AUTISM AND THE AMPLITUDE OF THE ABR WAVE I

A case-control retrospective study

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"O sonho é ver as formas invisíveis

Da distância imprecisa, e, com sensíveis

Movimentos da esp'rança e da vontade,

Buscar na linha fria do horizonte

A árvore, a praia, a flor, a ave, a fonte –

Os beijos merecidos da Verdade."

Fernando Pessoa

A todos os que me seguem neste meu pequeno percurso. O meu maior obrigado pela luz esperançosa. Ao meu mentor, Dr. Miguel Coutinho muito obrigado pela confiança depositada em mim e no meu trabalho, assim como pela aprendizagem oferecida neste pouco tempo de conhecimento. Também aos meus pais por todo o amor, ajuda, apoio e confiança nesta primeira aventura da minha vida., um muito obrigado por todo o esforço e sacrifício que têm feito por mim. Por último agradeço à minha pequena grande irmã por todo o apoio, paciência e amor que me dá e por me relembrar cada dia o longo caminho que ainda tenho no conhecimento.

SUMMARY

Autism is a behaviorally diagnosed disorder defined by failure to develop communicative and social skills, presence of mannerisms and great distress over minor changes (1). Characteristically autistic children present hypersensitivity to sensory stimuli, excessive calmness or psychomotor hyperreactivity, poor physical coordination even though a proper motor activity is present, aggression including self-aggression, sleeping disorders and multisensory integration (3,7).

Hearing disorders are common among children with autism (2). Autism spectrum disorder (ASD) children seems to have a higher prevalence of audiologic alterations such as sensorineural or conductive hearing loss, otitis media with effusion or hyperacusis (14). Abnormal auditory pathway functioning, can range from the cochlea to the cortex (10).

In this case-control retrospective study, children with ASD will have their hearing capabilities assessed by Auditory brainstem response (ABR) because of their lack of cooperation to perform audiological exams (15). The ABR results will be later compared to those of a group of children with suspected language delay in order to estimate the association between autism and a higher amplitude of the ABR wave I, and understand if this could be an early marker to ASD diagnosis.

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ABBREVIATIONS

ASD: Autistic spectrum disorder

ABR: Auditory brainstem response

OAE: Otoacoustic emission

RRSB: Repetitive reward-seeking behaviours

SPATS: Sense, perception, abilities and thinking systems

PDD-NOS: Pervasive developmental disorders not otherwise specified

SCD: Social communication disorder

IWL: Interwave latencies

nHL: Normal hearing level

CNS: Auditory central nervous system

OM: Otitis media

TM: Tympanic membrane

NHS: Newborn hearing screening

CI: Confidence interval

CHP: Centro Hospitalar do Porto

ORL: Otorhinolaryngology

INTRODUCTION

AUTISM

Autism is a behaviorally diagnosed disorder defined by failure to develop communicative and social skills, presence of mannerisms and great distress over minor changes (1). The etiology of autism is unknown, but many factors like genetic, neurochemical and neurobiological have been implied (1,2) being most likely multifactorial (3).

Autism spectrum disorder is currently diagnosed by the criteria (Annex I) in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (4) published by the American Psychiatric Association. The stage and functionality varies with the individual and their environment as also the manifestations of the disorder (4).

The prevalence of autism is approached to 1% of the population (4), and since the 1990's seems to be increasing (5) although it could be as a result of the higher awareness, changes in definition, broadening of the diagnostic criteria, and improved screening and detection (6,7). ASD presents itself with a ratio of 4:1, being more common among boys than girls (3).

Autism was first described in 1944 and viewed as a form of childhood schizophrenia. Only in 1980 was distinguished from this definition and were defined the diagnostic criteria in DSM. Many changes were made until the most recent update in 2013 when all subcategories were placed in a single branch as Autism Spectrum Disorder (ASD) that includes disorders like Asperger disorder, pervasive developmental disorder not otherwise specified and autism (8,9). Nowadays ASD prognosis regarding the cure is still poor (3).

