تنوعات وتغيرات كل من البث الأذني الصوتي ومايكروفونية القوقعة لدى الأطفال المصابين بطيف الاعتلال العصبي السمعي

فادي الشامي*

الملخص

خلفية البحث وهدفه: يعتبر الاعتلال العصبي السمعي مصطلحاً طبياً حديث التداول سريرياً حيث وصف لأول مرة عام 1996 ويعتمد تشخيصه على غياب أو تشوه في مورفولوجية موجات كمونات جذع الدماغ المحرضة ABR عند شدات تنبيه عالية مترافقة مع وجود البث الأذني الصوتي و/ أو ظهور موجات مايكروفونية القوقعة. يهدف هذا البحث إلى دراسة تنوعات ومواصفات كل من مايكروفونية القوقعة والبث الصوتي الأذني بين جمهرة من الأطفال الذين شخص لهم اعتلال عصبي سمعي إضافة لدراسة عوامل الخطورة لنقص السمع لديهم.

المواد والطرائق: دراسة تراجعية لمجموعة من الأطفال المراجعين لقسم الاستقصاءات السمعية في منظمة آمال في الفترة مابين 2018/1/1 و2019/11/1 والذين شخص لهم اعتلال عصبي سمعي حيث تضمن البحث دراسة نتائج اختبار البث الأذني الصوتي DPOAE – دراسة خصائص موجات مايكروفونية القوقعة (زمن الكمون – المطال – مدة الاستمرارية) وتنوعات كل من الاختبارين بوجود عوامل خطورة أو لا –إمراضيات الأذن الوسطى واستخدام للمعينات السمعية. تمت دراسة مطال موجات مايكروفونية القوقعة عبر قياس المطال من الذروة إلى الذروة وتقسيمها إلى ثلاث فئات،وتمت دراسة زمن الكمون والاستمرارية بدءاً من ظهور أول موجة جيبية وانقلابها عند تغيير القطبية ،وحتى انتهائها .

النتائج: بلغ عدد الحالات المشخصة باعتلال عصبي سمعي أحادي أو ثنائي الجانب 58 حالة (110 أذان) ، 52 حالة شخصت اعتلال عصبي سمعي ثنائي الجانب (واحدة منها اعتلال مؤقت) و 6 حالات أحادي الجانب، متوسط العمر 33 شهر ±23 شهر، الذكور 33 حالة (57%) والإناث 25 حالة (43%)، كان البث الصوتي الاذني (لـ 96 أذن أجري لها الاختبار) موجوداً لدى 31.5% من الأذان وغائباً لدى 68.5% ،تم تسجيل ظهور موجات CM لدى 99 أذن. تبين وجود فرق هام إحصائياً في مطال موجات مايكروفونية القوقعة بين مجموعة الأذان مع تواجد البث الأذني الصوتي وبين مجموعة الأذان مع غياب البث الأذني الصوتي، وفرق هام إحصائياً في المطال في الأذان غير المستخدمة للمعينات السمعية مقارنة بالأذان المستخدمة للمعينات السمعية ، كما وجد أيضاً فرق هام إحصائياً في استمرارية الموجات بين مجموعة الأذان مع مخطط معاوقة A أو As و مجموعة الأذان مع مخطط معاوقة B ولم يلاحظ وجود فروقات إحصائية في باقي القياسات. كان أشيع عامل خطورة موجود كعامل وحيد هو اليرقان النووي، ولم توجد أية فروق إحصائية بخصائص البث الصوتي الأذني وموجات مايكروفونية القوقعة تبعاً لوجود عوامل خطورة أو عدم وجودها

*طالب دكتوراه، قسم أذن أنف حنجرة، كلية الطب البشري، جامعة دمشق.

.من ضمن 10 حالات أجري لهم مرنان تبين وجود عدم تصنع (غياب) في العصب القوقعي لدى حالة واحدة – نقص تصنع لدى 3 حالات منها حالتان ترافقتا مع نقص تصنع في العصب الثاني(البصري)

الاستنتاجات: تتنوع خصائص ومواصفات كل من موجات مايكروفونية القوقعة والبث الصوتي الأذني بين الحالات تبعاً لتواجد البث الأذني الصوتي أو غيابه –تبعاً لإمراضيات الأذن الوسطى ، وقد يكون هناك تأثير واضح لاستخدام المعينات السمعية على غياب البث الأذني الصوتي أو غياب تسجيل موجات مايكروفونية القوقعة لكن هذا التأثير ربما يكون أيضاً مرتبطاً بالعمر أو من ضمن سير المرض وبحاجة لدراسات أوسع. يجب التأكيد على إجراء المرنان لجميع الحالات المشخصة باعتلال عصبي سمعي لنفي وجود إصابة عصبية مرافقة أو غياب أو ضمور للعصب القوقعي لوضع التشخيص الدقيق والتدبير المناسب للحالة

الكلمات المفتاحية: الاعتلال العصبي السمعي – البث الأذني الصوتي –مايكروفونية القوقعة –ضمور العصب القوقعي – عوامل الخطورة.

Variations And Characteristics Of Cochlear Microphonic And Otoacoustic Emissions In Children With Auditory Neuropathy Spectrum Disease

Fadi Al Shami*

Abstract

Research background and objective : Auditory neuropathy(AN) is a clinically recent medical term that was first described in 1996 and its diagnosis is based on the Auditory Brainstem Response (ABR) absent or with grossly abnormal morphology at high stimulus levels with Otoacoustic emissions (OAEs) and/or cochlear microphonic (CM) present. The aimed of this study to investigate The characteristics of both the CM and the OAEs among a group of children who have been diagnosed with AN in addition to analyze Hearing loss (HL)risk factors.

Materials and Methods : A retrospective review of the clinical records of a group of children reviewing the Audiology center at Syrian Organization for Persons with Disabilities -AAMAL between 1/1/2018 and 1/11/2019 and who have been diagnosed with AN,The research included studying the results of the Distortion Product otoacostic emissions(DPOAE) - characteristics of CM waves (latency - amplitude duration of CM),and variations of each of the two tests according to presence of risk factors or not, pathology of middle ear ,and the use of hearing aids(HAs) or not. Amplitude of CM waves was studied through the measurement of peak to peak amplitude and divided it into three categories , Latency and duration were studied from the appearance of a first sinusoidal wave that reverse when change polarity , and until the end of the waves.

Results : The number of cases diagnosed with unilateral or bilateral auditory neuropathy was 58 cases(110 ears).52 cases diagnosed with bilateral AN , one of which was transient AN, and 6 cases with unilateral AN. Mean age was 33 months ± 23 months , males 33 case (57%) and females 25 case (43). OAEs were conducted in 87 ears and were present in 26 ears (31.5)% and absent in 61 ears (68.5%) .CM was recorded in 99 ears. A statistically significant difference was found in CM amplitude mean between the ears with OAEs present and the ears with OAEs absent, and in the ears not used hearing aids compared to the ears used hearing aids .Also a statistically significant difference in the CM duration between the ears with tympanogram type A or As compared to the ears with tympanogram type B, and no significant statistical difference was observed in the rest of the measurements . The most common risk factor presented as a single factor was nuclear jaundice (Kernicterus) , and there were no statistical differences in the characteristics of the OAEs and CMs depending on the presence or absence of risk factors . Of the 10 cases that MRI were performed, it was found one case with absence of the cochlear nerve and 3 cases with cochlear nerve hypoplasia, of which, two cases were associated with hypoplasia of the optic nerve.

Conclusions : Characteristics and specifications of each of CMs and OAEs are varying between the cases , depending on the presence of OAEs or absence - depending on the pathology of the middle ear , and there may be a clear effect of using of hearing aids on the absence of OAEs or absence of CM but this effect may also be related to age or within the course of the disease, and needs further studies . Emphasis must be placed on the MRI for all cases diagnosed with AN to rule out the presence of a concomitant neurological injury, absence or atrophy of the cochlear nerve in order to establish an accurate diagnosis and appropriate management of the case.

The Keywords : Auditory Neuropathy - Otoacoustic Emissions - Cochlear Microphonic – Cochlear nerve Hypoplasia - Risk Factors

* Master's degree, Ear-Nose-Throat Department, Faculty of Human Medicine, Damascus University.

