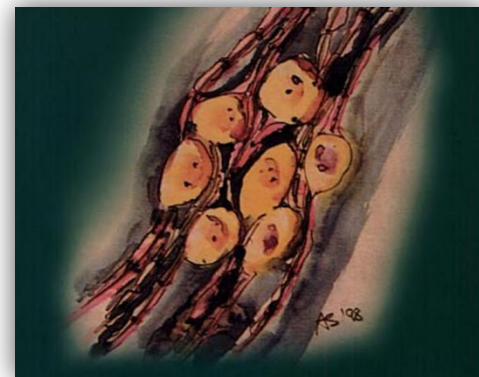


ANSD: APPROACHES TO DIAGNOSIS AND REHABILITATION

Prof. George Tavartkiladze, M.D., Ph.D.

National Research Centre for Audiology and
Hearing Rehabilitation, Moscow



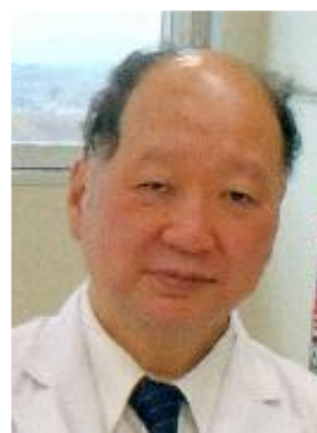
HISTORY

“Auditory neuropathy” is a clinical diagnosis used to describe patients with auditory temporal processing disorders who “can hear but not understand speech”.



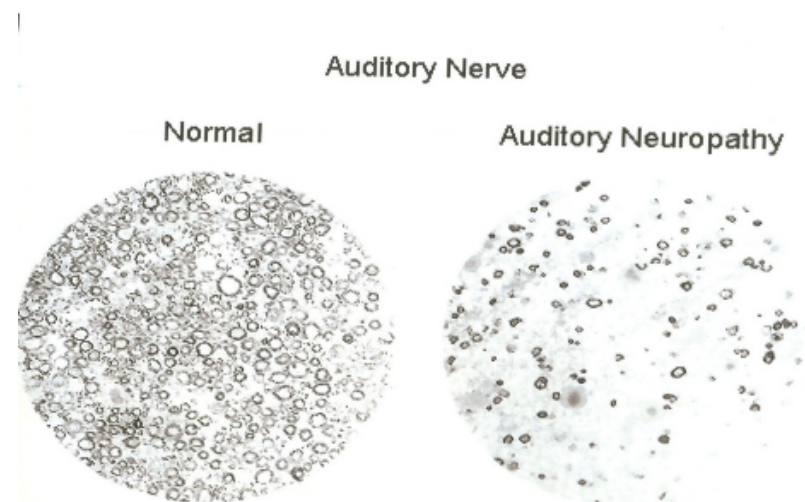
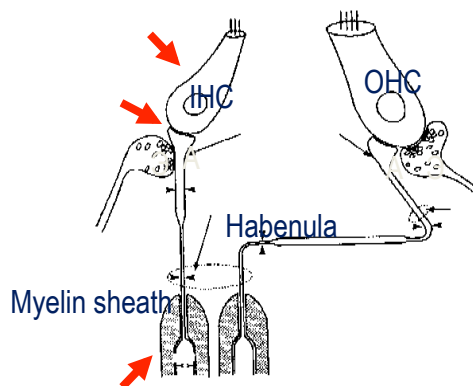
HISTORY

The term “Auditory neuropathy was originally proposed by Star and colleagues in 1996 to describe the specific auditory disorder which was characterized by evidence of normal OHC function (preserved OAEs and CM) and abnormal auditory pathway function beginning with the VIII nerve - absence or severely abnormal ABRs.

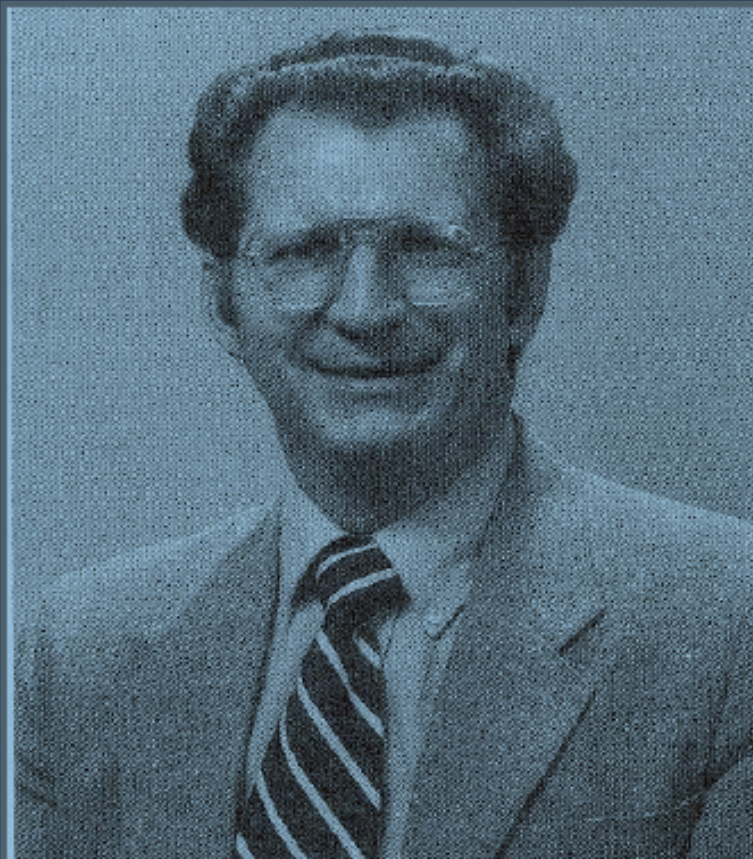


HISTORY

Patients exhibited common symptoms including hearing loss, present OAEs, absent or severely abnormal ABRs and poor speech perception. These changes could be due to the dysfunction of IHCs or synaptic transmission between IHC and the auditory nerve fibres and/or the dysfunction of the auditory nerve alone.



Don Worthington: Author of An Early Report of Apparent Auditory Neuropathy



**Worthington DW & Peters J.
Quantifiable hearing and no ABR:
Paradox or error.
Ear & Hearing 10: 231-234, 1980**



TERMINOLOGY

Many of investigators have expressed dissatisfaction with the term auditory neuropathy because the constellation of test results defining this disorder does not provide direct evidence of auditory nerve dysfunction or “neuropathy” (damage of IHCs, genetic factors – mutation of the otoferlin gen which results in synaptic dysfunction at the junction of the IHC/auditory nerve).

In 2001 Berlin and colleagues (2001) proposed the term “auditory dys-synchrony.

In 2008 in Como it was decided to identify simplified terminology that would unify the concept of auditory disorder with a range of presentations secondary to a variety of etiologies and rename the disease to the “auditory neuropathy spectrum disorder”.

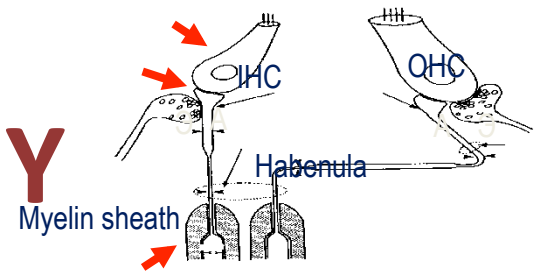


TERMINOLOGY

Three principle factors drove this conception:

- 1 Wide-spread acceptance of the term “auditory neuropathy”.
2. The existence of a spectrum ranging from limited or mild effects (complaints on of difficulty hearing in noisy listening conditions) to profound effects (inability to hear in any listening condition, functionally “deaf”).
3. The term “spectrum” was felt to expand the concept of this disorder to include sites of lesions other than the auditory nerve.

TERMINOLOGY

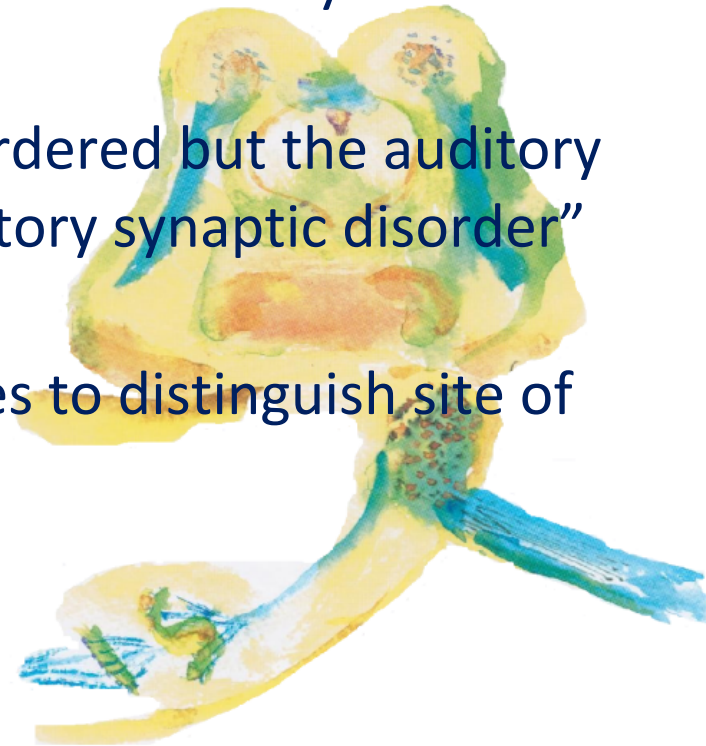


Star et al (2004) suggested segmenting the term auditory neuropathy into 2 types: Type I (Pre-synaptic), Type II (Post-synaptic).

If the auditory nerve is involved but IHCs and synapses were spared the disorder would be classified as “auditory nerve disorder”.

Similarly if the IHC synapses were disordered but the auditory nerve was normal than the term “auditory synaptic disorder” would be appropriate.

Currently there are no clinical measures to distinguish site of disorder with this degree of precision.



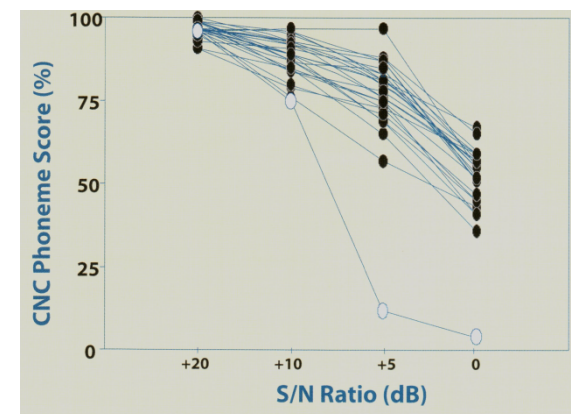
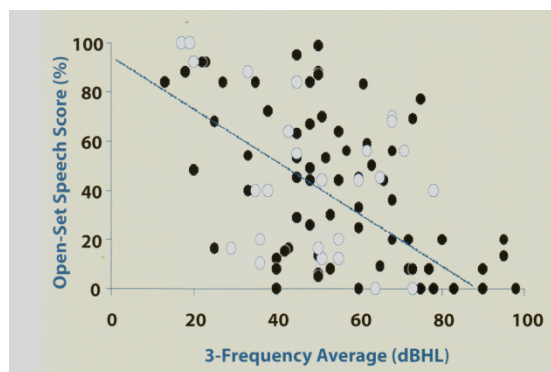
SYMPTOMS

- Problems with hearing and speech understanding or their absence together with pathological audiological tests.
- Deterioration of speech understanding (especially in noise) with normal hearing thresholds.
- Fluctuating hearing loss.
- Functional deafness.