In some cases, children with ASD experience developmental plateaus or regression in previously acquired social behaviors and use of language, usually during the first two years of life. These

losses could be considered “red flags” for the ASD suspected diagnosis (4).

Red Flags for Autism (8)**:**

- No smile or other warm, joyful expressions by the age of six months;
- No back-and-forth sharing of sounds, or facial expressions by the age of nine month;
- No babbling, back-and-forth gestures such as pointing, showing, reaching or waving by the age of 1 year;
- No words by the age of 16 months;
- No meaningful, two-word phrases by the age of 24 months;
- Loss of speech, babbling or social skills at any age once present;

Most commonly ASD starts before the end of the third year of life (3) but the disease is lifelong in nature (8). Many times subtle idiosyncrasies are present. Some children display very literal sense of language, which restrict their ability to understand jokes or sarcasm and the non-verbal communication is reduce, when expressing and interpreting facial and body language (5). An enormous heterogeneity has been stated regarding the communication skills of these children (10).

Characteristically autistic children present hypersensitivity to sensory stimuli, excessive calmness or psychomotor hyperreactivity, poor physical coordination even though a proper motor activity is present, aggression including self-aggression, sleeping disorders and multisensory integration (3,7). A significant distress could be caused when the child routines are disturbed or changed (5).

This pervasive and complex developmental disorder is also characterized by impaired social interaction (7), with avoidance of eye contact and preference to be alone (5), language delay, repetitive and stereotypical patterns of behaviors, activities and interests (7), which can lead to difficulties in achieving school readiness (3). All the symptoms can be presented in a wide range

of severity (7).

In addition, ASD children are usually indifferent to people, avoiding social interaction even with close relatives. To be able to maintain willingness emotional and verbal contact (3), even though the tone of voice may not match expressed feelings (8), triggering stimuli is also avoid, and tactile defensiveness and engagement in repetitive self-stimulating behaviors (7). There is also ample evidence of neuroanatomical dysmorphology in ASD, from differences in neural packing density, soma size, number of attenuated dendritic arbors (11) to neurochemical and muscular pathologies (12).

Hyper-responsiveness, has an ample range of displayed reaction, is the pattern of exaggerated behavioral reactions to sensory stimuli, which comprises hyperacusis, sensory modulation dysfunction, aversion, hypersensitivity, sensory defensiveness, avoidance, hyperarousal and lack of habituation to sensory stimuli (7).

Some reports that ASD patients have a different sense, perception, abilities and thinking systems (SPATS) that negatively influence behavior, learning and language development. Furthermore others report that this patients present features suggestive of hypersensitivity or hyposensivity (10), causing a significant impairment in function (8).

Some authors refer that sensory integration, the ability to take information through the senses and place together with the prior information, is altered and is vital in autism communication profile (10).

The sensory responsiveness is different in autistic children who can lead to a wide range of erratic behavior, like withdraw from certain types of touch, avoidance of certain activities, limited diets and strong emotional reactions to some stimuli (13).

Autism has been observed in a diverse group of pathologies, such as fragile X syndrome, seizure

disorders, tuberous sclerosis, phenylketonuria, neurofibromatosis, congenital rubella, and Down syndrome (14). Many others pathologies have been shown to have a higher prevalence in ASD children, such as attention deficit hyperactivity disorder, sleep disturbances, food allergies, eczema and asthma (8).

Hearing disorders are common among children with autism (2). Many times, parents manifest concerns about hearing during the first year of life (15), being the first suspected diagnosis (1). ASD children seems to have a higher prevalence of other audiologic alterations such as sensorineural or conductive hearing loss, otitis media with effusion or hyperacusis (14). ASD have been found to co-occur with hearing loss in about 4% of children (15,16).

Abnormal auditory pathway functioning, can range from the cochlea to the cortex, can act as a factor contributing to inhibition of typical language development leading to negative effects on communicative competence in autism (10). Many alterations have been reported throughout the time, such as neurodevelopmental brainstem abnormality manifested through prolonged neural responses and brainstem conduction times, brain overgrowth, that could affect the length of the cochlear nerve and auditory pathways (6), a maturational defect in myelination of the brainstem and macrocephaly (2).