Introduction :

Auditory neuropathy (AN) is a term that describes a disorder in the auditory system associated with the relatively normal function of the outer hair cell and characterized by an absent or grossly abnormal morphology of auditory brainstem response (ABR) at high stimulus levels, accompanied by presence of Otoacoustic Emission (OAE) and / or Cochlear Microphonic (CM) [1]. (Sininger., 2002,193)

This disorder was first described in 1996 by Starr A et al [2] (1996,741)

Other workers have preferred the term 'Auditory Dys-synchrony' (Berlin *et al*.,2002,210) [3] and other terms such as 'Auditory De-synchrony' , 'Auditory mismatch', 'Peri-Synaptic Audiopathy', 'Persistent Outer Hair Cell Function' and 'Neural Hearing Loss'[4]

(Rapin *et al*.,2003,707)

In June , 2008 at the International Guidelines Development Conference at Como- Italy , the term 'Auditory neuropathy (AN) ' had been changed to become 'Auditory Neuropathy Spectrum Disorder (ANSD) [5],

(Pearce *et al*., 2009,37)

as a result of the Rance G et al study (2002,239) [6],which showed that half of the children who had AN, had similar speech discrimination abilities to children who had sensorineural hearing loss (SNHL), while the other half had poor speech discrimination scores. The term ANSD was considered a description for a wide variety of auditory disorders, which range from auditory Dys-synchrony to auditory neuropathy and other disorders[3]. (Berlin et al.,2002,210)

Patients with ANSD show varying degrees of hearing loss ranging from mild to profound. which might be unilateral or bilateral , in addition to a poor speech discrimination disproportionately with behavioral hearing thresholds. [6] (Rance et al.,2002,239)

Also, the ABR show variety of results which may range from severe changes in the morphology of waves to absent waves , reflecting the multi - faceted nature and heterogeneous pathophysiology of this disorder.[7] (Foerst *et al*.,2006,1415)

Some studies show different prevalence of ANSD. Foerst A et al (2006,1415) [7] indicates in his study a prevalence of 8.44%, Mason et al(2003,45) [8] indicates a prevalence of 15%. Sininger et al (2002, 193)[1] estimates that ANSD occurs in about 1 in 10 children with permanent hearing loss. The management of this disorder needs special approaches regarding communication skills and speech and language rehabilitation in a different way to patients with peripheral (sensory) hearing loss [9] (Korver *et al*.,2012, 1710)

Some cases may benefit from the use of hearing aids [6] (Rance et al.,2002,239)and must therefore be tried, (and possibly with assisted devices such as FM system), before moving on to the second solution, via cochlear implantation. Fortunately, electrical stimulation via the cochlear implant can be useful in many cases with ANSD[10-12]

(Fabry.,2000,237)

(Zeng *et al*.,2006,167)

(Sininger *et al*.,2002,29)

The site of the injury in AN remains unclear, it may be in the synapses between inner hair cells and the auditory nerve fibers, a defect in afferent and efferent auditory nerve fibers, a defect in the spiral ganglion neurons, or abnormalities in neurotransmitters[13-15]

(Mason *et al*.,2003,45)/(Starr *et al*.,2000,215)

(Hood.,1998,1031)

The ANSD may related to several risk factors, including prematurity (less than 28 weeks), Severe hyperbilirubinaemia especially at levels that require exchange transfusion, hypoxia and admission to the NICU with mechanical ventilation for more than 5 days [16-19]

(Berg *et al*.,2005,933)/(Madden.,2002,1026)

(Rance *et al*.,1999,239)/(Berlin *et al*.,2010,30)

Also, an association has been observed of ANSD with autosomal dominant genes [20]

(Kim *et al*.,2004,872)

or auto- somal recessive not associated with syndromes[21]

(Varga *et al*.,2006, 576)

In addition to some syndromes that include peripheral neuropathies such as Charcot - Marie-Tooth syndrome[22].
(Postelmans *et al*.,2006, 508)
ANSD diagnosis is confirmed by using OAE, ABR and recording CM waves by using a special protocol via the ABR device or sometimes (in researches) by using EcochG test.
OAEs may not be present, and this may be due to several etiologies including : the middle ear pathology such as otitis media with effusion (OME), or it may be absent with aging [24-23],
(Santarelli *et al*.,2006,93)
(British Society of Audiology.,2019,14)
or perhaps after a previous trial of hearing aids [25] (Sininger & Starr.,2001,28)
so when the OAE is absent, the main test for confirming the diagnosis are the recordings of the CMs , which may also be affected by the same etiologies that may affect the OAEs results [24]
(British Society of Audiology.,2019, 13)
.Also these CMs waves may differ in their characteristics among patients, such as latency – continuity (duration)- and amplitude.
In the absence or abnormal morphology of ABR with a presence of OAE, it may not need to conduct CM test, where the diagnosis will be among the ANSD but it is best to do it[24].(British Society of Audiology.,2019, 13)
Also, the absence of OAEs and CM with the absence or abnormal morphology of ABR does not categorically rule out ANSD, as some reports that in some cases of ANSD, the OAE and/or CM can "burn out" with time [24].(British Society of Audiology.,2019,16)
The study aim is to investigate the variations and characteristics of both the CMs and the OAEs among a group of children diagnosed with ANSD through the ABR, CM and OAE tests, in addition to report risk factors associated with ANSD in the study group. Other aim is to investigate the effect of the presence of the middle ear pathology, or the use of hearing aids (for cases that underwent audiological reassessment tests) on the results and characteristics of the OAEs and the CMs.

Patients and methods:

1- Study design :

A retrospective review of clinical records of a group of children who have been diagnosed with ANSD.

2-Patients:

The study includes children reviewing the Audiology Center at Syrian Organization for Persons with Disabilities – AAMAL between 1/1/2018 and 1/11/2019.

Inclusion criteria:

1- ABR absent or with grossly abnormal morphology at or above 80dB nHL (unilateral or bilateral) with CMs present, OAEs present or absent .
2-ABR absent or with grossly abnormal morphology at or above 80dB nHL (unilateral or bilateral) with OAEs present , CM absent.
3-Cases in which audiological reassess- ment was performed due to previous ABR test showed absent or grossly abnormal morphology at or above 80dB nHL (unilateral or bilateral) and the OAE or CM test had not been performed, or where the behavioral hearing thresholds did not correspond to the old ABR results.
4- Cases with CMs present in one ear and absent in the second ear with the absence of ABR bilaterally, and the presence of OME or previous using of HA in CM absent ear, where it is assumed that the diagnosis is bilateral ANSD and not Unilateral and the OME or previous using of HA may affect on CMs recording.

Exclusion criteria:

A very small waves that may resemble CMs waves but have been doubted because of suspicion of unknown artifacts, only when the OAEs were absent.

3- Methods :

A questionnaire was created in which the following information was collected based on the patient's files and the results of the audiological assessment :

1. The personal identity of the child .
2. Results of tympanometry and acoustic reflexes. .
3. DPOAEs results.
4. ABR test result (absence or abnormal morphology).
5. CM test (absent i.e.: not recorded or present i.e. recorded).
6. Results of any previous tests and previous use of hearing aids or not.
7. Result of MRI (if conducted).

ABR test was conducted using Otometrics CS Chartr EP 200 instrument, one-channel system, same protocol for all cases (see Table 1) and the test was conducted under natural sleep.
Patient preparation was done before the beginning of the test. The skin is prepared by cleaning it with a NeruPrep® gel . Ambu® Neuroline 720 disposable electrodes were used.

The CM test was conducted for all patients with same protocol (see Table 2).

Table 1 :ABR test Protocol

Electrode Location:	• Positive : High forehead • Negative Ipsilateral mastoid • Ground: Contralateral mastoid
Stimulus	Click (100us) rate 21.1/s
Polarity	Rarefaction
Sweeps	2000 Clicks
Transducer	ER-3A (insert earphone)
Impedance	≤ 3 k Ω
Rejection	On (±10μV)
Filters	• Gain 100k: • High pass100 Hz • Low pass 3000 Hz
Window length	10ms
Display scale	0.25 μV=1 ms

Table 2 :CM test Protocol

Electrode Location:	• Positive : High forehead • Negative Ipsilateral mastoid • Ground: Contralateral mastoid
Stimulus	Click (100us) Rate : 87.1/s Level :85 dBnHL
Sweeps	2000 Clicks
Transducer	ER-3A (insert earphone)
Polarity	Separate runs of Rarefaction and Condensation clicks control run with tubing clamp
Impedance	≤ 2 k Ω
Rejection	On (±10μV)
Filters	• Gain 100k: • High pass100 Hz • Low pass 3000 Hz
Window length	5 ms
Display scale	0.10-0.15 μV=0.5 ms

Order of CM testing:
Separate runs of condensation and rarefaction polarity clicks at 85 dB nHL
If a CM is considered to be present then we obtained additional control runs with clamping the insert tube while the insert earphone unremoved from the ear, and without any modification in the head position.

Criteria to accept CM recording:
A sinusoidal segment that has mirror image (inverts 180 degree by inverting polarity, beginning within first 0.6-0.8 milliseconds(ms) and disappear in the control run.