APPROACHES TO DIAGNOSIS

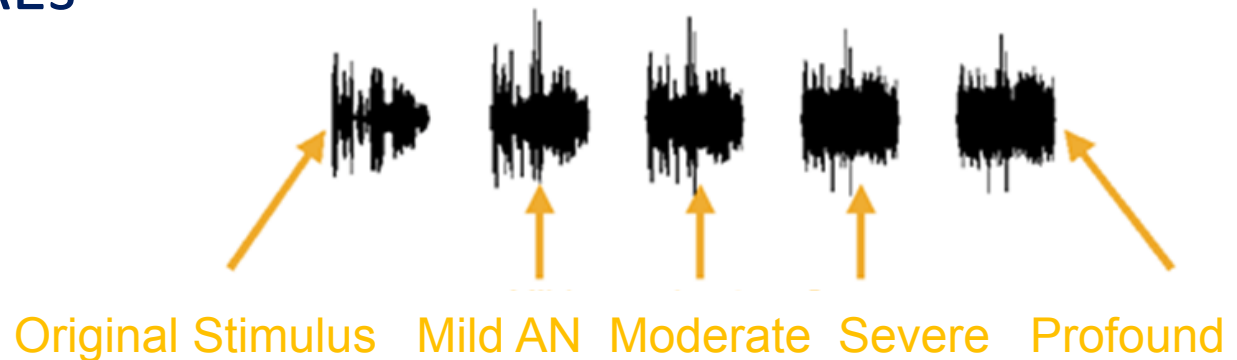
1. Elevated pure tone thresholds by air and bone conduction
2. Very pure speech discrimination/ especially in noise
3. Absent middle-ear muscle reflexes
4. Absent ABRs to any level of stimuli
5. Present CM
6. Present OAEs



APPROACHES TO DIAGNOSIS

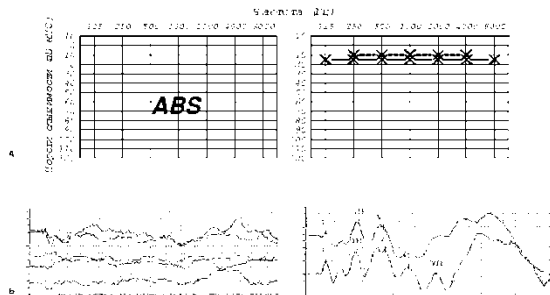
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ACOUSTIC STIMULATION IN AN



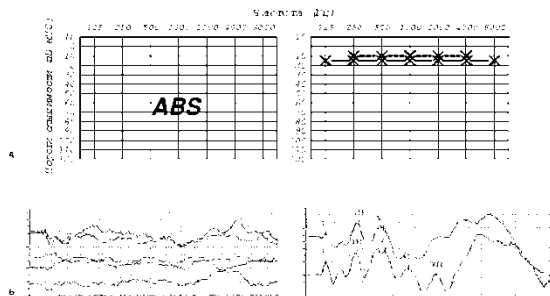
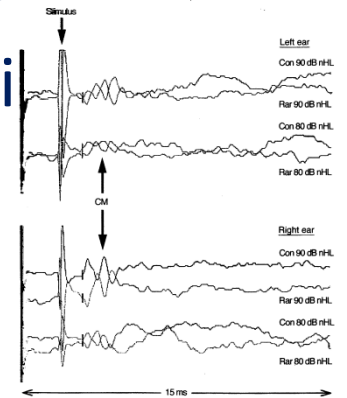
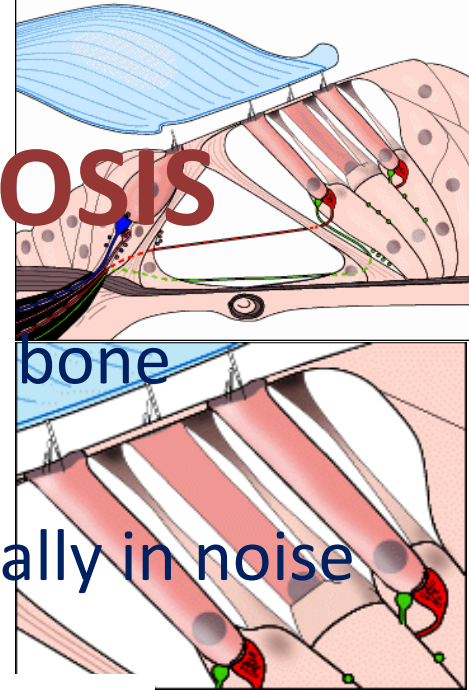
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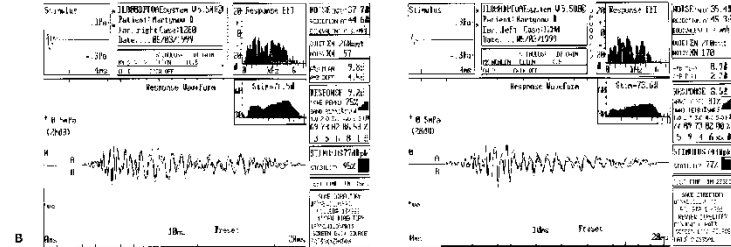
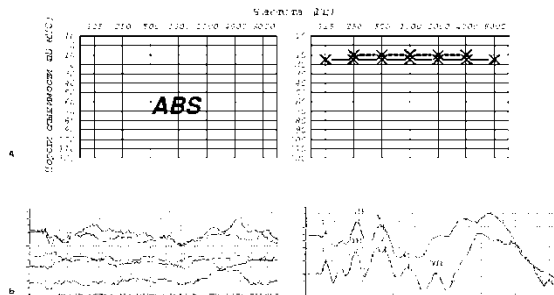
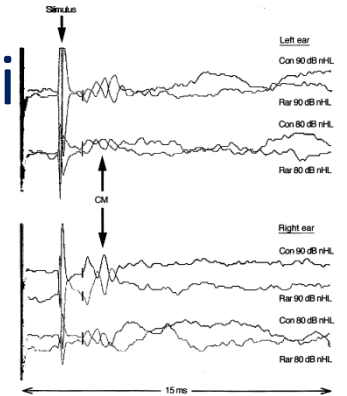
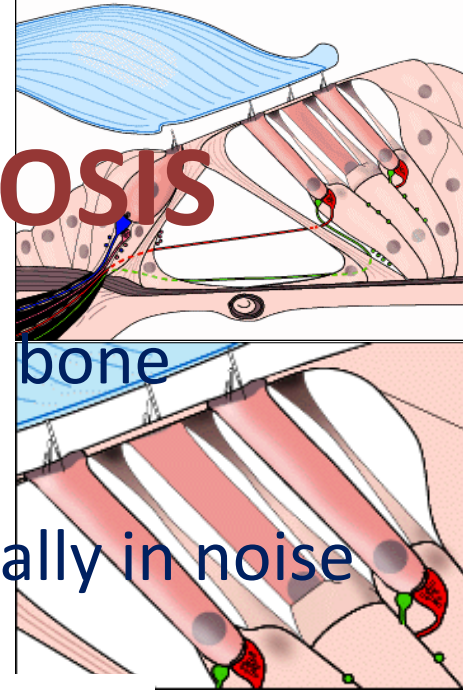
APPROACHES TO DIAGNOSIS

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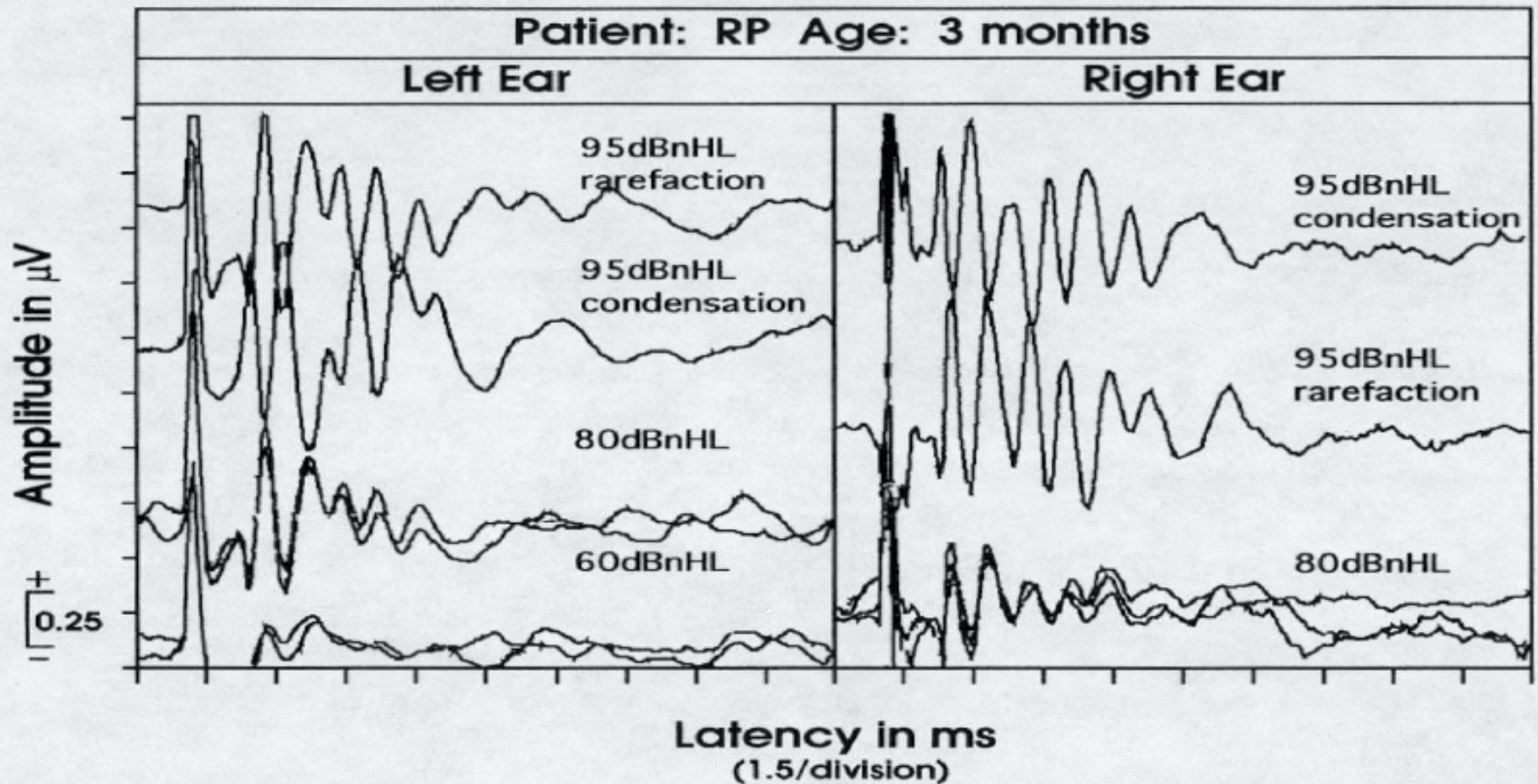


APPROACHES TO DIAGNOSIS

1. Elevated pure tone thresholds by air and bone conduction
2. Very pure speech discrimination/ especially in noise
3. Absent middle-ear muscle reflexes
4. Absent ABRs to any level of stimuli
5. Present CM
6. Present OAEs



CM



APPROACHES TO DIAGNOSIS

Today the criteria are not as clear

A significant number of children with the “disorder” will lose their TEOAEs or DPOAEs over time and the clinical significance or physiologic mechanism for this is unknown. At the same time the CM appears to be unchanged in these same subjects (as well as hearing thresholds).

How is the loss of OAEs to be interpreted?



APPROACHES TO DIAGNOSIS

POSSIBLE EXPLANATIONS

The loss of the low-level OAEs signifies the loss of the OHC motility or the cochlear amplifier.

Hearing thresholds do not seem to change in children when the OAEs disappear.



APPROACHES TO DIAGNOSIS

QUESTION 1

Was the cochlear amplifier not contributing to threshold sensitivity?



APPROACHES TO DIAGNOSIS

POSSIBLE EXPLANATIONS

There is no concomitant change in the amplitude of the CM when the OAEs disappear.

The CM is a reflection of the depolarization/repolarization of HCs in response to deflection of the stereocilia.



APPROACHES TO DIAGNOSIS

QUESTION 2

If the OHC had lost their normal depolarization capacity one would expect to see a large change in CM and conversely, no CM change would signify that the ionic exchange process in the HC has been maintained.

Why then are the contractile properties non functional?



APPROACHES TO DIAGNOSIS

POSSIBLE EXPLANATIONS

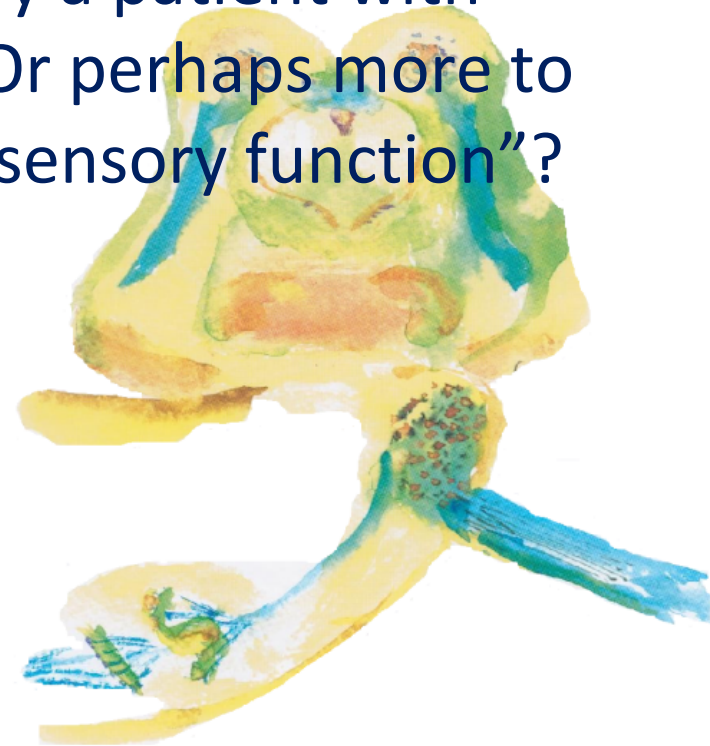
Some would argue that loss of the OAEs would reclassify the loss as “sensorineural”. It appears that the OHCs are present but not functioning at full capacity.



APPROACHES TO DIAGNOSIS

QUESTION 3

Should we only consider patients with OAEs present as having AN? How do we classify a patient with absent OAEs and a robust CM? Or perhaps more to the point what defines “normal sensory function”?