Many ASD children have showed hyperacusis, poor temporal and frequency resolution, difficulties using the information received through auditory perception (6,17), tinnitus, inattentiveness to verbal stimuli, selective auditory attention, atypical performance of the central auditory system (18) and difficulty to listen in the presence of background noise (7).

Even though autism has still no cure, the common courses of treatment comprise behavioral and speech therapy, sensory integration and even desensitization therapies. Nevertheless many times pharmacological treatment is used in order to control the associated symptoms (9).

AUDITORY PATHWAYS

The auditory pathway can be divided in Peripheral auditory system and Central auditory system (19).

Peripheral auditory system (20):

1. ***The outer ear:*** the pinna or auricle, collects sound and leads it to the ear drum or TM;
2. ***The middle ear:*** begins in the TM and comprises three bones, the malleus or hammer, incus or anvil and stapes or stirrup, transmits the sound signal to the inner ear;
3. ***The inner ear or cochlea***: is a fluid-filled structure that contains the hair cells, sensory cells of hearing. These cells when stimulated release neurochemicals to the auditory nerve;
    a. ***Auditory nerve (VIII):*** once receives the neural signal transmits it to the low brainstem where it will be processed, and then transmitted to the upper brainstem.

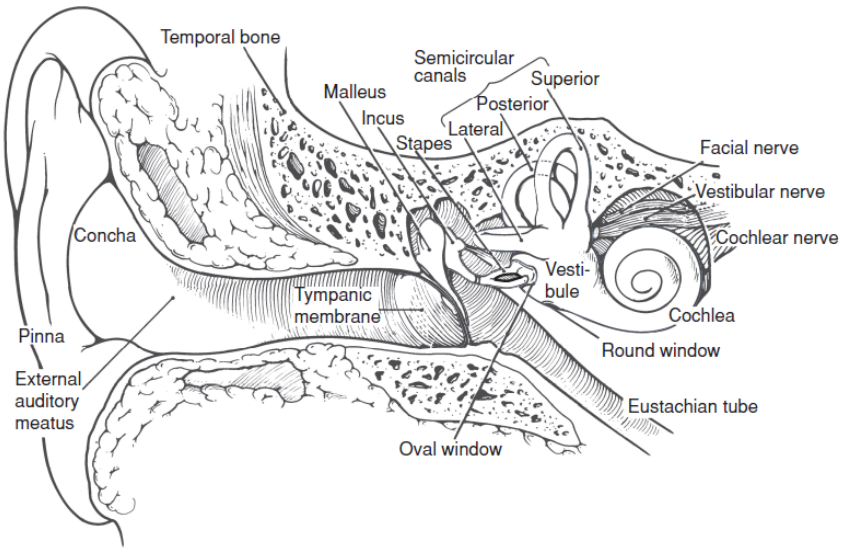


Figure 1 (21): The peripheral auditory system

Central auditory system (21):

1- ***Ascending auditory CNS***: all nerve fibers from the cochlea terminate at the cochlear nucleus homolaterally in the brainstem. From here several paths are available. The majority of nerve fibers cross over or decussate at some point along the auditory CNS, so that the activity on the left side of the cortex represents the right ear and vice versa. From the superior olives through the cortex is represented activity from both ears. One of the key functions of the auditory CNS is combining and integrating information from both ears, which is clinically referred as binaural processing, which determines the ability to locate sounds in space. All the fibers end in the medial geniculate before ascending to the cortex.