CM parameters:
We calculated latency, duration and amplitude as following:(Figure 1)

- Latency :Beginning of the waves(ms)
- Amplitude : Peak to Peak amplitude (P-P Amp) for the first large sinusoidal wave(microvolt- uV)
- Duration: from beginning to end of CMs recording as accepted criteria (ms)

CMs were classified according to (P-P) amplitude as following:

- Small : P-P Amp. less than 0.15 uV
- Medium : P-P Amp. between 0.15 - 0.30 μV
- Large : P-P Amp more than 0.30 uV .

As previously mentioned we excluded cases that have been doubt its outcome as unknown artifacts.

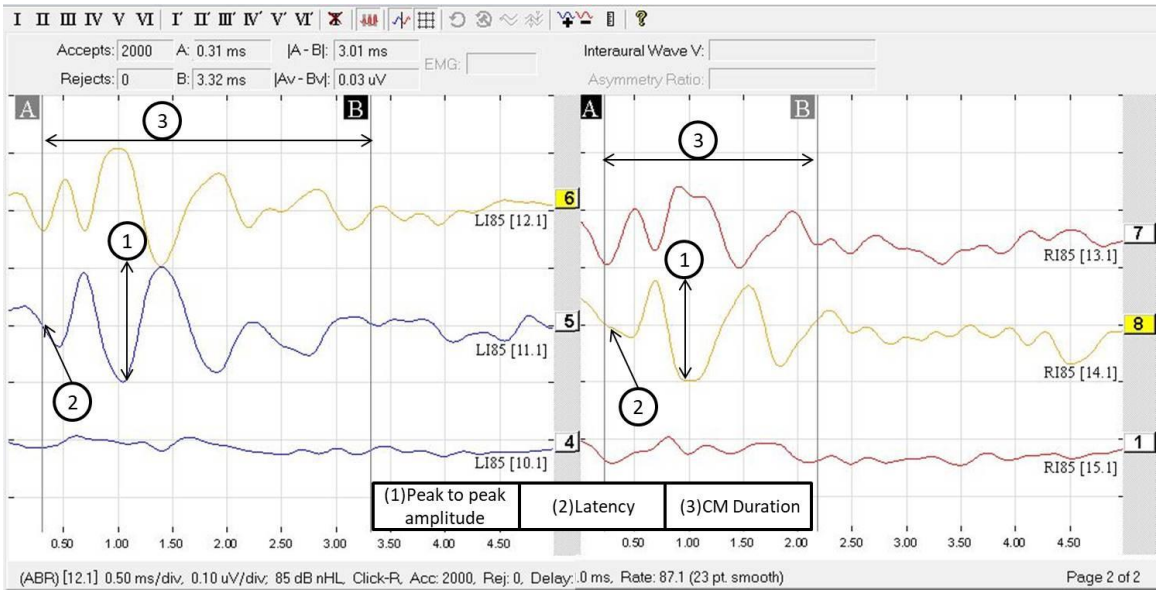

Figure 1 : Method for calculating the latency - amplitude - duration of CM waves

DPOAEs test was conducted using Biologic AuDx instrument, Which tests the frequencies 3000-4000-5000 Hz according to the following device settings:

Frequency (f): f2 / f1 = 1.22 kHz,

level (L) L 1 = 65 dB SPL

L2 = 55 dB SPL.

DPOAEs test was only conducted for cases with tympanogram type A or As , and not for type B or C or if there was a grommet tube.

Tympanometry was conducted using GSI38 tympanometer – with 226 Hz probe tone.

Ipsilateral acoustic reflexes were condu-cted at frequencies: 500-1000-2000-4000 Hz at an intensity level of 100 dB HL For the frequencies 500 and 4000 Hz, and 105 dB HL for the frequencies 1000-2000 Hz

Statistical analysis:

Data was collected and entered into a SPSS 17 software for conducting statistical analysis.

Calculating means and standard devia -tions (SD), and applying following tests:

One-Sample Kolmogorov-Smirnov Test: for normality of the distribution, and it was found that the majority of the data are not subject to the normal distribution (P value <0.05).

Thus, since the data is not within normal distribution, in addition to the large difference between subsamples sizes, we cannot use the parametric tests, and therefore the Mann-Whitney nonparam -etric test was used compared the differences between the study variables

Results:

58 cases were diagnosed as ANSD (unilateral or bilateral) according to inclusion criteria.

Two cases (other than 58 cases) had not criteria for ANSD diagnosis, but clinical impression is compatible with the diagnosis and will be discussed in a separate paragraph.

Mean age was 33 months ± 23 months (range: 2 m -13 y). Females 25 (43%) and males 33 (57%). 52 cases (104 ears) 90% with bilateral ANSD. Six cases (6 ears) 10% with unilateral ANSD, five of them had SNHL in the other ear, and one case had normal hearing thresholds in the other ear.

The total ears that included in the study as diagnosis of ANSD according to inclusion criteria were 110 ears.

One case (6 month old) out of 52 cases reviewed for reassessment second time at one year of age, and the ABR was absent at first visit

but in a second visit at 1 y old the ABR showed normal thresholds (Wave V was detectable at level of 20 dB nHL (Transient ANSD)

Another case (17 months old) reviewed after a year of diagnosis of ANSD with using of 2 HAs during this period, and reviewed for reassessment at the request of the parents and the new ABR showed absence of previously recorded CMs .

By analysis the risk factors, (Table 3) There were 10 cases (17.2%) without any risk factors, and 48 cases (82.8%) had risk factors , of whom, 31 cases had a single risk factor, and 17 cases had more than one risk factor (6 cases had 3 risk factors, and the remaining 11 cases had two risk factors)

Table (3): The distribution of risk factors for the study sample

Risk Factor(RF)	**RFs frequency**	**The number of cases with single RF**
Severe hyperbilirubinaemia with blood transfusion	17	9
Severe hyperbilirubinaemia without blood transfusion	5	2
Prematurity	7	1
Low birth weight < 1500 g	1	0
Hypoxia	15	4
Hypoxic ischaemic encephalopathy	1	0
Family history of HL	13	9
Consanguineous marriage	10	5
Septicemia	1	0
Meningitis	1	0
Intrauterine infection	1	1
Summary		
Cases with a single RF	(%53.5)31	
Cases with more than one RF	(%29.3)17	
Cases without RF	10(%17.2)	

The results of ABR test showed the absence of responses bilaterally in 46 cases, and abnormal waves at high intensity bilaterally in 4 cases , the absence of response in one ear with abnormal waves in the second ear in two cases , and the absence of response (in the affected ear) in the six cases with unilateral ANSD (see Table 4)

DPOAEs test was conducted for 96 ears only (out of 110 ears) and 14 ears were not tested by DPOAEs due to grommet tube or, tympanogram type B or C, as It was expected that the presence of OAE will not be recorded in the presence of a middle ear pathology (see Table 5).

DPOAEs were present in 30 ears (31.25%) and absent in 66 ears (68.75%).

CMs were present in 99 ears (out of 110 ears) and were absent in 11 ears with 4 ears (out of those 11 ears) with DPOAEs present , 5 ears with DPOAEs absent, and 2 ears were not tested by DPOAE but were diagnosis considered ANSD as the other ear was diagnosed as ANSD and the assumption that the presence of OME or the use of a HA was the reason for the absence of CMs recording. (see Table 6).

Acoustic reflexes were also absent in all ears with tympanogram type A or As (96 ears) and were not conducted to the ears with grommet tube or tympanogram type B or C.

Table 4 : ABR Results

	Result	N of Subjects
Bilateral ANSD (N =52)	Absent (Both Ear)	46
	Absent in one ear +Abnormal morphology in the Other Ear	2
	Abnormal morphology (Both ear)	4
Unilateral ANSD (N= 6)	Absent in one ear + SNHL in the Other Ear	5
	Absent in one ear + Normal threshold in the Other Ear	1

Table 5:CMs results according to tympanometry and DPOAEs results

		CM present (Ears)			CM Absent(Ears)		
		DPOAEs			DPOAEs		
		Pass	Refer	NT	Pass	Refer	NT
Tympanometry	Type A or As	26	61	0	4	5*	0
	Type C	×	×	2	×	×	0
	Type B	×	×	6	×	×	2
	NT (GT)	×	×	4	×	×	0
	TOTAL Ear	99			11		
Total ears diagnosed with ANSD according to acceptance criteria were 110 ears							
* Ears with previous using of Hearing aid							

Table (6) Characteristics of CMs Total Ears with CMs present =99 Ears

	Numbers of Ears		Latency (ms) (Mean)		Duration(ms) (Mean)		Peak-to-Peak Amplitude (uV) (Mean)	
	Right	Left	Right	Left	Right	Left	Right	Left
Large CM (> 0.3 uV)(16 ears)	10	6	0.24	0.27	2.98	2.75	0.39	0.41
Medium CM (0.15-0.3uV)(58ears)	26	32	0.25	0.27	2.74	2.38	0.21	0.22
Small CM (<0.15 uV)(25 ears)	12	13	0.3	0.32	1.86	2.19	0.10	0.12
All Ears	99		0.27±0.09		2.38±0.77		0.22±0.10	