APPROACHES TO DIAGNOSIS

QUESTIONS 4, 5, 6

Does a patient with no ABR, present OAE and normal thresholds and very good speech perception scores have “the disorder”?

How abnormal does the ABR need to be?

Does the patient with 25 dB HL with ABR threshold to clicks at 50 dB have “the disorder” or just a poorly measured ABR?



DIAGNOSTICS CRITERIA

One of the most robust criteria for the AN is the lack of middle ear reflexes.

Finally in regard to clinical diagnostic assessments, several groups have suggested that trans-tympanic ECoG may provide added information to help delineate site of lesion specifically distinguishing between pre- and post-synaptic lesions by careful assessment of the SP and CAP.



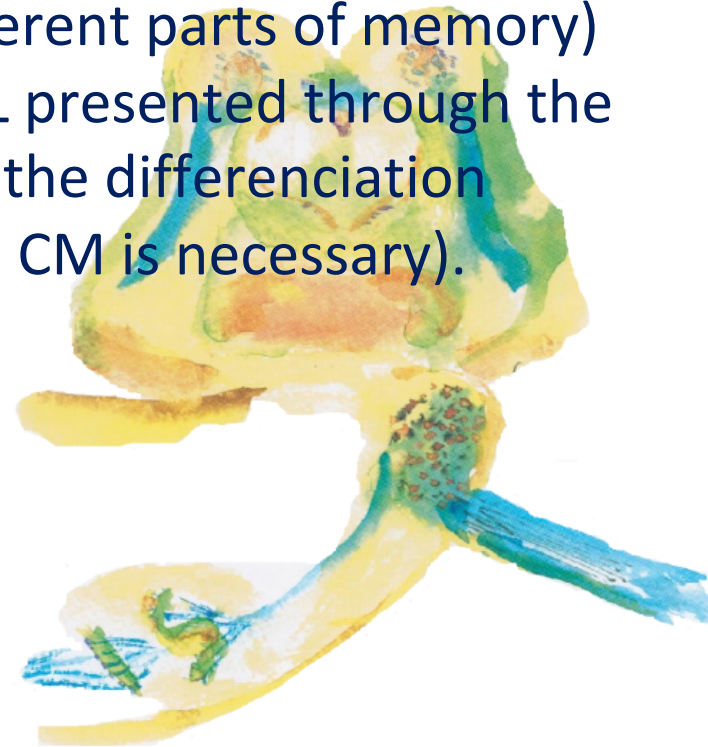
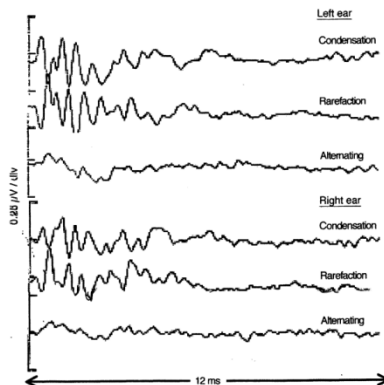
DIAGNOSTICS CRITERIA

Sensory (HC) function investigation

1. TEOAE and DPOAE

2. CM

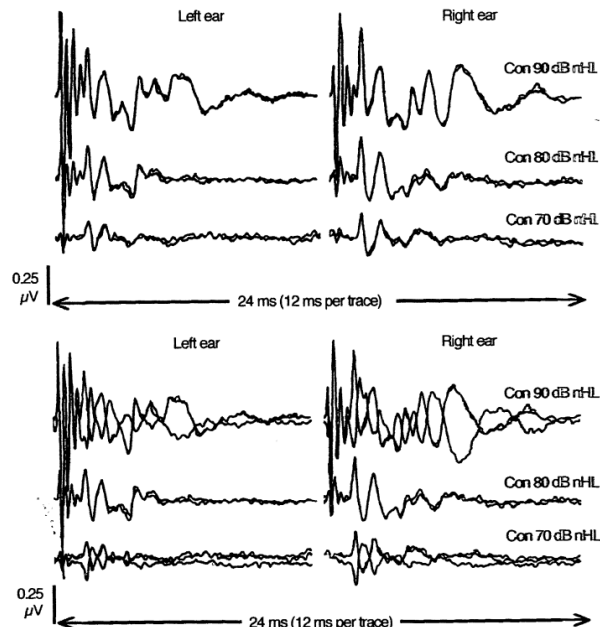
The registration of the ABRs to broad-band clicks of alternating polarity (stored in different parts of memory) with the intensity of 80-90 dB nHL presented through the inserted phone is recommended (the differentiation between the stimulus artifact and CM is necessary).



DIAGNOSTICS CRITERIA

Auditory nerve function investigation

The registration of the ABRs to broad-band clicks of alternating polarity (stored in different parts of memory) with the Intensity of 80-90 dB nHL presented through the inserted phone is recommended (the differentiation between the stimulus artifact and CM is necessary).



DIAGNOSTICS CRITERIA

Additional tests

1. Registration of the stapedial muscle reflexes (problematic children)
2. OAE suppression with contralateral noise

In children under 24 months the absence of the ABR should be considered very carefully!

In these children the follow-up investigation prior to the final decision on the rehabilitation should be performed!



ELECTROPHYSIOLOGY OF ANSD

Cochlea and Eight Nerve AEPs

1. CM with elevated amplitude, OAEs, no CAP and ABR: CM is registered even in absence of OAEs.

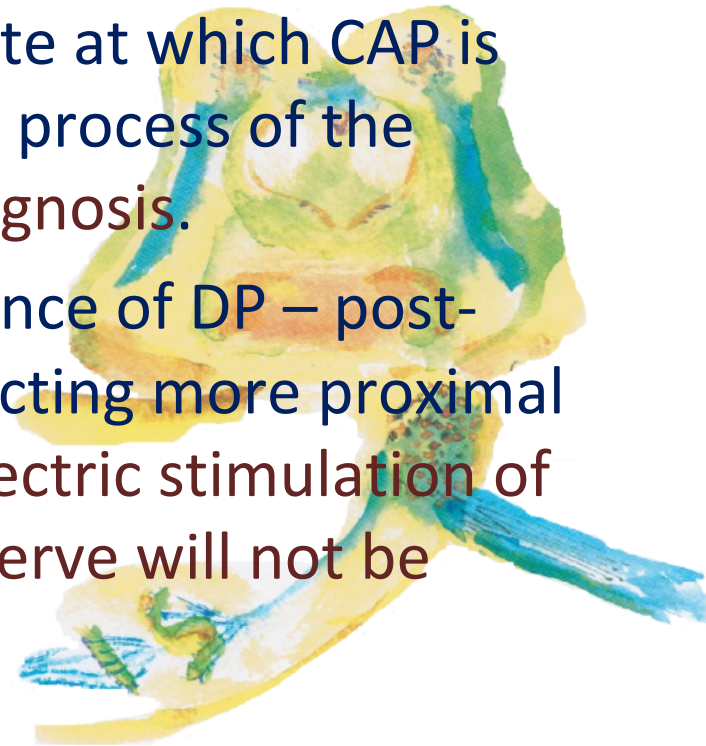
CM could be abnormally enlarged if there were no attenuation of the OHC response by stapedial or MOCB reflexes. It is also the case that neonates have immaturity of contralateral suppression due to immaturity of the MOCB reflex.



ELECTROPHYSIOLOGY OF ANSD

Cochlea and Eight Nerve AEPs

2. An enlarged SP (abnormal positive potential) with prolonged latency, no ABR, no CAP – receptor or pre-synaptic type of lesion, up to the site at which CAP is generated (along the unmyelinated process of the auditory nerve fibres – **good CI prognosis**.
Normal SP, abnormal AP and evidence of DP – post-synaptic or neural dysfunction affecting more proximal portions of the auditory nerve – **electric stimulation of the distal portion of the auditory nerve will not be effective!**

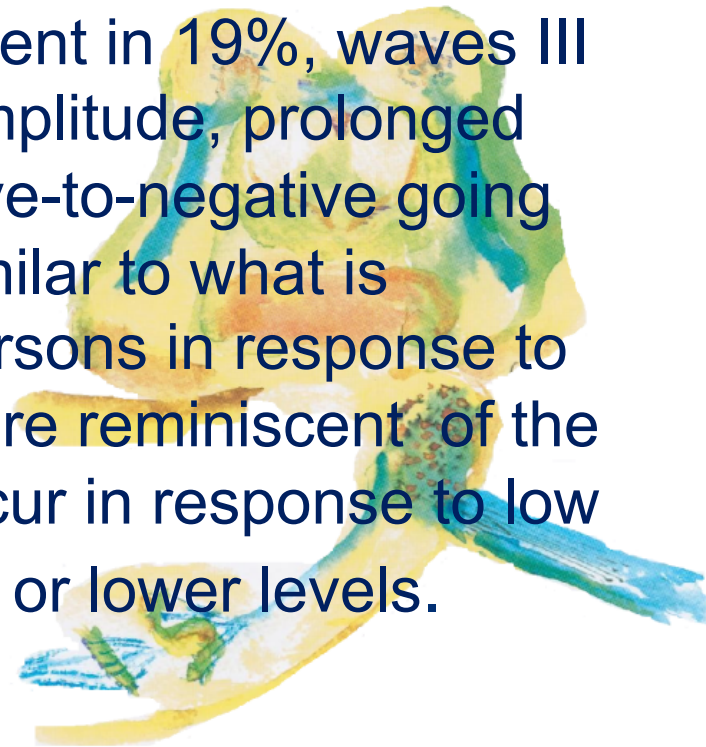


ELECTROPHYSIOLOGY OF ANSD

ABR

1. In the majority of cases ABRs to acoustic stimulation are absent.

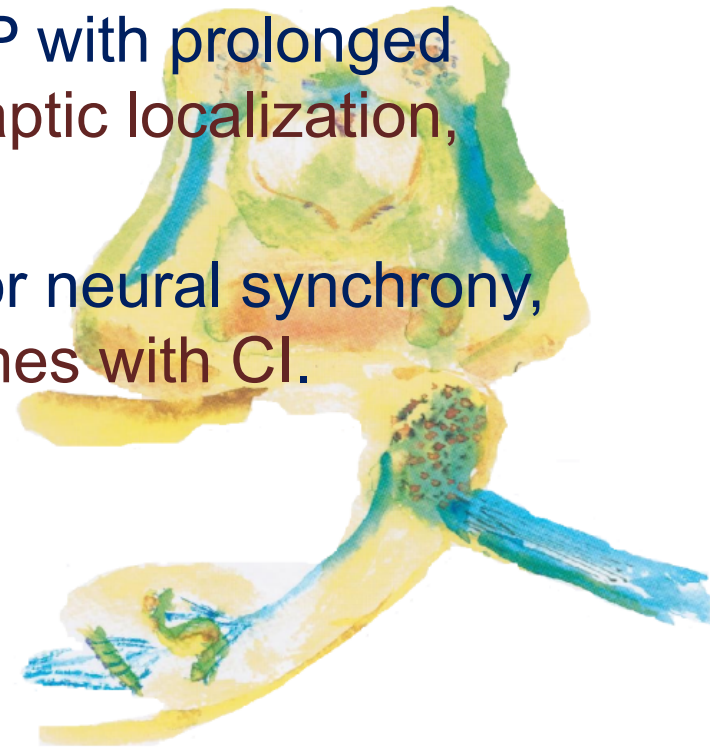
Pathological ABRs: wave V is present in 19%, waves III and V – in 6%. Wave V has low amplitude, prolonged latency, appears as a broad positive-to-negative going potential. These responses are similar to what is observed in the normal hearing persons in response to clicks at near threshold levels, or are reminiscent of the poorly synchronized ABRs that occur in response to low frequency tone bursts at moderate or lower levels.



ELECTROPHYSIOLOGY OF ANSD

ABR

2. Positive E-ABRs (waves II-V present): positive results, absence – pathology indicator.
 - a) Large CM, abnormal positive SP with prolonged latency, positive E-ABR – pre-synaptic localization, good CI prognosis.
 - b) SP + DP, negative E-ABR – poor neural synchrony, post-synaptic lesion – poor outcomes with CI.