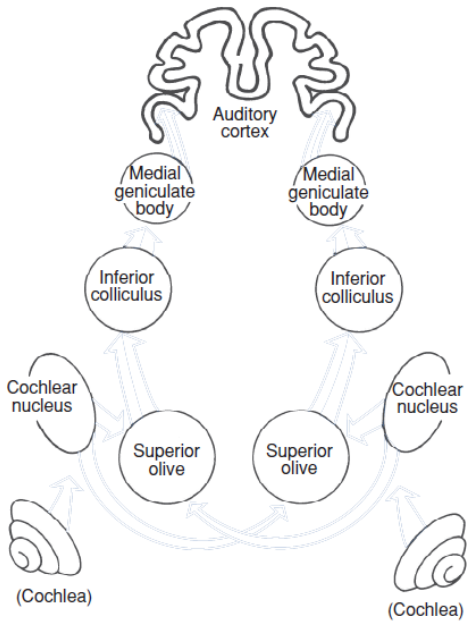


Figure 2 (21): The ascending pathways of the auditory central nervous system

2- ***Efferent or descending pathways:*** the nervous signal can also be transmitted toward the periphery fibers from the cortex and the brainstem centers.

HEARING AND AUDITORY HYPERSENSITIVITY

As previously defined in Lucker's article "*Hearing can be described as sensitivity to sounds." Hearing* is the ability of the individual to recognize once a sound has entered and then traveled from our ears to our brain, being registered as present; on the other hand *perception* is the individual cognitive ability to give meaning to a sound (20).

Auditory hipersensibility can be described as "*abnormally sensitive hearing in which normally tolerable sounds are perceived as excessively loud"* (20,22). This hipersensibility can also be present in form of hyperacusis, phonophobia and auditory recruitment (2,16). Some studies speculate that the presence of sound sensitivity, which is usually associated with over-responsitivity (13), may be related to complex cortical phenomena (16), while others believe it is due to a peripheral auditory dysfunction (20). Sensory dysfunction can be defined as "*being sensory sensitive or having a low threshold for response to stimuli"* (23).

Many times, parents of ASD children have reported that in some situations their children put their hands over their ears, run away from sounds or even lose control of their behaviors in the presence of certain sounds (20).

AUDIOLOGICAL ASSESSMENT

In neurotypical children assessment of hearing is generally based on audibility tests of subjective audiometry such as reported theresholds for pure tones or speech (9). Perform subjective tests in autistic children can be challenging once making contact with these patients can be difficult (3), even though it is recommended a complete audiological assessment in all cases of suspected ASD (7). For this reason, seems to be most suitable to use objective methods to evaluate hearing

in these children (3), once a large range of alterations, such as hyperacusis and hypersensitivity to loud noises, bright lights and strong smells, have been reported (5,8).

There is growing evidence of a higher incidence of abnormal findings in at least one audiological exam in children with ASD when compared to the general population (16). Some of these evidence points towards a different sensory integration and functioning of the auditory brainstem in ASD diagnosed children (10,13) while others point to a dysfunction or an immature central auditory nervous system (24). Even though a solid relationship between autism and prolonged ABR times that implies a role for the brainstem in the autism pathogenesis (23), being of especial importance to access and treat hearing loss among this children (9).

ABR – Auditory brainstem response

The activity of the auditory pathway from the ipisilateral eight nerve to higher midbrain structures can be reflected in several waveform components in the ABR exam (1). The presentation of a auditory stimuli induces a brains response that is captured by the brainstem auditory-evoked potentials, that are time-linked to the specified events presented. These events consist of a sequence of deflections, positive and negative, or peaks and latency (time in relation to the stimulus onset) (10).

Types of ABR (19)**:**

- ***Early or short latency evoked potentials***: in this group include the cochlear potentials and the potentials of the brainstem.
- ***Semi-early or middle latency evoked potentials***: this group includes the myogenic potential (posterior auricular muscle) and neurogenic potential (potential semi-early,, response to 40 Hz).

- ***Late/cortical or long latency evoked potentials***: this group include late or cortical auditory responses and the auditory response P300.

Five waves can be detected during the execution of this test (10,19).