Table (6) shows the characteristics of CMs waves in all CMs recorded ears (99 ears):
By calculating the amplitude of all the ears in which the CMs waves were recorded we found that :

- 16 ears (16.1%) with large amplitude
- 58 ears (58.6%) with medium amplitude
- 25 ears (25.3%) with small amplitude

By calculating the means of amplitude, latency and duration of CMs in all CMs recorded ears (99 ears), the values were :

- Mean latency was 0. 27 ± 0. 09 ms (range: 0.13-0.6 ms)
- Mean Duration was 2.38 ± 0.77 ms (range :0.81-4.02 ms)
- Mean amplitude was 0.22 ± 0.1 0 uV (range :0.8-0.55 uV)

The characteristics of the CMs were analyzed based on the results of the DPOAEs (see Table 7-8) and were divided into two groups :
Group 1 with DPOAEs present (26 ears)
Group 2 with DPOAEs absent (61 ears)

A statistical analysis were done in order to compare the mean of two groups (See Table 10) .There was no significant statistical difference between the two groups regarding the latency and duration means of CMs, but a significant statistical difference was observed in the amplitude mean, as the amplitude mean of the ears with DPOAEs present (0.27 uV) was higher than the amplitude mean of the ears with DPOAEs absent (0.20 μV) with a significant statistical difference (P Value = 0.001)

By studying cases that had previous use of HAs (see Table 9), there were 15 ears using HAs, the CM was present in 10 ears (with small amplitude), and was absent in 5 ears, 2 ears of these 5 (in one case) had a previous CMs recorded before used HA (as previously mentioned)

By comparing a group of ears used HAs (9 ears) with a group ears did not use Has (89 ears), (see Table 10) we found no significant statistical difference between the two groups with regard to the latency and the duration means of CMs, but there was significant statistical difference (P value = 0.001) observed in the amplitude mean, as the amplitude mean of the ears were not used hearing aids (0.23 μV) higher than the amplitude mean of the ears used HAs (0.13uV).

By studying ears with tympanogram type B (see Table 9) there were 8 ears, the CMs were present in 6 ears, and were absent in 2 ears. By comparing a group of ears with tympanogram type A or As with group ears with tympanogram type B, it was found that there was no significant statistical difference between the two groups regarding the latency and amplitude mean, but it was noticed that there was a significant statistical difference (P Value = 0.031) in the duration mean, as the duration mean of the ears with tympanogram type A or As (2.40 ms) higher than the duration mean of the ears with tympanogram type B (1.76 ms).

Only two ears with tympanogram type C and 4 ears with grommet tube, and the CMs were present in them.(.See Appendix for more details).

Table (7) characteristics of CMs in ears with DPOAEs present (PASS)N =26 Ears

	Numbers of Ears		Latency (ms) (Mean)		Duration(ms) (Mean)		P-P Amp. (uV) (Mean)	
	Right	Left	Right	Left	Right	Left	Right	Left
Large CM (> 0.3 uV)	5	3	0.26	0.25	2.63	2.67	0.38	0.4
Medium CM (0.15-0.3uV)	7	9	0.24	0.27	3.12	2.68	0.23	0.24
Small CM (<0.15 uV)	1	1	0.22	0.22	1.6	1.8	0.8	0.12
All Ears	26		0.25±0.08		2.71±0.80		0.27±0.09	

Table (8)characteristics of CMs in ears with DPOAEs absent (Refer)N=61 ears

	Numbers of Ears		Latency (ms) (Mean)		Duration(ms) (Mean		P-P Amp. (uV) (Mean)	
	Right	Left	Right	Left	Right	Left	Right	Left
Large CM (> 0.3 uV)	4	3	0.20	0.28	2.92	2.84	0.39	0.42
Medium CM (0.15-0.3uV)	17	19	0.24	0.27	2.20	2.28	0.21	0.20
Small CM (<0.15 uV)	7	11	0.26	0.32	1.85	2.23	0.11	0.12
All Ears	61		0.27±0.08		2.27±0.71		0.20±0.09	

Table (9)Characteristics of CMs in ears using HAs and in ears with tympanometry Type B

		N(Ears)	Latency (ms) (Mean±SDT)	Duration(ms) (Mean±SDT)	P-P Amp. (uV) (Mean±SDT)
Using HA N=14*	CM Absent	5			
	CM present	9	0.31±0.12	2.14±0.36	0.13±0.03
Tympanometry Type B N=8	CM Absent	2			
	CM present	6	0.35±0.14	1.76±0.68	0.15±0.07
*Total ears using HAs were 15 but we excluded 1 Ear using HA with Tympanometry type B					

Table 10: Statical analysis of the Means of the CMs parameters according to DPOAE results, using of HAs , tympanometry type –Risk Factors(RFs) Mann Whitney Test

		Total ears	Latency (ms) (Mean±SDT)	Peak-to-Peak Amplitude (uV) (Mean±SDT)	Duration(ms)
DPOAE	PASS	26	0.25±0.08	0.27±0.09	2.71±0.80
	REFER	61	0.27±0.08	0.20±0.09	2.27±0.71
Mann-Whitney Test	P Value		0.841	0.001	0.18
Risk Factors	With RFs	83	0.26±0.09	0.22±0.10	2.39±0.78
	Without RFs	16	0.31±0.13	0.20±0.78	2.29±0.73
Mann-Whitney Test	P Value		0.174	0.43	0.537
Using HAs[a]	Yes	9	0.31±0.13	0.13±0.03	2.14±0.38
	No	89	0.27±0.09	0.23±0.10	2.41±0.79
Mann-Whitney Test	P Value		0.451	0.001	0.325
Tympanometry[b]	Type A or As	87	0.26±0.08	0.22±0.10	2.40±0.76
	Type B[c]	6	0.35±0.15	0.15±0.07	1.76±0.74
Mann-Whitney Test	P Value		0.142	0.08	0.031
All ears		99	0.27±0.09	0.22±0.10	2.38±0.77

a.Total ears in Using HAs category were 98 and not 99 because we excluded 1 Ear using HA with Tympanometry type B
b.Total ears in Tympanometry category were 93 and not 99 because we excluded 6 ears with tympanometry type c or Not Tested(Grommet tube)
c.We included 1 ear with using HA and Tympanometry Type B in this category (5 ears with type B tympanometry, 1 ear using HA with type B tympanometry)

The mean of the CMs parameters were compared with respect to the presence/absence of risk factors, and divided into two groups: (see Table 10)
Group 1 with risk factor(s): 83 ears
Group 2: without risk factors: 16 ears

A statistical analysis was done to compare the two group (See Table 10).
There were no difference between the two groups with respect to latency, duration and amplitude mean between 2 groups.
When reviewing our patients' data, we found only 10 cases in which MRIs for the brain and the

internal auditory canal nerves were conducted, and the results are listed according to Table (11) Where it was found that there was an absence of cochlear nerve in one case (2 ears) – hypoplasia of cochlear nerve in 3 cases (6 ears), two of which were associated with hypoplasia of optic nerve. The rest of the cases (6 cases-12 ears) with normal MRI

Table (11) MRI Results for 10 cases

	Subject	Gender	Age (months)	Risk Factors (RF)	DBOAE		CM		Notes
					Rt	Lt	Rt	Lt	
1	2	F	17	Anoxia- Hyperbili	NT	R	Pres	Pres	Bilateral CN VIII aplasia
2	49	M	24	FH of HL	P	P	Abs	Abs	CN (VIII) hypoplasia
3	28	F	8	No RF	P	P	Pres	Pres	CN(II)hypoplasia CN(VIII) hypoplasia
4	58	M	156	No RF	P	P	Abs	Abs	CN(II)hypoplasia CN(VIII) hypoplasia
5	3	M	54	No RF	NT	P	Pres	Pres	Normal MRI
6	4	F	24	FH of HL	P	P	Pres	Pres	Normal MRI
7	12	F	36	Anoxia	R	R	Pres	Pres	Normal MRI
8	13	F	26	Consa	R	R	Pres	Pres	Normal MRI
9	15	M	39	Anoxia	R	R	Pres	Pres	Normal MRI
10	22	M	53	Prem	R	R	Pres	Pres	Normal MRI
See Appendix for more details about subjects and abbreviations									

Special cases: (will be discussed later in the discussion paragraph):

The first case: a 13 year old male had been diagnosed with SNHL at the age of two years – (but the OAEs or CM tests were not conducted at that time), a family history of hearing loss in a younger brother – he has been using two high power hearing aids since the diagnosis.
He was reviewed for audiological reassessment due to the presence of hearing thresholds on the pure tone audiogram within the moderate to severe range (Figure 2:Audiogram) and parents' complaint of poor speech discrimination although he had good threshold with HAs
The new assessment was as follows:
ABR showed Absence of responses bilaterally
CMs were Absent bilaterally.
DPOAEs were absent bilaterally (Refer)

The second case: a 9 years old male had been diagnosed with SNHL at the age of 8 years according to pure tone audiometry only (Figure 3 :Audiogram) without using of HAs, In his past medical history, we found that the child was premature and had low birth weight (1400g) so we decided to do reassessment by ABR-CM – OAE tests and the results were as in the first case. MRI was conducted to the 2 cases and the results were within normal with no abnormality in cochlear nerves.