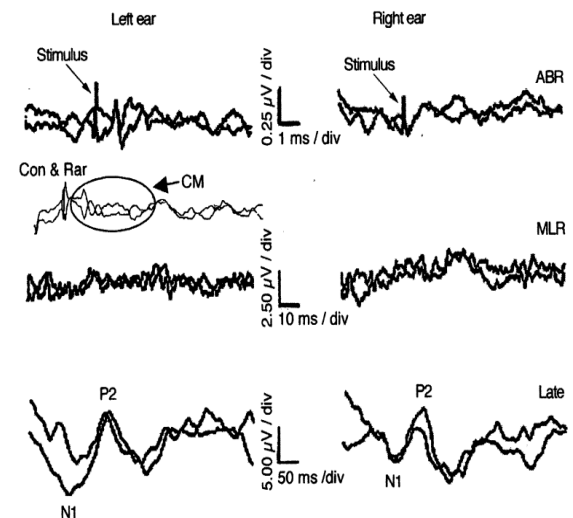
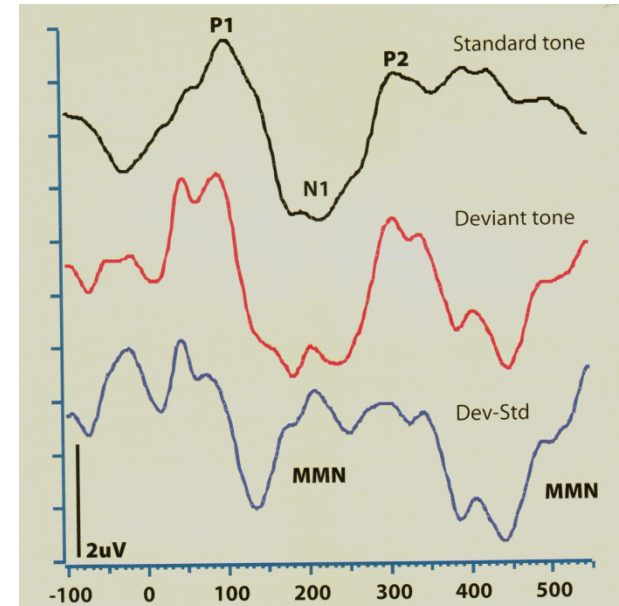


ELECTROPHYSIOLOGY OF ANSD

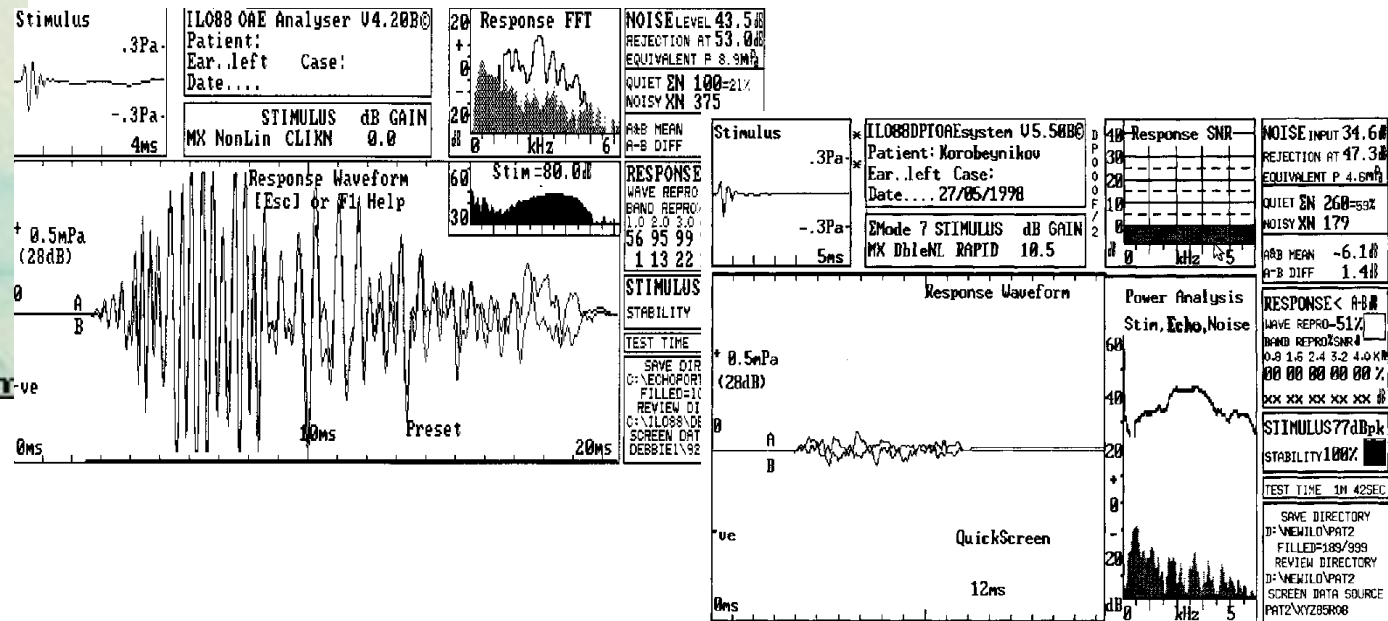
CORTICAL AEPS: MIDDLE LATENCY RESPONSE, CAEP, MMN AND P300

The findings appear to support the concept that the presence of obligatory CAEP, including MMN, are associated with better speech perception outcomes for children with AN with amplification.

The presence of EMLR and ECAEP has strong association with speech perception scores.



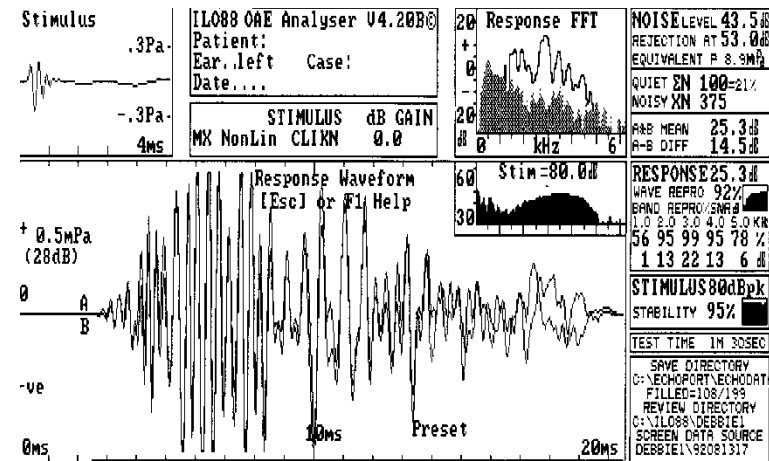
SCREENING



SCREENING

It is impossible to reveal the ANSD during the screening based on OAE registration.

At the same time about 10% of newborns could have the ANSD symptoms.



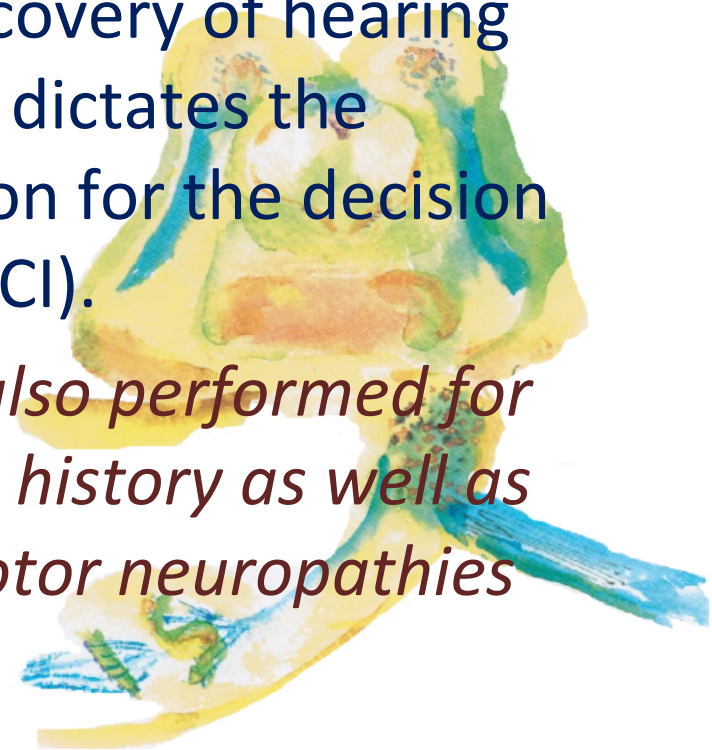
SCREENING

Joint Committee of Infant Hearing (2007):

For NICU newborns (more than 5 days) the ABR registration should be performed!

In babies with hyperbilirubinemia and/or low birthweight the spontaneous recovery of hearing function is quite frequent which dictates the necessity of follow up observation for the decision on the rehabilitation algorithm (CI).

The ABR registration should be also performed for children with hearing loss family history as well as for children with sensory and motor neuropathies



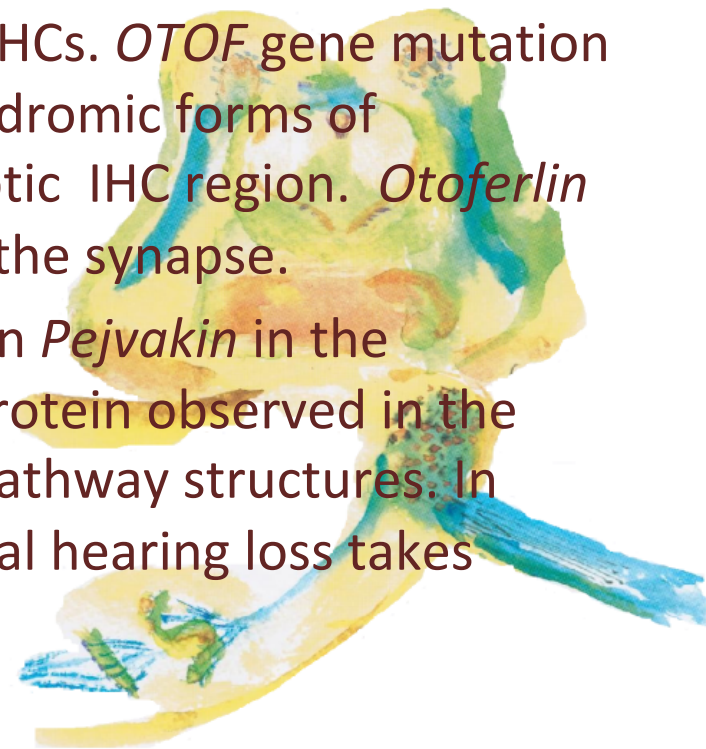
GENETICAL INVESTIGATION

If it is impossible to localize the pathology (SNHL) the genetic testing for the mutation determination (especially in non-syndromic cases) is recommended

1. *DFNB9 (OTOF)* gene mutation on Chromosome 2p 22-23 is found to be responsible for the *Otoferlin* protein production.

This protein is located specifically in the IHCs. *OTOF* gene mutation may be responsible for multiple non-syndromic forms of neuropathies mainly located in the synaptic IHC region. *Otoferlin* is a sensor of Ca^{2+} entry in the IHC from the synapse.

2. *DFND59* gene mutation, coding protein *Pejvak* in the 2q31.1-31.3 chromosome destroys the protein observed in the spiral ganglion cells and in the auditory pathway structures. In contrast with *OTOF* mutation the neuronal hearing loss takes place.



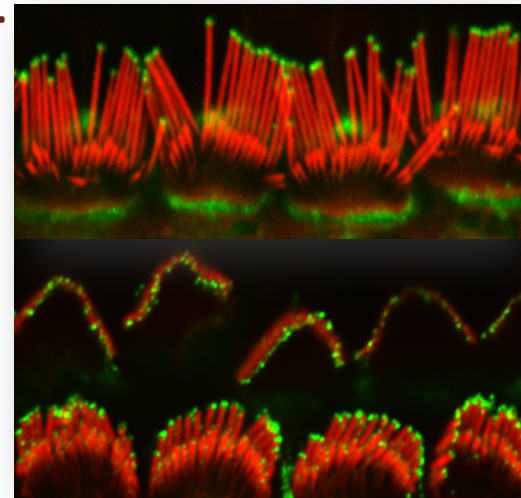
GENETICAL INVESTIGATION

If it is impossible to localize the pathology (SNHL) the genetic testing for the mutation determination (especially in non-syndromic cases) is recommended

3. Non-syndromal dominant type of the progressive ANSD caused by 13q14-21 (*AUNA1*) chromosome pathology. The gene as well as the mechanism are unknown. Symptoms are the same.

4. Mutation of gene *DIAPH3*, coding *diaphanous* protein causes actine regulation, microtubular stabilization disruption which is following by the synaptic transmission disruption.

Non-syndromal dominant type of ANSD.



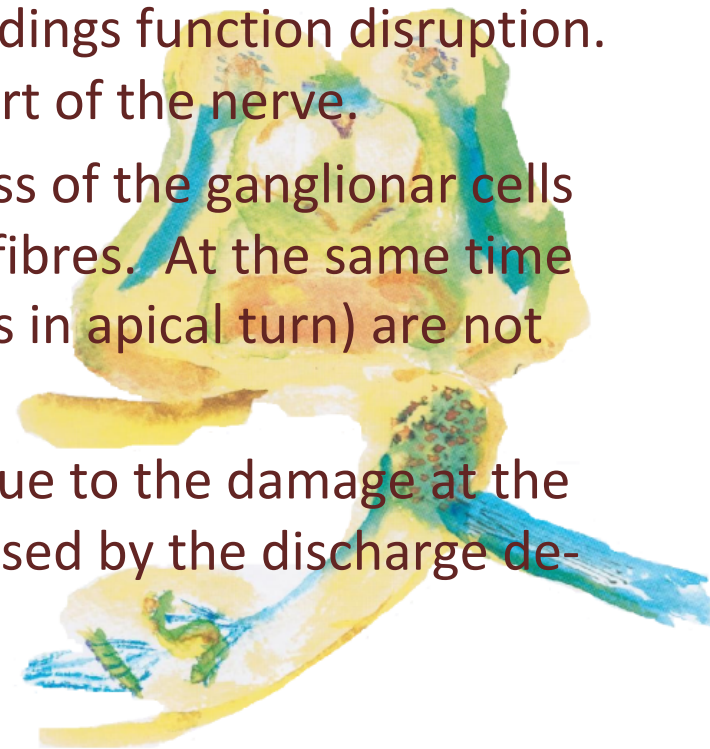
GENETICAL INVESTIGATION

If it is impossible to localize the pathology (SNHL) the genetic testing for the mutation determination (especially in non-syndromic cases) is recommended

5. The *R445H* gene mutation causes the *OPA1* protein synthesis disruption. As a result develops postsynaptic ANSD due to non-myelinated part of the auditory nerve endings function disruption. CI activates only proximal myelinated part of the nerve.