- ***Wave I***: is generated in the first afferent auditory neuron in the distal part of the nerve VIII;
- ***Wave II*** – is produced in the cochlear nucleus;
- ***Wave III***: is originated in the ipsilateral cochlear nucleus;
- ***Wave IV*** : is formed in the lateral lemniscus;
- ***Wave V:*** is created in the inferior colliculus with input from multiple anatomical structures;

Even though most of the times only three main waves are detected an analyzed, wave I, III and V (20).

This test is a reliable method to detect hearing loss in children (1) and has been demonstrated that should be the main examination method used once is a reliable method to obtain information in hyperactive or autistic children with lack of cooperation (14). The ABR test can be performed under sedation, anesthesia or spontaneous sleep, once it is resistant to their effects (1), which do not require the patient cooperation (2).

The latency and amplitude values of ABR can vary in early childhood. The increase of age leads to the maturation of the brainstem, synchronizing the synaptic transmission, and the nervous structures. This progress results in a better impulse of conduction which is reflected in increasing ABR amplitudes. On the opposite, latencies shorten postnatally with age. In early life only waves I, III and V can be detected. Wave I has higher amplitude than wave III and V but in time changes becoming wave V much more prominent (14). Latency changes are probably due to increasing

myelin density in the VIII nerves (23). The values of amplitude, latency and conduction velocity are usually equivalent to those of the adults at two years old (25).

Regarding the data of children with ASD results are contradictory (14). Some studies show that ABR does not change with age as it does in general population (25) while others report prolonged I-III and I-V intervals (14,23) or the prolongation of wave I (5). The alterations in wave I can be explained by the presence of retro-coclear pathology or affection of the crossed olivocochlea bundle (5). Others report that absolute latencies and IWLs are prolonged and that laterality of alterations is a significant finding (6). Even though the increase of interwave latencies I-V is the most frequent finding (2). Many of the alteration have been related with variance in communication skills and sensory integration dysfunction (10). Many recent studies support the previous studies, referring abnormal ABR findings in ABR in ASD children population (16).

CONCLUSION

Many studies have reported that a pronounced to profound sensorineural hearing loss, can be 10 times greater, has a higher prevalence in children with ASD than in general population (5,7). Some of these studies, like in this protocol study, exclude children with abnormal tympanometry, otoscopy and OEA (7). It has also been shown that these children also have an increased rate of middle ear infections, and abnormalities of the cochlear nerve and brainstem auditory pathways, like cortical and brainstem neurodevelopmental abnormalities (5,6).

Children with ASD can be challenging when evaluating their hearing capabilities. In one hand this deficit can result in a late diagnose of ASD and in the other hand hearing loss children have an additional disability in nearly 40% (15). The abnormalities in auditory processing are contributors to the functional deficits presented by these patients (16). It is important that all the clinicians and

especially the otolaryngologist understand the disease and how recognizing it can affect the management of these patients (8, 26).

It is reasonable to ask if children with ASD, which are more likely to have hearing loss, have in fact an alteration of the auditory pathway. As displayed before ASD can affect the ABR waves even though the results in several studies are various (14). Although of these results it seems clear that abnormal findings in audiological exams has a higher incidence in children with ASD (16).

JUSTIFICATION

Literature reveals us a controversy regarding the prevalence of hearing impairment among children with ASD (7). Still does not exist a universal agreement with regard to abnormalities in children with ASD (24). A combination of autism and hearing loss was found in some studies. This association makes the communication problems more noticeable. For this reason, it is of a vital importance to evaluate the auditory ability of these children, being this an important condition to diagnose and treatment of ASD (1). Children with a suspected ASD diagnosis should seize a complete audiological assessment so that hearing loss can be diagnosed early towards an improved treatment and education program (7). Otolaryngologists have a unique opportunity to assess hearing loss and to recognize early presentation of autism (14) once many times caregivers seek help from this specialist as they think their child might have hearing loss (3) and an early intervention have a positive effect improving social, academic and self care (24).

Coutinho et al. in a case report has showed that a prevalent Peak I can be one of the alterations of the ABR waves (14). The cochlea dysfunction can potentially heighten maladaptive behavior,

exacerbating a negative relationship between the child and their environment (5). Although we do not know if an association between ASD children and this alteration can be made. Data regarding this matter are scarce (13).