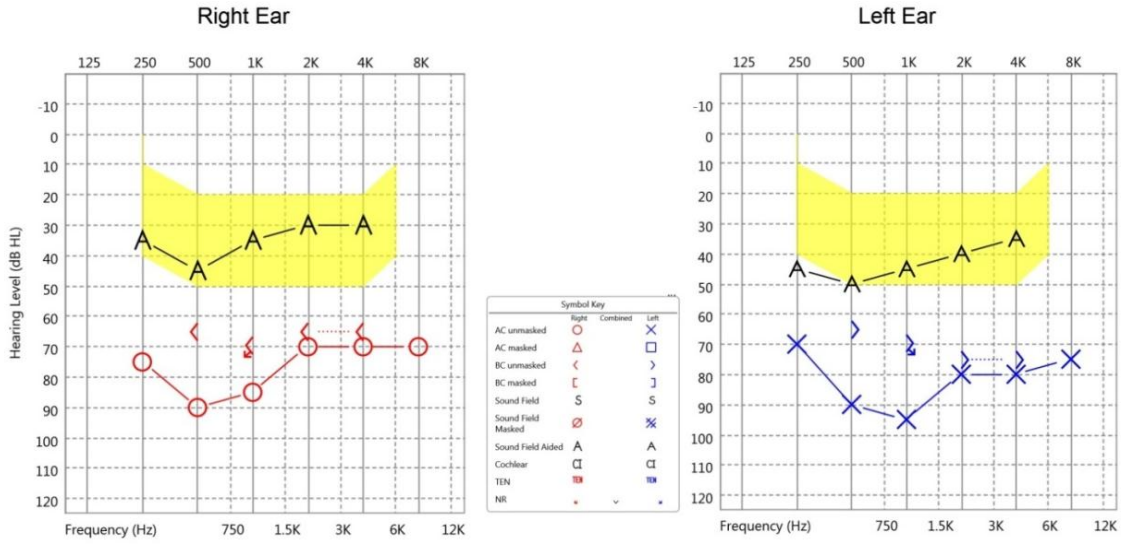

Figure (2) :Pure Tone Audiogram & Aided Sound Field for case 1

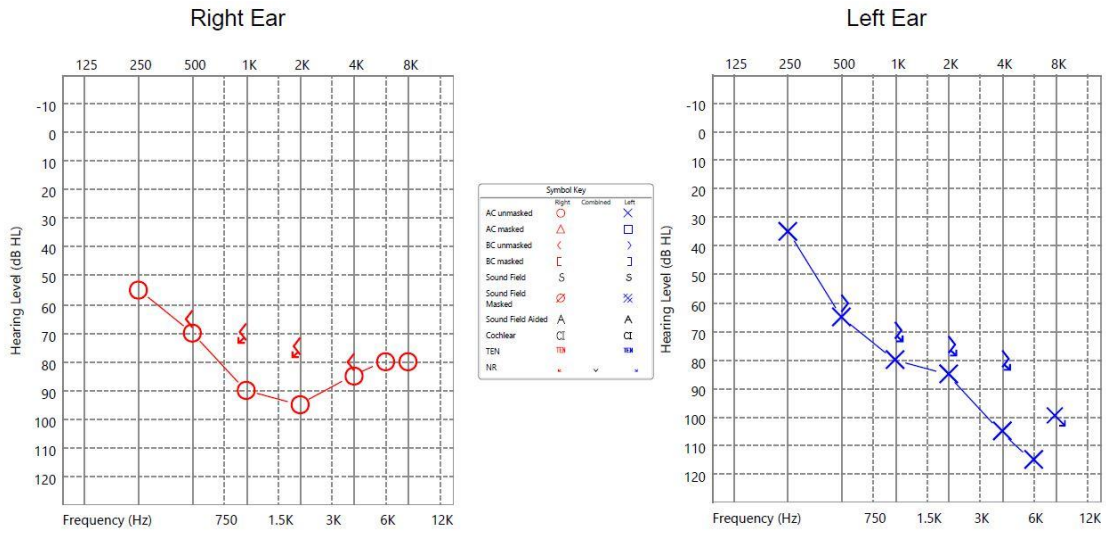

Figure (3) :Pure Tone Audiogram for case 2

Discussion:

Diagnosis ANSD depends on a set of audiological tests that include ABR-CM-OAE in addition to complement tests such as tympanometry-acoustic reflexes and behavioral test (Sound field or pure tone audiometry). It is considered very common when there are risk factors such as severe hyperbilirubinaemia and prematurity, which are considered to be the most important risk factors.

Madden et al(2002,1026) [17]reported the presence of risk factors in 68% of the study sample (15 out of 22) with a participatory risk factor, where the most risk factor was kernicterus, (50%), prematurity (45%) and a family history of hearing loss (36%).

Our study showed that the most common risk factor presented as a single factor was kernicterus, followed by a family history of hearing loss and Consanguineous Marriage.

Prematurity, which is may considered as the second most important risk factor, it is not rated as a high single factor in our study, but rather associated with another risk factor such as hypoxia and severe hyperbilirubin-aemia, but it is still one of the most important predisposing factor for ANSD due to its effect on the maturation of the auditory system and may be considered one of the most important causes of transient ANSD. .

There were no statically differences in the characteristics of CM or present of OAE regarding the presence or absence of risk factors. In our study, the presence the DPOAEs were present only in 31.25 %.

Lingyan Mo et al (2010,75)[26] reported the presence of OAEs in 40% of the ears diagnosed with ANSD via ABR & CM test, therefore, newborn hearing screening programs that use OAE test only may not detect ANSD due to the absence of OAE at least in two-thirds of the patients with ANSD, as in our study.

The absence of OAE does not rule out ANSD, as it may also be absent in middle ear pathology or it may disappear during the course of the disease due to a secondary damage of the outer hair cells, which follows the primary dysfunction of the peripheral synapse and auditory nerve [27]

(Starr *et al*.,1996,744)

Or may after using hearing aids [25].

(Sininger and Starr.,2001, 29)

Making use of the OAE with ABR and CM tests (or the use of AABR with OAE in newborn hearing screening programs) preferably using either of these two tests separately, especially for newborns and children with risk factors [28-29] .

(Ngo *et al*.,2006,1305)

(Joint Committee on Infant Hearing..,2007,903)

Our study showed the presence of bilateral ANSD, unilateral ANSD with SNHL in the other ear , unilateral ANSD with normal hearing thresholds in the other ear, and transient ANSD (in one case with no risk factors)

The mean latency of CMs in our study for all ears (99 ears) was 0.27 ±0.09 ms and in the group with OAEs present was 0.25±0.08 ms and in group with OAEs absent was 0.27±0.08. comparing this study with some other studies, the latency in ours was earlier. Starr et al (2001,93) [30]

reported that the latency mean in his study group was 0.2 ± 0.42ms, Shi et al.(2012, 193) [31] compared the latency means according to the presence or absence of OAE, where the mean for the OAE present group was 0.63±0.04 ms and for the OAE absent group was 0.63±0.07ms

While Rance et al(1999,240) [32] reported that the tubal of insert earphone make time delay of 0.9 ms. This delay was not observed in our study as the mean latency of the CMs in our study was 0.27±0.07 ms.

Although in our study, the latency is less than the average for other studies, it is closer to Starr et al study (2001,93)(0.2 ± 0.42 ms) [30]. The difference can be due to the settings of the ABR instrument, especially regarding the time delay in starting the recording of waves, or the difference in the method of calculating, for example: calculating the latency from beginning of the large clear wave and not the first wave that inverse with changing polarity.

Our study showed that the mean amplitude of all ears was 0.22±0.10 uV and in the group with OAEs present was 0.27±0.09 uV and in group with OAEs absent was 0.20±0.09 uV .Shi et al (2012,188)[31] reported in his study that included

60 ears: group 1 (30 ears) with OAE and CM present, and group 2 (30 ears) with CM present and OAE absent, there was no statistically significant difference between the two groups regarding latency but found a statistically significant difference in CM amplitude, as the amplitude was lower in the group 2 compared to group 1. This is compatible with our results.