6. The *MPZ* gene mutation causes the loss of the ganglionar cells in central and peripheral auditory nerve fibres. At the same time the OHC and IHC (damage up to 30% cells in apical turn) are not damaged.

In this case of the ANSD hearing loss is due to the damage at the axonal level. The additional effect is caused by the discharge desynchronization in the lasting fibres.

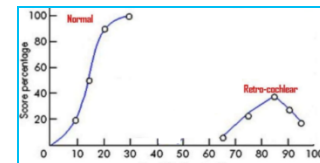
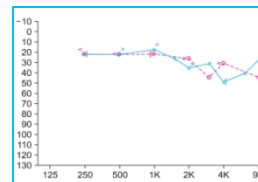
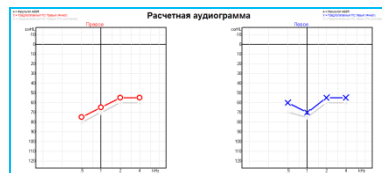
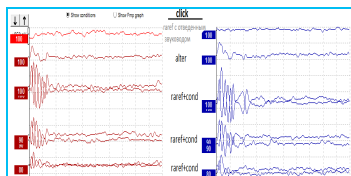


AUDIOLOGICAL CRITERIA:

Hearing thresholds could vary from normal values to deafness, could fluctuate and do not correlate with with ABR

Deterioration of speech understanding (especially in noise), dissociation in tonal and speech audiometry results

The ASSR could be obtained but are not in accordance with ABR thresholds (frequently absent) as well as with tonal hearing



DEMOGRAPHY

100 children with ANSD:

95 - bilateral

5 - single sided

Age - from 2 months to 9 year

78 % - children under 3 years

SCREENING

In 24 from 49 – OAE was absent from one or two ears **(50% FAILED)**

In 25 from 49 – OAE was registered in 2 ears **(50% PASS)**

In 51 child results were not reliable or the audiological screening was not performed

Reason to audiologist's referral: questionable reactions to sounds, delayed speech development

ALGORITHM IN CHILDREN WITH ANSD

Audiological Tests

1. ABR registration with CM extraction
2. OAE registration

Additional audiological tests:

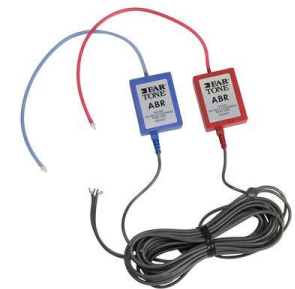
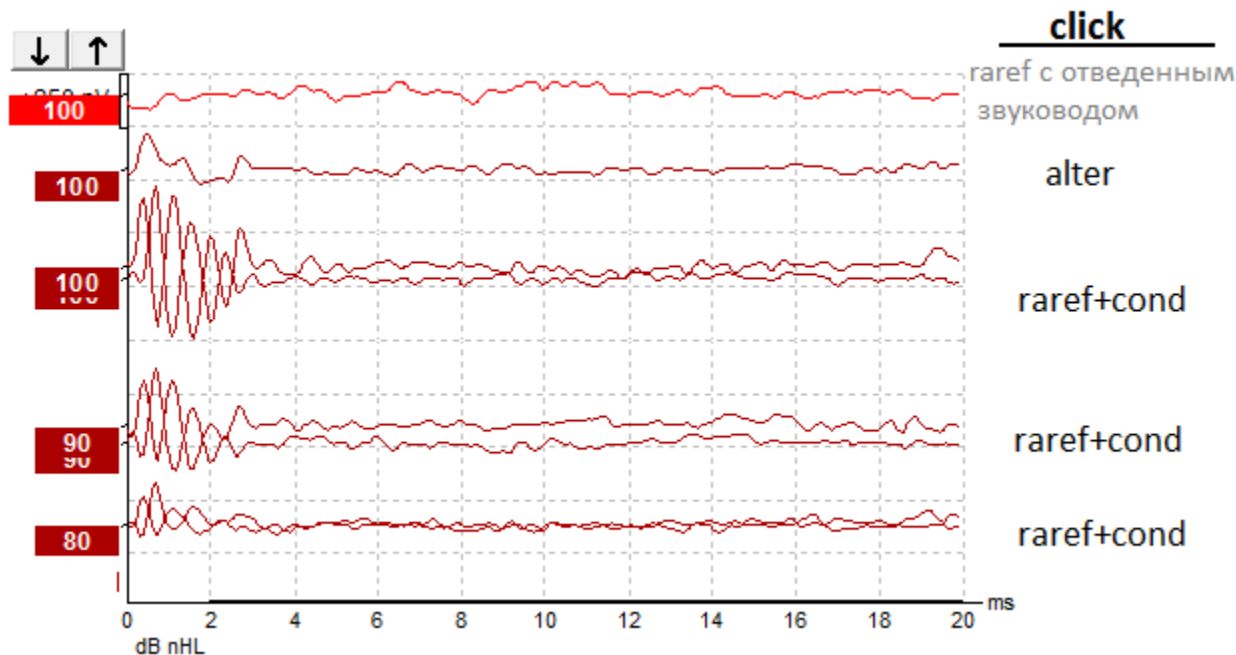
3. Tonal threshold and visual reinforcement audiometry
4. Registration of the stapedial muscle reflexes (problematic in children)
5. OAE suppression with contralateral noise
6. ASSR registration
7. CAEP registration (if possible)
8. Testing by speech therapist

Non-audiological methods::

7. MRI (VIII nerve hypoplasia, demyelination)
8. Neurologist
9. Ophthalmologist
10. Genetic consultation (OTOF, MPZ, PMP22, OPA1...)

ABR AND CM REGISTRATION

1. Insert phones
2. ABR registration to rarefaction and condensation clicks even in absence of OAEs and ABR thresholds ≥ 70 dB nHL
3. Registration with pressed sound tube

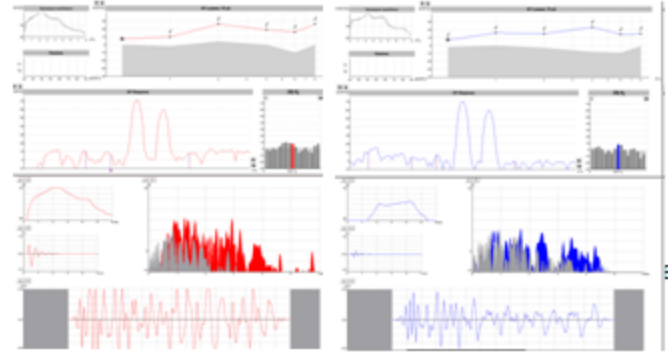
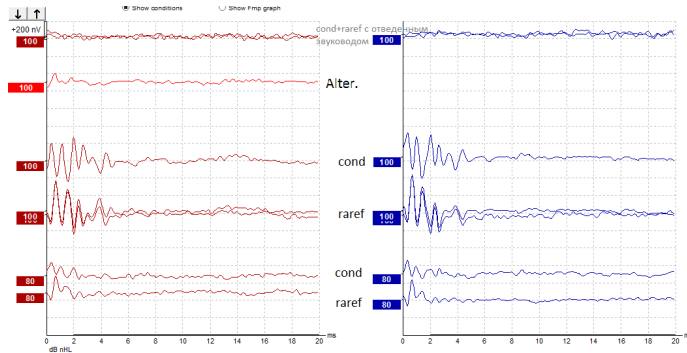


For the CM extraction the presentation rate could be higher than for ABR registration - about 80 per sec.

Filters must be shifted to high frequency region: HF – 300 Hz, LF – 3-5kHz

1. ABR «-» , CM «+» , OAE «+»

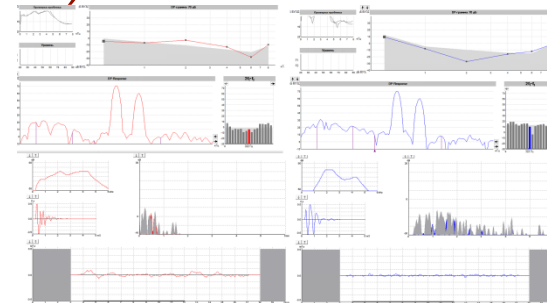
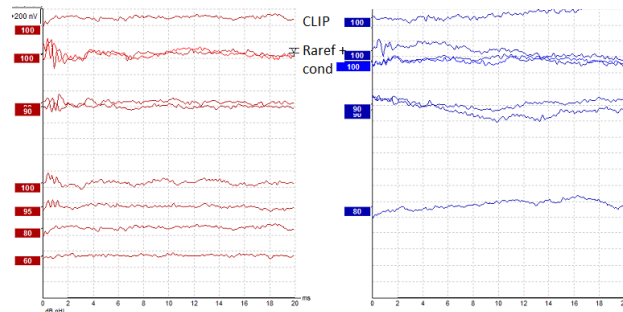
45% of bilateral ANSD (43 from 95)



Patient 1. Hyperbilirubinemia

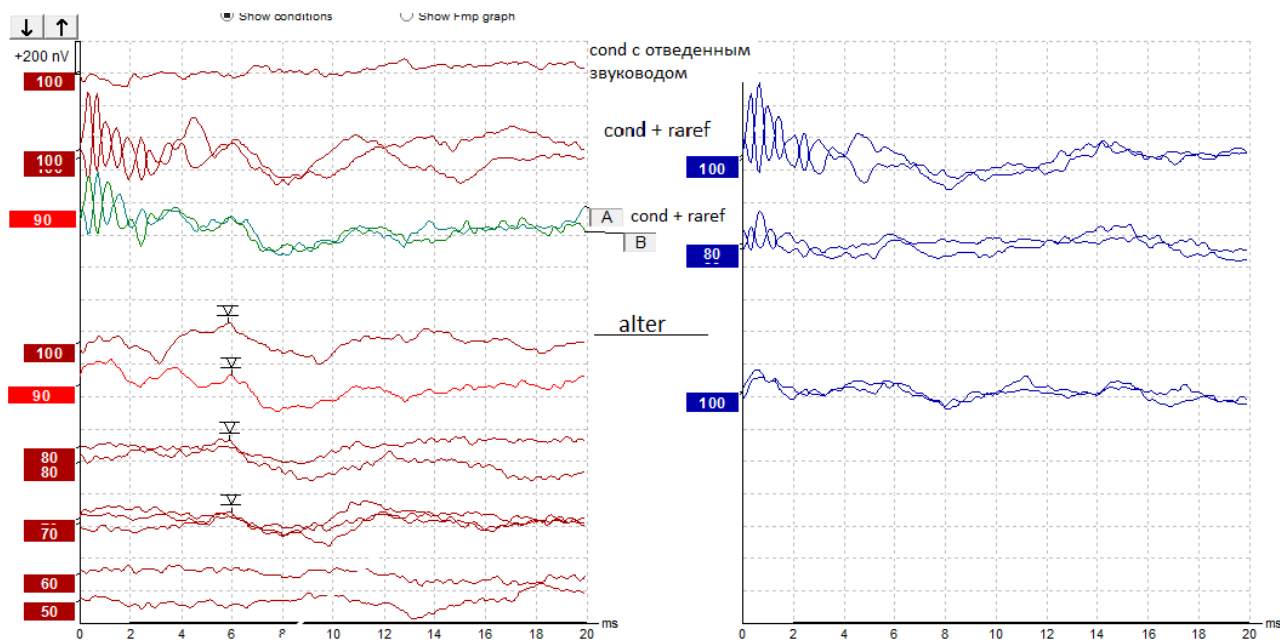
2. ABR «-» , CM «+» , OAE «-»

27% of bilateral ANSD (26 from 95)



Patient 2. Prematurity (25 weeks), 750 g

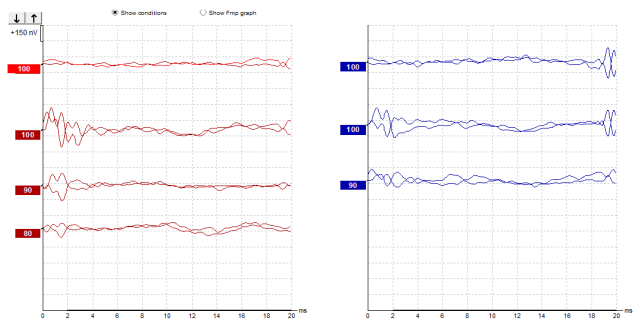
3. ABR «+» (with abnormal morphology) , CM «+» 25% of bilateral ANSD (24 from 95)