The association between autism and hearing alteration started a crescent body of work in several fields (27). Since this matter can alter the course of diagnosis and treatment of ASD children, this study aims to determine if higher amplitude in wave I can be associated with the diagnosis of autism. The point of this protocol lies in the fact that, in literature, numerous results have been found regarding the alterations of the ABR waves but none regarding the alteration of wave I amplitude, so their association remains unclear.

Thus, the results obtained by this study could be used as a foundation for further researchers and projects to explore the possibility of an early marker of autism.

HYPOTHESIS

In this study we will assess the following hypothesis: Children with an autistic spectrum disorder will have a higher frequency of alterations in the amplitude of wave I in ABR than age and sex matched typically developing children with suspected language delay.

OBJECTIVES

Primary

The aim of the present study is to examine if there is any correlation with Wave I amplitude alterations and autism when in comparison with their age and sex matched typically developing children with suspected language delay, in patients followed in the Pediatric ORL consultation in Centro Hospitalar do Porto, in Oporto.

Secundary

- To describe the unilateralization or bilaterization of the higher amplitude in ABR wave I;
- To assess and describe latencies in ABR waves I to V characteristics in autistic children and compare them with children with suspected language delay;
- To evaluate the interwave peaks in ABR in children with autistic disorder and children with suspected language delay and to describe their characteristics;
- To analyze and collect demographic data about our population with autism and children with suspected language delay;

METHODS

Study design

This case-control study is an analytical, observational and retrospective study, performed in patients followed in the ORL consultation diagnosed with autism and their normal pears also followed in the ORL consultation, at Centro Hospitalar do Porto, in Oporto.

Participants

This study will include consecutive patients between 2 and 6 years old, followed in the pediatric ORL service, with an ASD diagnose or with suspected language delay without any other associated pathology, of Centro Hospitalar do Porto, from January 2008 to November 2015.

Inclusion Criteria

CASES	CONTROLS
– Previous diagnosis of ASD, with the standardize autism assessments and performed by a child and adolescent psychiatrist or pediatric neurologist; – Age between 2 to 6 years old at the moment of the audiological exams; – Patients followed in the ORL service at CHP; – ABR done under sedation or spontaneous sleep; – Data of hearing screening at birth;	– Typical developing children with no associated pathology; – Age between 2 to 6 years old at the moment of the audiological exams; – Patients followed in the ORL service at CHP; – Requirement to perform ABR test (suspected language delay); – Data of hearing screening at birth;

Exclusion Criteria

CASES	CONTROLS
– Late diagnose of ASD (> 6 years old); – Associated pathology such as: neurological (epilepsy), congenital infections, chromosomal abnormalities (Down's syndrome, X-fragile), neurocutaneal syndromes, endocrine and metabolic disorders (phenylcetonuria), cleft palate or facial malformations; – History of prematurity; – Active ear pathology (otitis media, CAE infection or malformation); – Presence of deafness risk factors: TORCH infections, family history of hearing loss, neurodegenerative disease, severe hypoxic-ischemic encephalopathy; – Refusal to integrate the study;	– Late diagnose of ASD (> 6 years old); – Social deficit; – Associated pathology such as: neurological (epilepsy), congenital infections, chromosomal abnormalities (Down's syndrome, X-fragile), neurocutaneal syndromes, endocrine and metabolic disorders (phenylcetonuria), cleft palate or facial malformations; – History of prematurity; – Active ear pathology (otitis media, CAE infection or malformation); – Presence of deafness risk factors: TORCH infections, family history of hearing loss, neurodegenerative disease, severe hypoxic-ischemic encephalopathy; – Refusal to integrate the study;

Sample selection

A consecutive, non-probability sampling will be taken in this study. The sample recruitment will comprise Pediatric ORL patients between 2 to 6 years old, who are followed in Centro Hospitalar do Porto, within January 2008 and November 2015. This center was chosen once it is one of the reference centers in Portugal for the hearing assessment of children with an autistic spectrum disorder. Parents or legal tutors of the patients who meet the required inclusion criteria will be contacted by letter with the information sheet (Annex II.I) and invited to join the present study. If

there is interest in join the study, an appointment will be set with the patients parents or legal tutor to clarify possible questions and to give the informed consent (Annex II.II). The same procedure will take place for the children with suspected language delay.