In our study, the duration mean of CMs waves which reversed with changing polarity in all ears (99 ears) was 2.38±0.77 ms, in the group with OAEs present was 2.71±0.80 ms, and in the group with OAEs absent was 2.27±0.71 ms, while Shi et al(2012,192) [31] did not consider the waves that lasted more than 1 m following the stimulus as true CMs, he reported that components, which had a phase inversion with polarity reversal, disappeared after 1 ms. So the reversal components after 1 ms were not 'residual responses' of CMs, but possible non-synchronized responses in subjects who have good synchronization in auditory nerve activity.

Shi also found that the CM receptor potential originates from outer hair cells and inner hair cells. In cases of small CM amplitudes in ANSD patients with absent DPOAEs, responses are likely from inner hair cells. Sites of lesion could be at the synapses between inner hair cells and the eighth nerve, and he mentioned that the site of lesion could be predicated by studying the amplitude according to Input\Output curve on different intensity level.

He summarized in his study that, in the absence of the OAE, it could not be determined that CM originate from the outer or inner hair cells, or both, but it is necessary to make amplitude analysis and CM I/O function analysis

By the analysis the effect of using HAs on OAE results, we found that all ears with previous use of HAs had absent DPOAEs, but we do not have previous results before using the hearing aids and that may have an effect on its absence, and perhaps the OAE disappeared with age, and we need more studies before and after using the hearing aids. And analyzed correlating mainly with age and the duration of hearing aids use.

By analysis the effect of using HAs on CMs parameters, It was found that the CM amplitude in ears that used HAs (which were re-evaluated after using the hearing aids) was lower than the amplitude of ears that did not use HAs and there was no effect on latency or duration.

Regarding the absence of CM recordings in ears that used HAs (which we previously assumed as it had ANSD) we cannot confirm their effects because all cases (except for one) did not have a previous result of CM test before using the hearing aid, and it may had CM previously and was absent after the use of hearing aids, and it may not have been present. As for the only case in which we have a result before and after the use of hearing aids, it was absent after a year of using the hearing aid, and therefore we cannot be sure of the effect of the hearing aids on the absence of waves due to the uncertainty of the diagnosis from the beginning, but we can conclude that the hearing aids may affect, even a little, on the amplitude of the waves. We need large samples to compare the results before and after using the hearing aids, in addition to its relation with the period of using HAs and age. .

Through the analysis of the effect of middle ear pathologies on CMs, there were 14 ears: 6 with type B tympanogram- 2 ears with type C tympanogram and 4 ears with Grommets. It was found that the CMs were absent in 2 ears with type B tympanogram, and present in 12 ears but with a small amplitude. Thus perhaps the middle ear pathology did not cause the absence of CM recordings, and the effect observed is a slight delay in latency - decrease in amplitude and decreased in duration, but because of the small number of cases with OME and CM present (6 cases) compared with cases with type A or As tympanogram (87 cases). It seems that it is the main factor for no significant statistical difference in comparing means of amplitude and duration, so we need a larger sample to study there effects and correlate them with the chronicity of OME and the clinical examination to estimate the severity of OME, especially in the presence of two cases of OME that CMs were absent (as we mentioned previously, we assumed that the diagnosis in this 2 ears was ANSD)

Lingyan Mo et al(2010,78) [26] reported 35 ears with ANSD ,in five of them the CMs were

present in spite of presence of middle ear pathology.

Due to recording CMs waves in our study, was made by surface electrodes (and not by transtympanic ECochG) and in a method similar to record ABR waves (but with different protocol), so we can compare the properties of CMs and the affects of OME with the effect of OME on ABR waves. where it was Borges et al (2020,)[33] had studied the characteristics of ABR waves in the presence of OME, and showed the presence of delay in the latency of the waves III and V By 0.1 ms, with a statistically significant difference from those with normal middle ear function, in addition to a decrease in amplitude of 0.06 μV and 0.05 μV respectively.

Among the cases in which a MRI was performed (See table 10), one case with CMs present bilaterally and OAE present in one ear and not tested in the second ear because of grommet, the MRI showed an absence of cochlear nerve bilaterally. In 3 cases the MRI showed hypoplasia of the cochlear nerve bilaterally, two of them were associated with hypoplasia of the optic nerve and the OAEs were present in this 2 cases bilaterally but the CM was absent in one case and present in the other

The third case with cochlear nerve hypoplasia was with OAEs present, and CM absent bilaterally.

In those three cases, two of them had absent CM recordings, it was registered in one case.

This association suggests that the pathology in second and eighth cranial nerve may be caused by the same mechanism, Rosamaria *et al* (2002,38) [34] mentioned to a one case associated with aplasia of the second and eighth cranial nerves.

Injury in ANSD may be isolated or as part of a generalized neuropathy such as charcot marie tooth syndrome and other peripheral neuropathies .(14,27)

(Starr *et al*.,2000,215)\(Starr *et al*.,1996,731)

Regarding absent of CMs in 2 cases (4 ears) but with presence of OAEs, Kirkim et al(2008,1465) [35] reported 10 cases with ANSD, 6 of them with CM absent without discussed the etiology for the absence, as he relied on diagnosis of ANSD on the absence of ABR and the presence of OAE in all 10 cases.

Buchman et al (2006, 399)[36] reported 65 cases with unilateral or bilateral ANSD and found two cases had hypoplasia of cochlear nerve bilaterally and 7 cases with aplasia of cochlear nerve bilaterally, five of them with CMs present in one ear and absent in the other, the other 4 cases with CMs present bilaterally and only one ear in these 9 cases (18 ears) with OAE present, and absent in others.

This variation in results may confirm the complicated and not clear pathophysi- ology of ANSD. Present of OAEs with absence of CMs may predict the presence of cochlear nerve hypoplasia or aplasia, and this is also true when CMs were present in one ear and absent in the other.

MRI for brain and the internal auditory canal nerves was not routinely done despite the majority of parents being informed of the necessity of performing MRI. This issue is due to several reasons, including the high cost of the MRIs comparing to the parents' income, very high cost of cochlear implantation (if it is indicated), and weak health insurance system.

However, this may cause a loss of diagnosis of hypoplasia or aplasia of the cochlear nerve and another abnormality in the brain, especially in cases who do not have risk factors for ANSD.

Special cases discussion:

With regards to special cases, it is clinically consistent with ANSD in terms of behavioral thresholds not compatible with ABR result, but it does not meet the diagnostic criteria due to the absence of both OAEs and CMs. The reason for their absence in the first case may be the advanced age (13 years), or the use of hearing aids for a long period, or both. In the second case, it is not possible to predict cause of its absence. Perhaps if a we performed transtympanic EcochG test, we might be able to record CM but this test not routinely used.

Conclusions :

Characteristics and specifications of each of CM and OAEs are varying between the cases, depending on the presence or absence of OAEs -

depending on the pathology of the middle ear, and there is a clear effect of using of hearing aids on the absence of OAEs or absence of CMs, but this effect may also be related to age or within the course of the disease, and needs further studies. No differences were noted between cases with and without RFs. Emphasis must be placed on the MRI for all cases diagnosed with ANSD in order to rule out the presence of a concomitant neurological injury, hypoplasia or aplasia of the cochlear nerve in order to establish an accurate diagnosis and appropriate management of the case.

Study limitations:

The DPOAEs test was not performed at all frequencies, but only at frequencies 5000-4000-3000 Hz, as it is must be performed at all frequencies according to recommendations for the ANSD diagnosis[24].

(British Society of Audiology.,2019,12)

Cases of suspected weak CMs waves (suspected an unknown artifacts) were not included in the study and may need to perform an EcochG . Stuermer, K. J et al(2015,139)[37] concluded in his study that the ECochG can add valuable information for a precise differential diagnosis of ANSD, especially in babyhood.

MRI for brain and the internal auditory canal nerves was not done for all case , and may if was done , we would see more case with cochlear nerve hypoplasia or dysplasia

We assumed diagnosis of ANSD was bilateral (and not unilateral) in cases with CMs and OAEs absent in one ear while the other ear diagnosed with ANSD,

This assumption is made to study probable effect of HAs or OME on CM and OAE, as some cases used HA according to ABR result only without OAE or CM test and some case didn't repeat ABR and CM after resolving of OME.