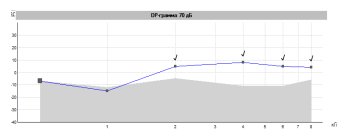
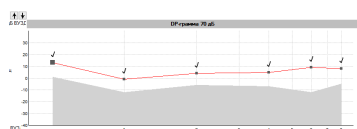
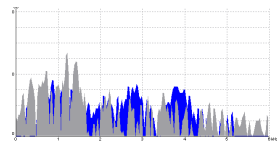
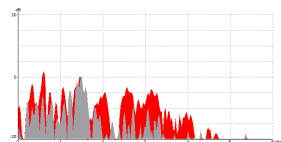
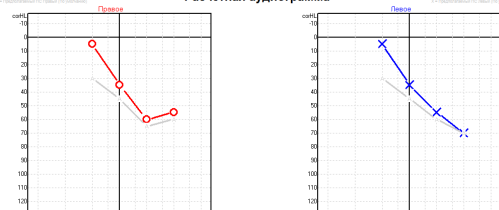
Patient 3. Prematurity (26 weeks), 870 g

3.2. «Wave V with significantly prolonged latency»

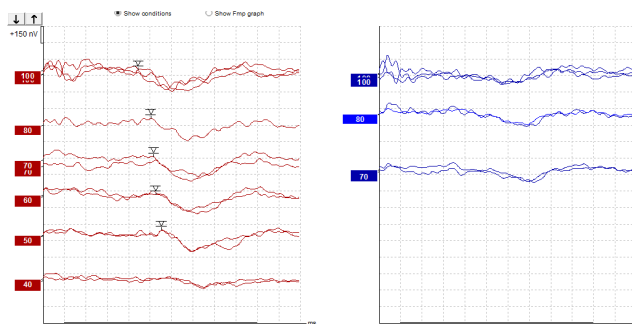
4 г



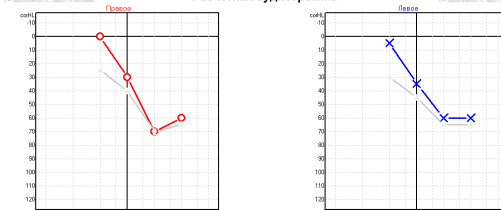
Расчетная аудиграмма



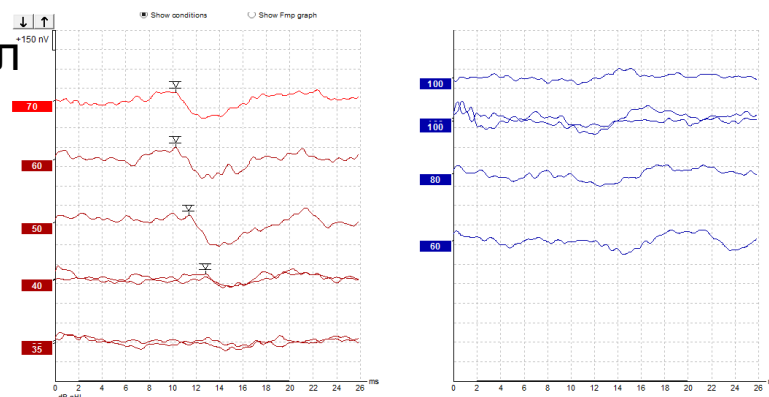
5л



Расчетная аудиграмма

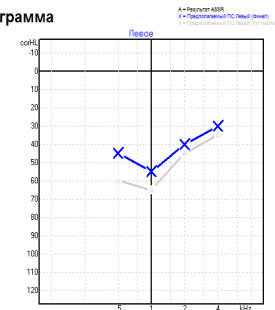
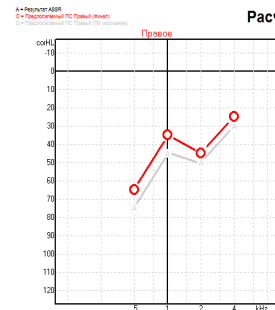
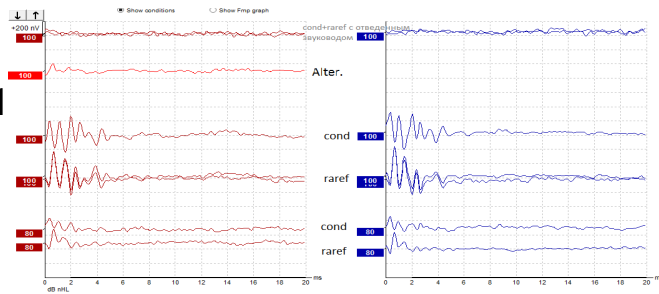


6л



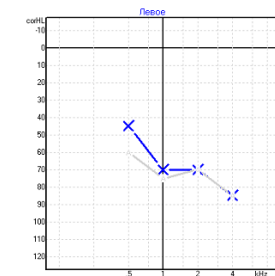
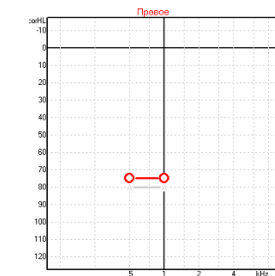
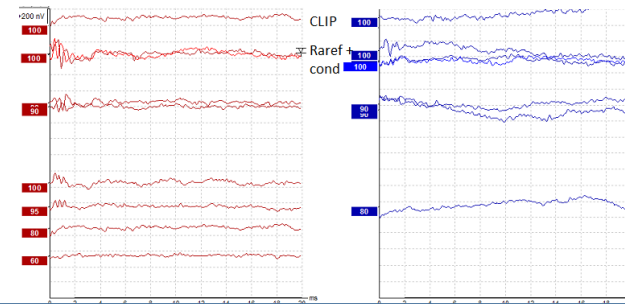
Patient 4. Hyperbilirubinemia (≥ 400). Hearing improvement, stopped the HA use

Patient 1



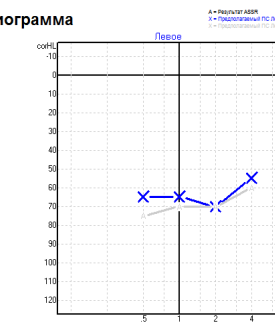
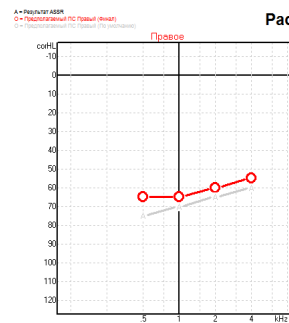
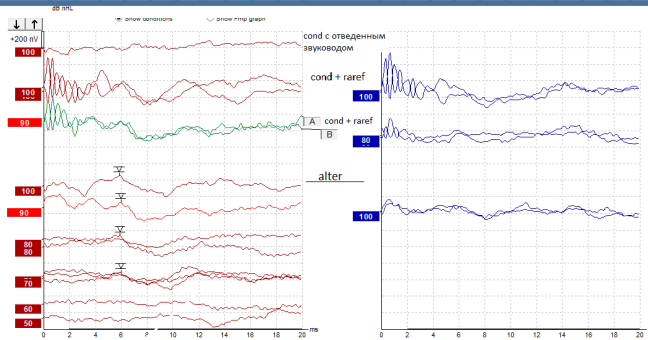
profound - deafness

Patient 2



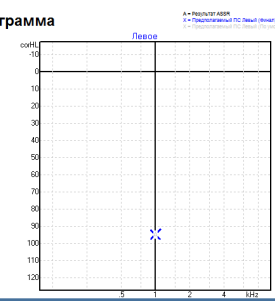
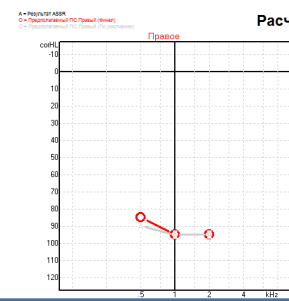
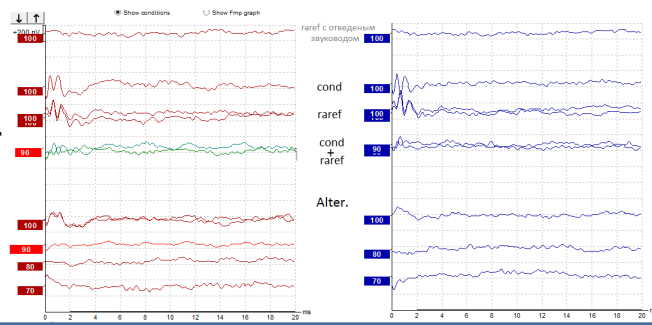
Mild-to-moderate

Patient 3



sever

Patient 4



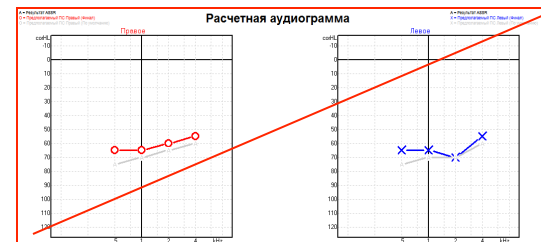
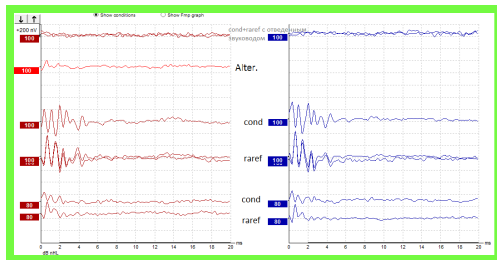
profound - deafness

AUDIOLOGICAL BASIS FOR ANSD DIAGNOSIS IN CHILDREN

ABR registration with CM extraction even in absence of the OAE

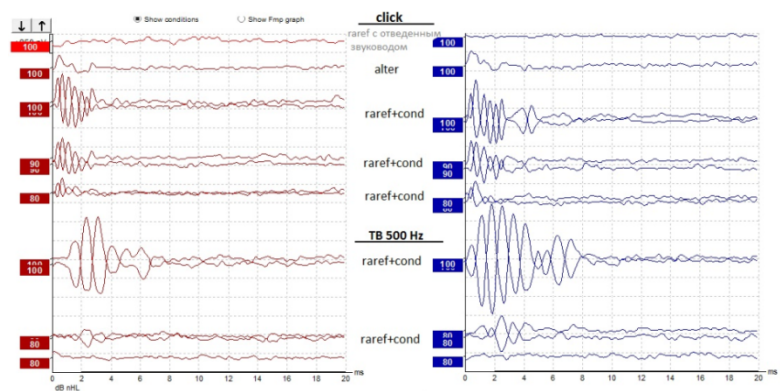
ASSR registration in patients with ANSD does not provide information on hearing thresholds but could be helpful for the diagnosis

The audiological investigation which was started and limited with ASSR could lead to false diagnosis

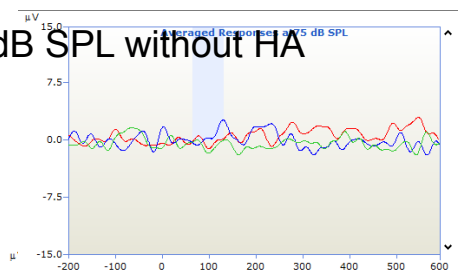


CAEP in audiological investigation of patients with ANSD

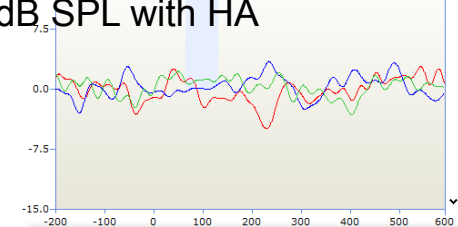
*Patient 3. 4 yrs,
OAE «+»*



75 dB SPL without HA

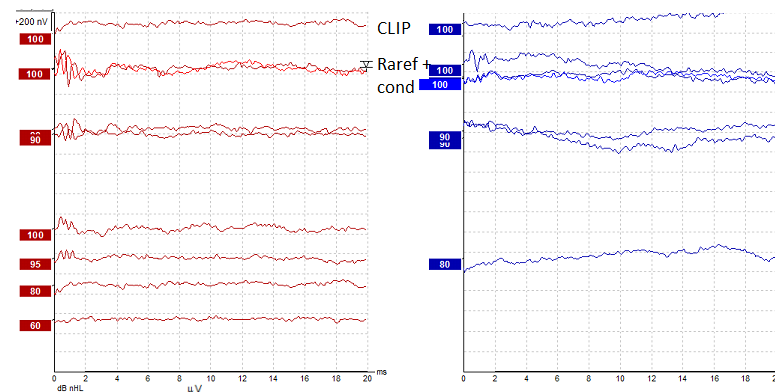


75 dB SPL with HA

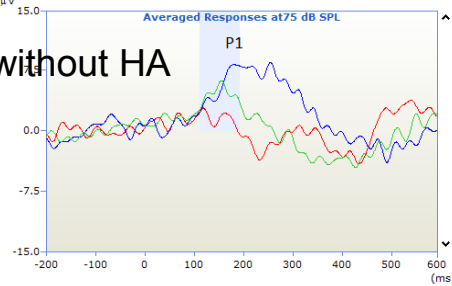


Speech therapist – profound - deafness

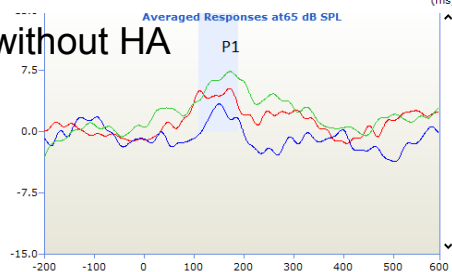
*Patient 4. .11 m, Prematurity (25 weeks),
750g, OAE «-»*



