recommendations for follow-up and treatment.
[Tab. 2 is placed here, see end of document].

Due to the possible improvement in findings over the course of time as a result of secondary maturation of the auditory pathway, a re-evaluation should be carried out 2-3 and 5-6 months after the initial examination if auditory synaptopathy/neuropathy is suspected, especially in premature babies. From the age of 12-18 months, an improvement in findings due to maturation is no longer likely. The interpretation of the findings is difficult because the results of the various examinations do not match, in contrast to the usual situation. It therefore requires particular care and expertise to differentiate between inadequate findings due to unfavourable underlying conditions and the typical constellation of findings of an auditory synaptopathy/neuropathy. As the FAEP usually shows more severe pathological changes than behavioural audiometry, a final decision on hearing aid treatment can only be made after the FAEP has been performed.

The fitting of hearing aids should be based on the results of the subjective audiometric procedures. Possible fluctuations in hearing ability should also be taken into account. For patients for whom a subjective hearing threshold cannot (yet) be quantified with certainty, a hearing aid fitting should initially be started with a low amplification and then gradually increased (without excessive loss of time for speech development) until reactions can be observed. Hearing aids with an appropriate gain reserve should be selected so that readjustments can be made in due course. If necessary, both the amplification and the output sound pressure level can be changed until hearing reactions can be observed.

In the case of childhood hearing impairments with a hearing loss of less than 80 dB (HL), therapy should initially be trialled with hearing aids. The success of the fitting must be checked regularly using subjective and objective methods, in particular by observing the child's behaviour and speech development. Due to the particularly pronounced problems in understanding speech in noise, the additional fitting of an FM system is particularly advisable at school age.

Cochlear implant fitting should only be considered if a subjective and objective benefit of hearing aid fitting cannot be determined after a wearing period of 6-9 months. Earlier fitting is always justifiable in exceptional cases if deafness or hearing loss bordering on deafness is confirmed by electrocochleography and other objective hearing test procedures. With cochlear implant treatment, similarly good results can be achieved in auditory synaptopathy/neuropathy as in children with sensorineural hearing disorders of other origins [21, 24, 25, 29, 16].

A comparison of a differentiated therapy for patient groups with synaptopathy and neuropathy is still pending. The first cochlear implants in patients with pure auditory synaptopathy DFNB9 were successful [34, 35]. If the cochlear implant also fails, an auditory brainstem implant may be indicated [7].

Regular auditory speech therapy should promote children's speech development. For children with auditory synaptopathy/neuropathy, methods that support spoken language as synchronously as possible have proven successful in initiating spoken language. This has proven to be

"cued speech" has proven to be a particularly suitable tool [3a]. Learning to see through the mouth and, in individual cases, sign language (to accompany spoken language) can be useful.

Additional conditions such as middle ear infections and tympanic effusions, which can exacerbate hearing disorders, should be recognised and treated at an early stage. In older children and adults affected after speech acquisition, a cochlear implant can also lead to an improvement in speech understanding if hearing aid treatment is not sufficient [25, 15]. In these groups, the promontory test can provide useful information on the electrical excitability of the auditory nerve and thus on the prognosis of the cochlear implant fitting.

If the results of the promontory test in adults are in doubt as to whether the auditory pathway can be activated, functional imaging can provide valuable information. Positron emission tomography, which can also be used in children under anaesthesia, is the first choice here [22]. The subjective promontory test must be replaced by the recording of electrically evoked FAEP in children of non-cooperative age. This can be done either by placing the needle at the promontory or at the round window.

If no clear answers can be derived, invasive placement of the stimulation electrode in the cochlea may also be necessary. If the result is positive, this can then be combined with an cochlear implantation.

Conclusion for practice

Auditory synaptopathy/neuropathy can be both hereditary and acquired in humans. The acquired form occurs, for example, in premature babies requiring intensive care or in patients with metabolic polyneuropathies such as diabetes and hypothyroidism. Auditory synaptopathy/neuropathy is suspected if the FAEPs are not detectable or only detectable at high levels (80 dB HL) despite the presence of OAEs. Premature babies should be re-examined around 2 and 5 months after the initial examination; maturation can lead to an improvement in findings up to the age of 12-18 months. Children's speech development should be promoted with regular hearing and speech therapy. For children with a hearing loss of less than 80 dB (HL), a therapy trial with hearing aids is recommended. If this is not successful, treatment with a cochlear implant should be considered. This can also improve speech understanding in adults.

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Table 1 Age-dependent 2-step diagnosis for suspected auditory synaptopathy/neuropathy

Newborns	Children up to 6 years	Children >6 years, adults
Basic diagnostics		
DPOAE/TEOAE	DPOAE/TEOAE	DPOAE/TEOAE
Tympanometry (1 kHz probe tone)	Tympanometry	Tympanometry
Stapedius reflexes	Stapedius reflexes	Stapedius reflexes
Click-threshold ABR (suction and pressure, plug-in receiver)	Click-threshold ABR (suction and pressure, plug-in receiver)	Click-threshold ABR (suction and pressure, plug-in receiver)
Reflex audiometry	Behavioural audiometry: distraction reactions/ play audiometry/ speech audiometry, also in background noise	Pure tone and speech audiometry, also in noise
Suspected diagnosis: auditory synaptopathy/neuropathy		
Further diagnostics		
Electrocochleography (subjective promontory test before CI, for older children/adults, E-BERA if necessary)		
Contralateral suppression of DPOAE/TEOAE		
Middle/late ABR		
Psychoacoustics		
Vestibular function		
Examination of language, receptive and productive		
Imaging: cranial and petrous bone MRI (detection of neuronal structures, in particular of the auditory nerve, as well as morphologically detectable damage along the auditory pathway)		
Check hearing aid care if necessary		
Supplementary diagnostics		
High-resolution petrous bone CT		
Neurological examination		
Ophthalmological examination		
Human genetics testing		
Positron emission tomography (if available)		

CI: cochlear implant, ABR: auditory brainstem response.