References

1. Sininger YS (2002). Identification of Auditory Neuropathy in Infants and Children. Seminars in Hearing 23 (3):193-200
2. A Starr, TW Picton, Y Sininger, LJ Hood, CI Berlin, Auditory neuropathy, Brain, 119 (Pt 3) (1996), pp. 741–753.
3. Berlin C, Li L, Hood L et al (2002). Auditory Neuropathy/Dys-Synchrony: After the Diagnosis, then what? Seminars in Hearing 23 (3): 209-214
4. Rapin I, Gravel J (2003). "Auditory neuropathy": physiologic and pathologic evidence calls for more diagnostic specificity. Int J Ped Otorhinolaryngol 67: 707-728
5. Pearce W, Martin RL. On auditory neuropathy, aka auditory neuropathy spectrum. Hear J. 2009;62(2):38-9.
6. Rance G, Cone-Wesson B, Wunderlich J, Dowell R. Speech perception and cortical event related potentials in children with auditory neuropathy. Ear Hear. 2002;23(3):239-53
7. Foerst A, Beutner D, Lang-Roth R, Huttenbrink KB, Von Wedel H,Walger M. Prevalence of auditory neuropathy /synaptopathy in a population of children with profound hearing loss. Int J Pediatr - Otorhinolaryngol . 2006;70:1415-22.
8. Mason JC, De Michele A, Stevens C, Ruth RA, Hashisaki GT. Cochlear implantation in patients with auditory neuropathy of varied etiologies. Laryngoscope. 2003;113(1):45-9.
9. Korver AM, van Zanten GA, Meuwese-Jongejeugd A, van Straaten HL, Oudesluys-Murphy AM. Auditory neuropathy in a low-risk population: a review of the literature. Int J Pediatr Otorhinolaryngol. 2012;76(12) :1708-11.
10. Fabry, L. (2000). Identification and management of auditory neuropathy: A case study. In RC Seewald (Ed.), A Sound Foundation through Early Amplification: Proceedings of an International Conference. Switzerland: Phonak. 237-246.
11. Zeng. F. G., & Liu, S. (2006). Speech perception in individuals with auditory neuropathy. Journal of Speech, Language, and Hearing Research: JSLHR, 49, 367-380.
12. Sininger. V. S & Trautwein. P. (2002). Electrical stimulation of the auditory nerve via cochlear implants in patients with auditory neuropathy. Annals of Otology. Rhinology &' Laryngology. Supplement. 189.29-31.
13. Mason JC, De Michele A, Stevens C, Ruth RA, Hashisaki GT. Cochlear implantation in patients with auditory neuropathy of varied etiologies. Laryngoscope. 2003;113(1):45-9.
14. Starr A, Sininger YS, Pratt H. The varieties of auditory neuropathy. J Basic Clin Physiol Pharmacol. 2000;11(3):215-30.
15. Hood LJ. Auditory neuropathy: What is it and what can we do about it? Hear J. 1998;51(8):10-8
16. Berg AL, Spitzer JB, Towers HM, Bartosiewicz C, Diamond BE (2005.) Newborn hearing screening in the NICU: Profile of failed auditory brainstem response/passed otoacoustic emission. Pediatrics 116(4): 933-938
17. Madden, C., Rutter, M., Hilbert, L., Greinwald Jr, J. H., & Choo, D. I. (2002). Clinical and audiological features in auditory neuropathy. Archives of otolaryngology–head & neck surgery, 128(9), 1026-1030
18. Rance G, Beer DE, Cone-Wesson B et al (1999). Clinical findings for a group of infants and young children with auditory neuropathy. Ear Hear 20: 238-252
19. Berlin CI, Hood LJ, Morlet T, Wilenski D, Li L, Mattingly KR, Taylor-Jeanfreau J, Keats BJB, St.John P, Mongomery E, Shallop JK, Russell BA, Frisch SA, (2010). Multi-site diagnosis and management of 260 patients with Auditory Neuropathy/Dys-synchrony (Auditory Neuropathy Spectrum Disorder). Int J Audiol 49 (1): 30-43
20. Kim. T. B., Isaacson. B. Sivakumaran. T. A., Starr. A. Keats. B.J & Lesperance. M. M. (2004). A gene responsible for autosomal dominant auditory neuropathy (AUNA1) maps to 13q14-21.journal of Medical Genetics. 41, 872-876.
21. Varga, R .. Avenarius. M. R., Kelley. P. M .• Keats. B. J .• Berlin. C. I.. Hood. l. j.. et al. (2006). OTOF mutations revealed by genetic analysis of hearing loss families including a potential temperature sensitive auditory neuropathy allele. Journal of Medical Genetics. 43, 576- 581.
22. Postelmans,J. T., & Stokroos, R.J. (2006). Cochlear implantation in a patient with deafness induced by Charcot-Marie- Tooth disease (hereditary motor and sensory neuropathies). journal of Laryngology and

Otology, 120, 508-510.
23. Santarelli R, Scimemi P, Dal Monte E, Arslan E. Cochlearmicrophonic potential recorded by transtympanic electro-cochleography in normally-hearing and hearing-impaired ears.Acta Otorhinolaryngol Ital. 2006;26:78---95.17.
24. Assessment and Management of Auditory Neuropathy Spectrum Disorder (ANSD) in Young Infants.British Society of Audiology, January 2019
25. Sininger, Y., & Starr, A. (Eds.). (2001). Auditory neuropathy: A new perspective on hearing disorders. Cengage Learning. P28-29
26. Mo, L., Yan, F., Liu, H., Han, D., & Zhang, L. (2010). Audiological results in a group of children with auditory neuropathy spectrum disorder. ORL, 72(2), 75-79
27. Starr, A., Picton, T. W., Sininger, Y., Hood, L. J., & Berlin, C. I. (1996). Auditory neuropathy. Brain, 119(3), 741-753
28. Ngo, R. Y., Tan, H. K., Balakrishnan, A., Lim, S. B., & Lazaroo, D. T. (2006). Auditory neuropathy/auditory dys-synchrony detected by universal newborn hearing screening. International journal of pediatric otorhinolaryngology, 70(7), 1299-1306.
29. Joint Committee on Infant Hearing. (2007). Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs. Pediatrics, 120(4), 898-921
30. Starr, A., Sininger, Y., Nguyen, T., Michalewski, H. J., Oba, S., & Abdala, C. (2001). Cochlear receptor (microphonic and summating potentials, otoacoustic emissions) and auditory pathway (auditory brain stem potentials) activity in auditory neuropathy. Ear and Hearing, 22(2), 91-99
31. Shi, W., Ji, F., Lan, L., Liang, S. C., Ding, H. N., Wang, H., ... & Wang, Q. J. (2012). Characteristics of cochlear microphonics in infants and young children with auditory neuropathy. Acta oto-laryngologica, 132(2), 188-196
32. Rance G, Beer DE, Cone-Wesson B, Shepherd RK, Dowell RC, King AM, et al. Clinical findings for a group of infants and young children with auditory neuropathy. Ear Hear 1999;20:238–52.
33. Borges, L. R., Donadon, C., Sanfins, M. D., Valente, J. P., Paschoal, J. R., & Colella-Santos, M. F. (2020). The effects of otitis media with effusion on the measurement of auditory evoked potentials. International Journal of Pediatric Otorhinolaryngology, 109978
34. Santarelli, R., & Arslan, E. (2002). Electrocochleography in auditory neuropathy. Hearing research, 170(1-2), 32-47
35. Kirkim, G., Serbetcioglu, B., Erdag, T. K., & Ceryan, K. (2008). The frequency of auditory neuropathy detected by universal newborn hearing screening program. International journal of pediatric otorhinolaryngology, 72(10), 1461-1469.
36. Buchman, C. A., Roush, P. A., Teagle, H. F., Brown, C. J., Zdanski, C. J., & Grose, J. H. (2006). Auditory neuropathy characteristics in children with cochlear nerve deficiency. Ear and hearing, 27(4), 399-408
37. Stuermer, K. J., Beutner, D., Foerst, A., Hahn, M., Lang-Roth, R., & Walger, M. (2015). Electrocochleography in children with auditory synaptopathy/neuropathy: diagnostic findings and characteristic parameters. International journal of pediatric otorhinolaryngology, 79(2), 139-145.