75 dB SPL without HA



65 dB SPL without HA

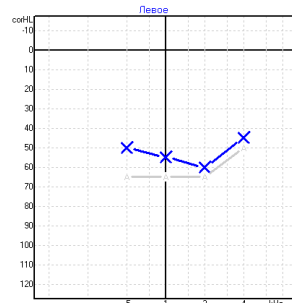
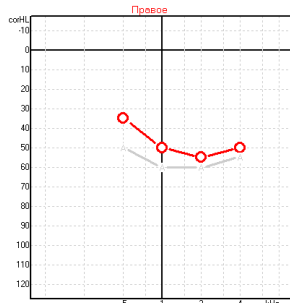
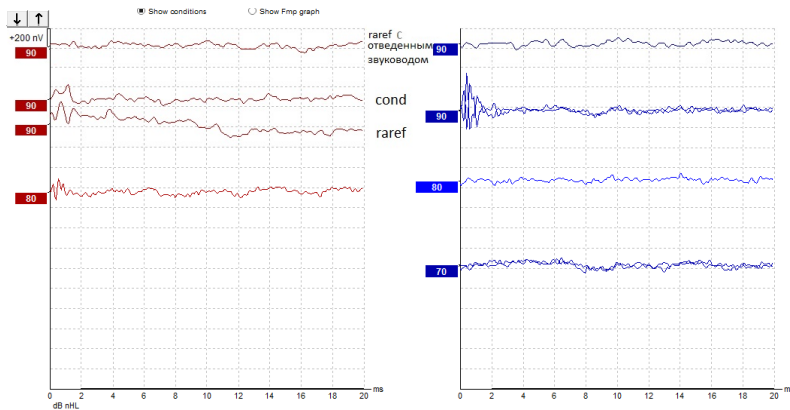


Speech therapist – mild

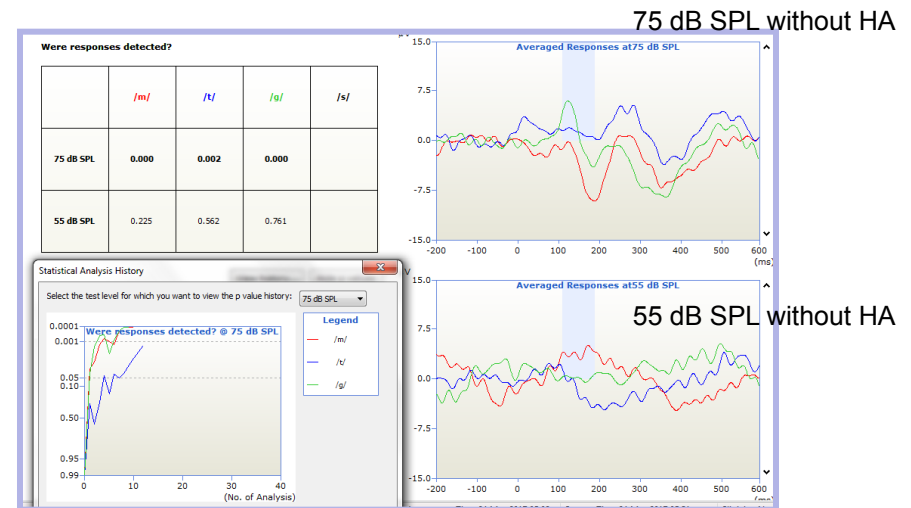
CAEP in audiological investigation of patients with ANSD

Patient 6 .12 months, `prematurity (26 weeks), 990 g, Apgar 3\8, pneumonia, hyperbillirubinemia, cerebral ischemia.

OAEA AD AS «-»



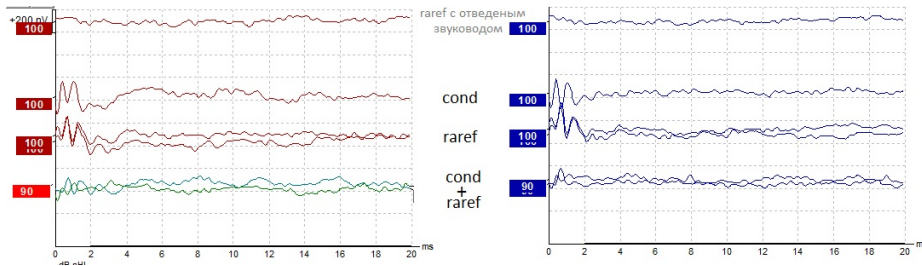
Polyphasic CAEPs



Speech therapist – whisper 5-6 m !!!

CAEP in audiological investigation of patients with ANSD

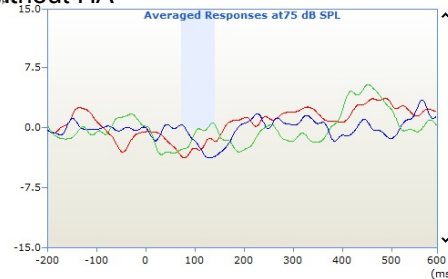
*Patient 5. Prematurity 34 weeks,
hyperbilirubinemia. HA from 10 months*



75 dB SPL without HA

Were responses detected?

	/m/	/t/	/g/	/s/
75 dB SPL	—	—	—	—

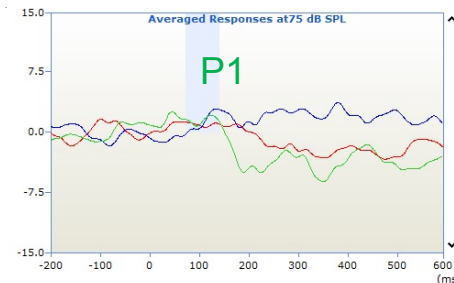


Speech therapist – profound - deafness

75 dB SPL with HA

Were responses detected?

	/m/	/t/	/g/	/s/
75 dB SPL	—	—	✓	—

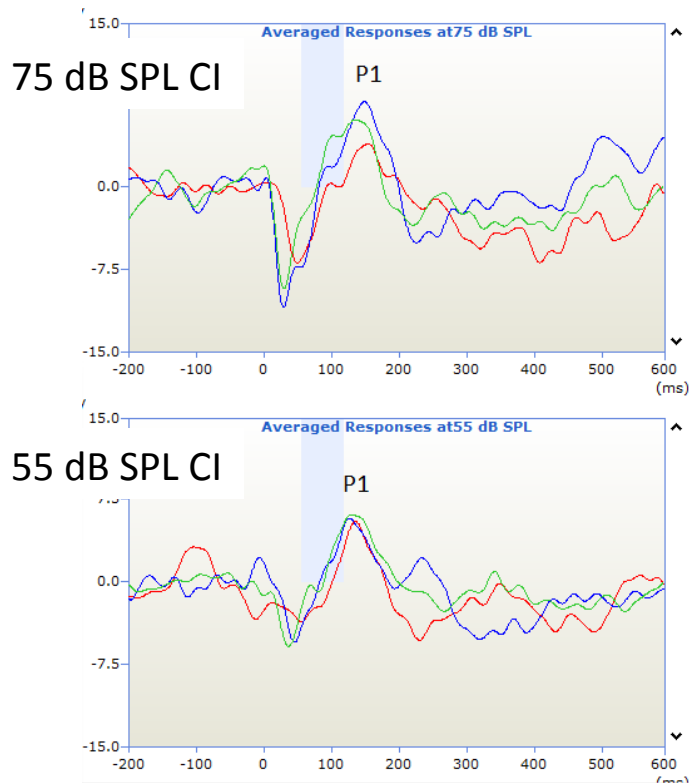


Indication for CI

CAEP in audiological investigation of patients with ANSD after CI

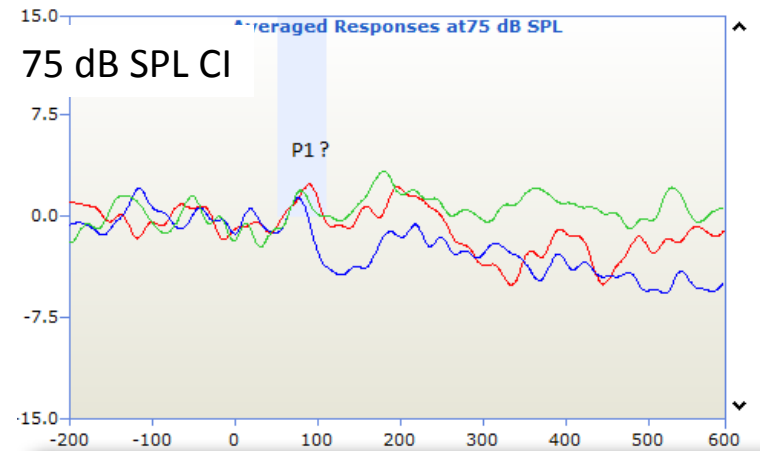
6 years. CI from 5 yrs
Prematurity (28 weeks), 1090 g

CAEP in 1 year after SP switch-on



7 years, CI in 33 months
Prematurity 34 weeks, hyperbilirubinemia

CAEP in 5 years after SP switch-on



CONCLUSION

In the diagnosis of the ANSD the ABR registration with CM extraction even in absence of the OAE is of vital importance

The ASSR as well as ABR are not informative for hearing threshold determination

The CAEP registration is a perspective method for estimation of the auditory system functionality in children with ANSD as well as for the prognosis of rehabilitation

REHABILITATION

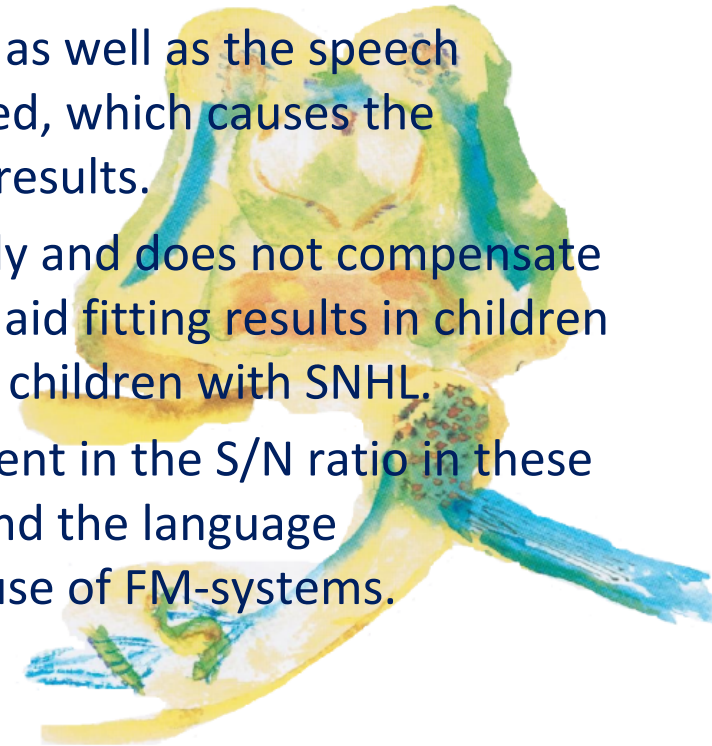
HEARING AID FITTING

PROBLEM: It's impossible to register the electrophysiological responses. It is necessary to make a decision only based on the behavioral reactions on sounds and speech.

In case of the negative dynamics the hearing aid fitting is recommended. In ANSD the temporary processing of speech as well as the speech temporary characteristics coding are disrupted, which causes the dissociation in tonal and speech audiometry results.

Because the HA provide the amplification only and does not compensate the temporary processing deficit the hearing aid fitting results in children with the ANSD are worse in comparison with children with SNHL.

Based on the assumption that the improvement in the S/N ratio in these children will improve the speech reception and the language development it is necessary to consider the use of FM-systems.



REHABILITATION

HEARING AID FITTING

Questions: Presence of the OAEs indicates the normal function of the OHCs

Is it possible to damage OHC with the amplification?

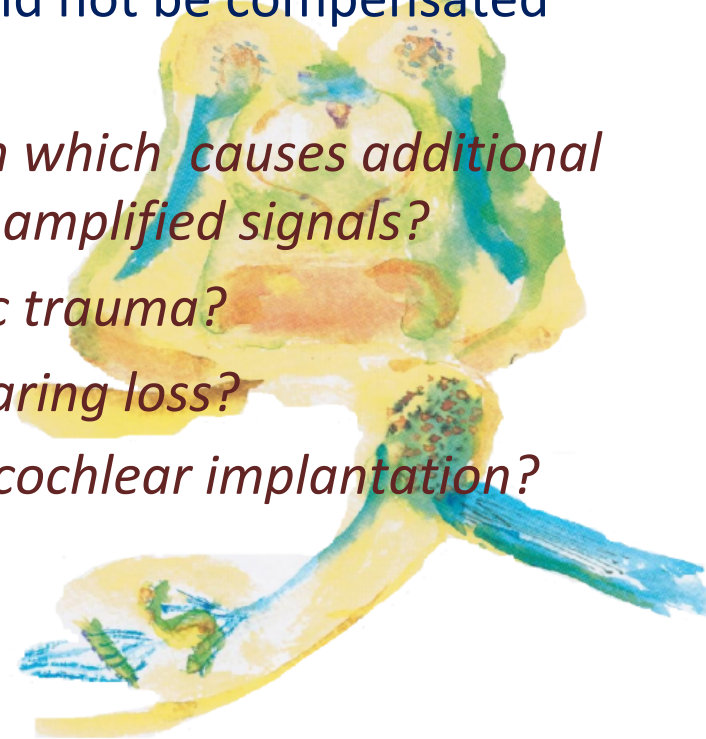
The temporary processing disruption could not be compensated by the amplification.

Is it necessary to exclude the compression which causes additional distortion in the temporary processing of amplified signals?

If yes, how could be excluded the acoustic trauma?

What is necessary to do in fluctuating hearing loss?

When it's necessary start to think on the cochlear implantation?



REHABILITATION

HEARING AID FITTING

Based on the protocol (2008) it is recommended to use the linear amplification (no compression), low frequency filtration or high frequency transposition.

It was shown that in 50% of children with ANSD hearing aid fitting is effective. In these children cortical AEP were registered.

The modern hearing fitting techniques dictate the necessity to measure RECD and formulas of gain and output prescription (DSLv5, NAL). For this purposes the hearing thresholds determination is necessary. The problem is that if in children with SNHL it was possible to register frequency specific ABRs and ASSRs in children with ANSD it is impossible.



REHABILITATION

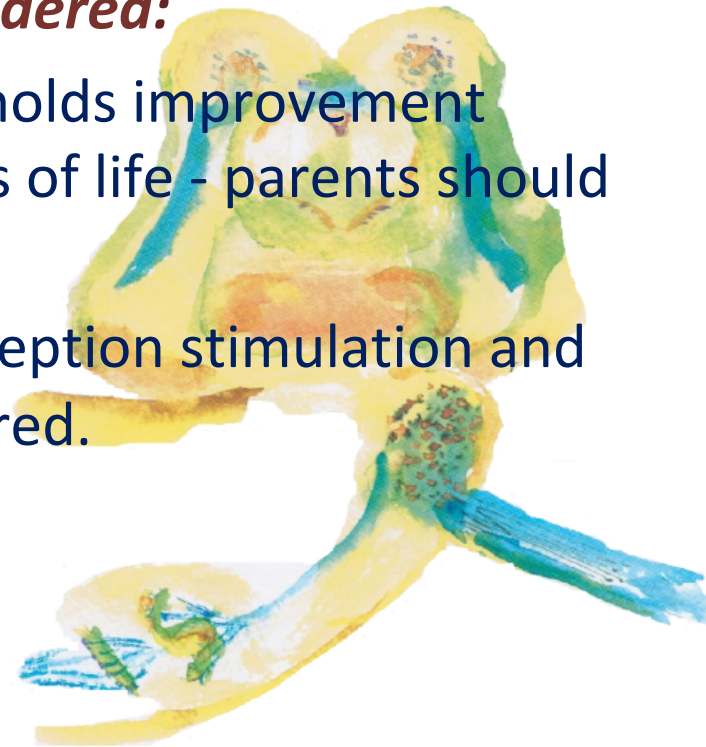
COCHLEAR IMPLANTATION

Children without progress in speech perception and production should be considered as CI candidates without any dependence on hearing thresholds.

The following factors should be considered:

1. In some children the hearing thresholds improvement could take place during first two years of life - parents should be informed on it.

Early rehabilitation based on the perception stimulation and speech production should be considered.



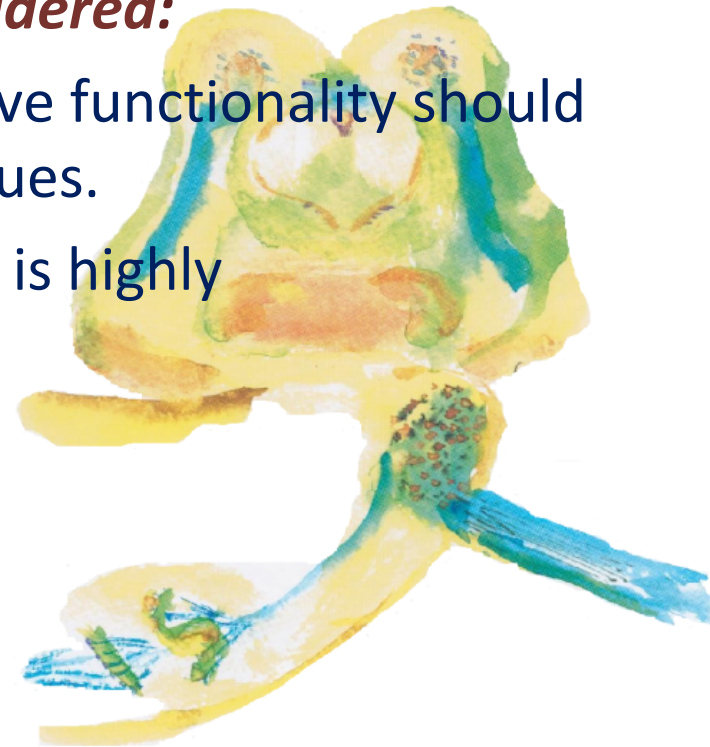
REHABILITATION

COCHLEAR IMPLANTATION

Children without progress in speech perception and production should be considered as CI candidates without any dependence on hearing thresholds.

The following factors should be considered:

2. The conclusion on the auditory nerve functionality should be based on the modern MRI techniques.
3. The pre-operative promontory test is highly recommended.



REHABILITATION

COCHLEAR IMPLANTATION

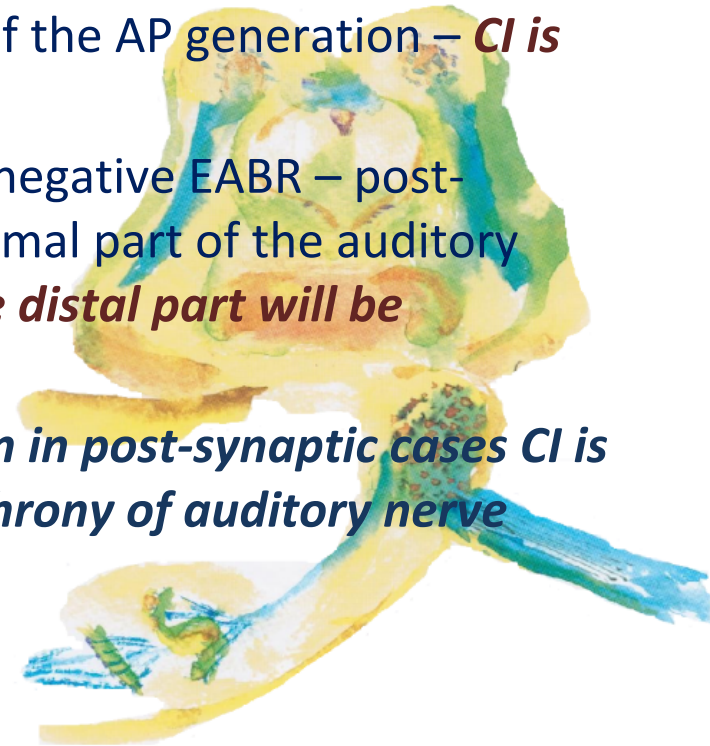
Cochlear implantation improves temporary processing stimulating synchronized discharges of auditory nerve fibres.

Electrophysiological prognosis

High amplitude positive SP with prolonged latency, positive EABR – receptor, pre-synaptic location before level of the AP generation – ***CI is recommended.***

Normal SP with pathological AP and DPOAE, negative EABR – post-synaptic location (neural dysfunction) – proximal part of the auditory nerve is involved – ***electric stimulation of the distal part will be ineffective.***

It is necessary to mention that last time even in post-synaptic cases CI is recommended because it improves the synchrony of auditory nerve fibres discharges that leads to better results



REHABILITATION

COCHLEAR IMPLANTATION

Cochlear implantation improves temporary processing stimulating synchronized discharges of auditory nerve fibres.

Electrophysiological prognosis

SP	DPOAE	TEOAE	CM	CAP	EABR	Localization	Prognosis
High amplitude positive SP with prolonged latency	-	+	+	-	Positive	Pre-synaptic	CI+
Normal	+	+	+	Pathological	Negative	Post-synaptic	CI-



REHABILITATION



PRE-SYNAPTIC	POST-SYNAPTIC
<i>DFNB9 (OTOF) - Otoferlin</i>	<i>DFND59 - Pejvakin</i>
Chromosom 13q14-21 – <i>AUNA1</i>	<i>R445H - OPA1</i>
<i>DIAPH3 – diaphanous ?</i>	<i>MPZ</i> - loss of the ganglionar cells

MAIN CONCLUSION

FOLLOW-UP!!!

In children under 24 months the absence of the ABR should be considered very carefully!

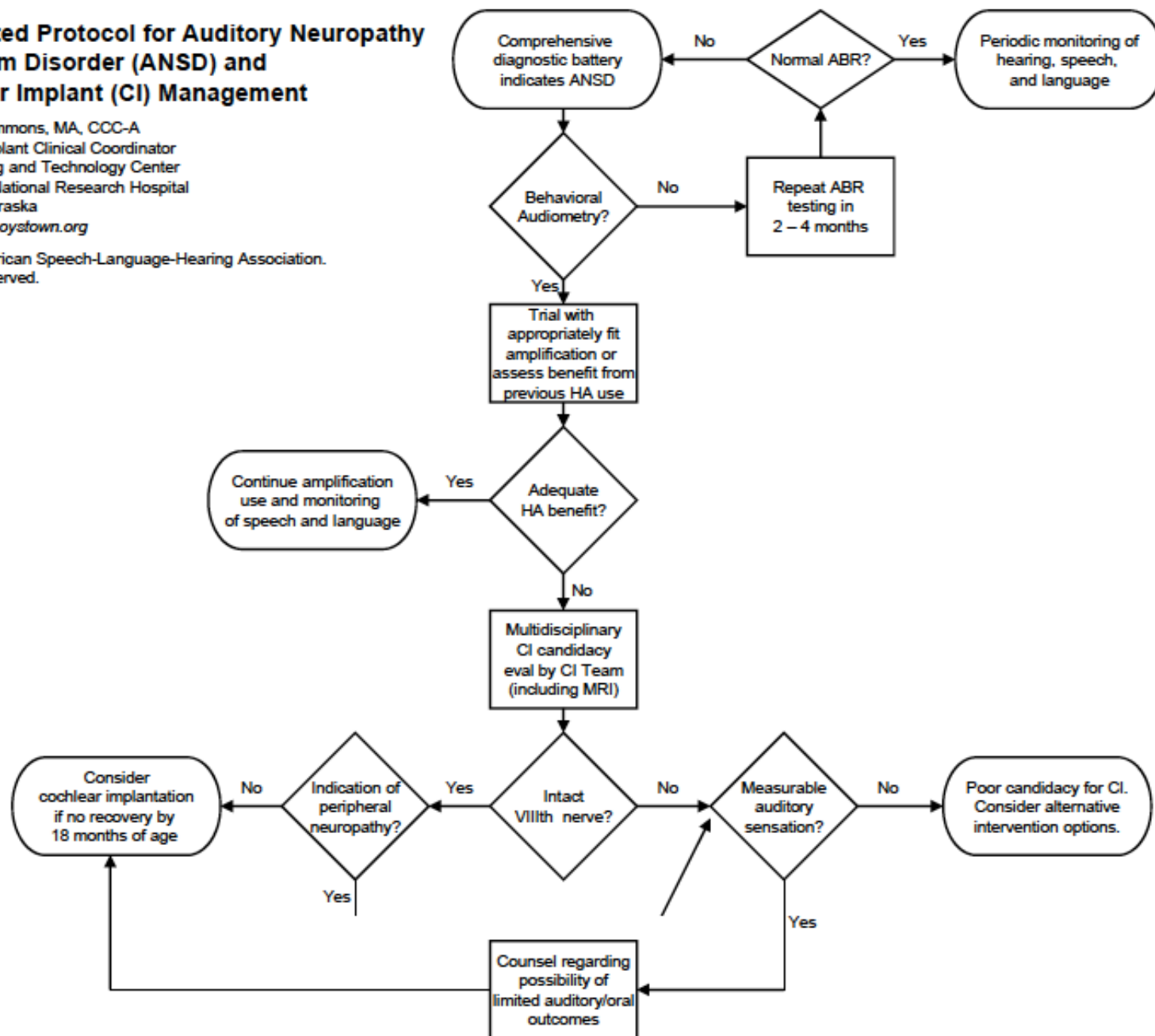
In these children the follow-up investigation prior to the final decision on the rehabilitation should be performed!



Suggested Protocol for Auditory Neuropathy Spectrum Disorder (ANSD) and Cochlear Implant (CI) Management

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THANK YOU!