Appendix : All patients DATA

Subject	Gendar	Age (months)	Risk Factors (RF)	Otoscopy		DBOAE		Tymp.T		ABR		CM		Amplitude (uV)		Latency(ms)		Duration(ms)	
				Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	RT	Lt	Rt	Lt
1	M	2	Anoxia-FH of HL-Consa	WNL	WNL	R	R	As	As	Abs	Abs	Pres	Pres	36	28	0.18	0.19	3.5	3.69
2	F	6	FH of HL	WNL	WNL	P	P	A	A	Abs	Abs	Pres	Pres	21	20	0.19	0.29	3.41	3.33
3	M	7	Kerni-Consa	WNL	WNL	P	P	A	A	Abs	Abs	Pres	Pres	42	42	0.29	0.34	2.24	2.09
4	F	8	No RF	WNL	WNL	P	P	A	A	Abs	Abs	Pres	Pres	28	30	0.29	0.45	3.71	2.34
5	M	9	Kerni	WNL	WNL	P	P	A	A	Abs	Abs	Pres	Pres	25	27	0.24	0.29	3.21	3.46
6	F	9	FH of HL	WNL	WNL	R	R	As	As	Abs	40 dB nHL	Pres	NT	18		0.26		1.54	
7	M	10	Kerni-Anoxia	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Pres	22	19	0.32	0.37	2.42	2.52
8	F	11	Consa	WNL	WNL	R	R	As	As	Abn Morph 90 dB nHL	Abn Morph 90 dB nHL	Abs	Pres		10		0.58		2.42
9	M	12	Prem-Anoxia-Kerni	WNL	WNL	P	P	A	A	Abs	Abs	Pres	Pres	31	33	0.4	0.3	2.6	3.05
10	M	12	No RF	WNL	WNL	P	P	A	A	Abs	Abn Morph 90 dB nHL	Pres	Pres	18	24	0.25	0.25	3.25	3.09
11	M	12	Prem- Hyperbili-Mene	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Pres	8	9	0.23	0.21	1.42	0.89
12	M	15	Kerni	WNL	Retr.	R	NT	A	C	Abs	Abs	Pres	Pres	50	30	0.19	0.19	2.91	2.91
13	F	17	Anoxia- Hyperbili	OME	WNL	NT	R	B	A	Abs	Abs	Pres	Pres	8	19	0.19	0.19	0.81	0.94
14	F	17	No RF	OME	WNL	NT	R	B	As	Abs	Abs	Pres	Pres	8	16	0.33	0.5	1.8	2.16
15	F	17	Consa	WNL	WNL	P	P	A	A	Abs	Abs	Pres	Pres	41	45	0.24	0.13	2.76	2.87
16	F	17	Prem-Kerni-Anoxia	WNL	WNL	P	P	As	As	Abs	Abs	Pres	Pres	35	25	0.19	0.24	2.55	2.36
17	M	24	IUI	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Pres	13	11	0.29	0.33	2.29	2.6
18	M	24	Kerni-Consa	Retr.	OME	NT	NT	C	B	Abs	Abs	Pres	Abs	45		0.29		2.53	
19	F	24	FH of HL	WNL	WNL	P	P	A	A	Abs	Abs	Pres	Pres	20	20	0.13	0.29	1.2	1.3
20	M	24	FH of HL	WNL	WNL	P	P	A	A	Abs	Abs	Abs	Abs						
21	F	24	Kerni	WNL	WNL	P	P	A	A	Abs	Abs	Pres	Pres	22	27	0.23	0.32	4.02	3.8
22	M	26	Prem-Kerni	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Pres	26	29	0.31	0.33	3.11	3.31
23	F	26	Consa	WNL	WNL	R	R	As	As	Abn Morph 95 dB nHL	Abn Morph 100 dB nHL	Pres	Pres	22	25	0.29	0.34	1.88	1.89
24	F	29	FH of HL	WNL	WNL	R	R	A	A	Abn Morph 100 dB nHL	Abs	Pres	Pres	12	11	0.28	0.19	2.44	2.18
25	M	29	FH of HL	WNL	WNL	R	R	A	A	Abs	Abs	Abs	Pres		15		0.23		1.89
26	F	29	Prem-Anoxia,LBW	WNL	WNL	R	R	As	As	Abs	Abs	Pres	Pres	16	20	0.37	0.36	2.18	2.01
27	M	30	Hyperbili	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Pres	12	13	0.19	0.19	2.23	2.28
28	F	30	Anoxia	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Pres	11	13	0.27	0.29	1.85	2.02
29	F	30	No RF	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Pres	10	17	0.34	0.28	1.66	3.22
30	F	35	Prem-Anoxia	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Pres	28	30	0.24	0.29	1.76	1.71
31	M	36	Hyperbili	WNL	WNL	R	R	A	A	Abs	Abs	Abs	Pres		13		0.27		3.27
32	M	36	FH of HL	WNL	WNL	R	R	A	A	70 dB nHL	Abs	NT	Pres		14		0.31		1.93
33	M	36	Kerni	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Pres	19	23	0.19	0.23	2.81	1.95
34	M	36	No RF	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Pres	18	15	0.21	0.27	2.79	2.47
35	F	36	Anoxia	WNL	WNL	R	R	As	As	Abs	Abs	Pres	Pres	22	20	0.2	0.19	1.8	1.81

Subject	Gendar	Age (months)	Risk Factors (RF)	Otoscopy		DBOAE		Tymp.T		ABR		CM		Amplitude (uV)		Latency(ms)		Duration(ms)	
				Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	RT	Lt	Rt	Lt
36	M	36	FH of HL	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Pres	17	16	0.22	0.24	1.53	1.47
37	M	36	FH of HL-Consa	WNL	WNL	R	R	A	A	Abs	50 dB nHL	Pres	NT	25		0.19		3.43	
38	M	37	No RF	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Abs	28		0.19		1.81	
39	M	39	Anoxia	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Pres	13	14	0.26	0.22	1.12	1.92
40	M	40	Anoxia-FH of HL-Consa	OME	OME	NT	NT	B	B	Abs	Abs	Abs	Pres		27		0.2		1.8
41	M	40	Kerni-Anoxia	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Pres	18	19	0.19	0.19	1.25	1.81
42	F	41	Kerni	WNL	WNL	P	P	A	A	Abs	Abs	Pres	Pres	8	12	0.22	0.22	1.6	1.8
43	F	41	Consa	WNL	WNL	R	R	A	A	Abs	Abs	Abs	Pres		12		0.43		2.92
44	M	41	Kerni	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Pres	18	21	0.28	0.31	1.9	3.18
45	F	41	Kerni-severe sepsis	GT	GT	NT	NT	NT	NT	Abs	Abs	Pres	Pres	25	23	0.17	0.29	3.8	2.49
46	F	42	FH of HL	GT	OME	NT	NT	NT	B	55 dB nHL	Abs	NT	Pres		23		0.4		1.51
47	F	46	Hyperbili-Anoxia	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Pres	42	40	0.19	0.23	3.78	3.36
48	M	48	Kerni	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Pres	22	24	0.19	0.26	3.43	3.44
49	M	48	No RF	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Pres	31	33	0.26	0.22	1.51	2
50	M	50	No RF	WNL	WNL	R	R	A	A	70 dB nHL	Abs	NT	Pres		12		0.5		2.13
51	F	51	Consa	OME	WNL	NT	R	B	A	Abs	Abs	Pres	Pres	12	55	0.4	0.4	3.1	3.17
52	F	52	Kerni	GT	GT	NT	NT	NT	NT	Abs	Abs	Pres	Pres	14	12	0.6	0.5	2.1	2.2
53	M	53	Prem	WNL	WNL	R	R	As	A	Abn Morph 100 dB nHL	Abn Morph 100 dB nHL	Pres	Pres	20	22	0.3	0.3	2	2.12
54	M	54	No RF	OME	WNL	NT	P	B	A	Abn Morph 90 dB nHL	Abn Morph 90 dB nHL	Pres	Pres	15	18	0.6	0.13	1.57	1.2
55	M	58	Anoxia	WNL	WNL	P	P	A	A	Abs	Abs	Pres	Pres	45	30	0.19	0.21	3.04	3.25
56	F	60	Kerni	WNL	WNL	R	R	A	A	Abs	Abs	Pres	Pres	22	18	0.2	0.22	1.8	1.76
57	M	70	Anoxia-Enceph	WNL	WNL	P	P	As	As	Abs	20 dB nHL	Pres	NT	30		0.4		3.1	
58	M	156	No RF	WNL	WNL	P	P	A	A	Abs	Abs	Abs	Abs						

M :Male , **F** :Female , **RF** :Risk Factors , **Rt** :Right Ear , **Lt** : Left Ear , **FH** : Family History , **HL** :Hearing Loss , **Kerni**:Kernicterus, **Prem**:Prematurity , **LBW** :Low birth weight **Consa** :consanguineus, **Hyperbili** :Severe hyperbilirubinaemia , **Enceph**:Hypoxic ischaemic encephalopathy, **Tymp.T**: Tympanometry Type , **WNL** :Within Normal Limits , **OME** :Otitis Media with Effusion , **GT** :Grommet Tube , **NT** :Not Tested, **DPOAE** :Distortion Product Otoacoustic Emmisions , **ABR** :Auditory Brainstem Responses , **CM** :Cochlear Microphonic , **CN** : Cranial Nerve , **HA** :Hearing Aid , **P** :Pass , **R** :Refer , **Abs** :Absent , **Pres** :Present , **Abn Morph** :Abnormal Morphology , **ms** :milliseconds , **uV** :Microvolt