Sample size

GRANMO was used in order to calculate the sample size. An alpha risk of 0,05 and a beta risk of 0,2 were accepted in a two-side test. Once autism has a prevalence of 1% (DSM-V) and the subjects of our study have a small range of age, two to six years old, a proportion of controls/cases of 3 were used, in order to increase the potency of the test.

It will be necessary a total of 216 patients, 54 cases and 162 controls to recognize as statistically significant an odds ratio greater than or equal to 5, which we consider significant to demonstrate this association. From previous studies we accessed that a 3% of the control group will present alterations on the ABR exam. It has been anticipated a dropout rate of 1%. The Poisson approximation was used.

Variables

The ***independent variable*** of our study is the alterations in amplitude of wave I in the ABR exam. This variable will be measured in higher or normal amplitude, which make this a qualitative nominal variable. This variable will be represented in a frequency table, in this case it will be described in function of the dependent variable in a double entry frequency table. The results of higher amplitude in ABR wave I will be posteriorly divided in three groups, right ear, left ear and bilateral. These groups will be later represented in a frequency table.

The ***dependent variable*** of the study is the presence or absence of a diagnosis of ADS. This variable is also a qualitative nominal variable. This variable will be described in a frequency table.

Our ***co-variables*** are Sex an Age and as our control and case group are individually paired this variables are only relevant to describe our sample. In order to access our secondary objectives and as this information will be collected at the same time as the wave I amplitude, latencies and interwaves alterations in ABR test will also be used as descriptive variables, which will be assessed with means and medians.

Instrumentalization

After the inclusion of the patients in our study the followed information will be collected from the medical database. In order to explain their relevance for our study, a resume of their importance will be made. All the information will be collected in the patient information sheet (Annex Alpha).

MEDICAL DATABASE: the medical database will be assessed in order to access patients recorded information relevant for the present study.

OTOSCOPY: Once there is an increased prevalence, can be up to ten times (9), of serous otitis media (OM) (7) and temporary conductive hearing impairment (16) in children with ASD an exam, like an otoscopy, should be performed to exclude pathology of the external auditory canal or middle ear. The pathologies of the ear canal and middle ear can influence on the results of the exams performed to assess the condition of the middle ear (3), like the ABR exam. The ORL specialist will perform the otoscopy.

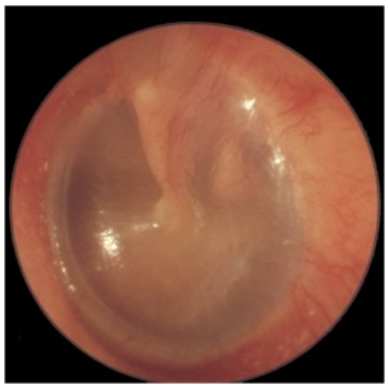


Figure 3: Normal MT (Ana Pinto MD., ORL-CHP)

NEWBORN HEARING SCREENING (NHS): All children must be presented, when born until 30 days of age, to a hearing assessment (28). Hearing loss screening among newborns, can detect sensorineural hearing loss before de age of 6 months (3) and a precocious intervention can positively change the prognosis of language, social and cognitive development (28,29).

NHS - Portugal (28): uses OAEs (peripheral) and ABR (central). These techniques are fast, non invasive and easily to apply and should be performed in both ears. These tests evaluate different segments of the auditory system and are therefore important to perform the OAEs (peripheral) and/or ABR (central). When a hearing loss is identified, will be duty-trigger immediately the diagnostics and early intervention, and the process of confirmation of deafness should be completed up to 3 months of age and intervention should be started up to 6 months.

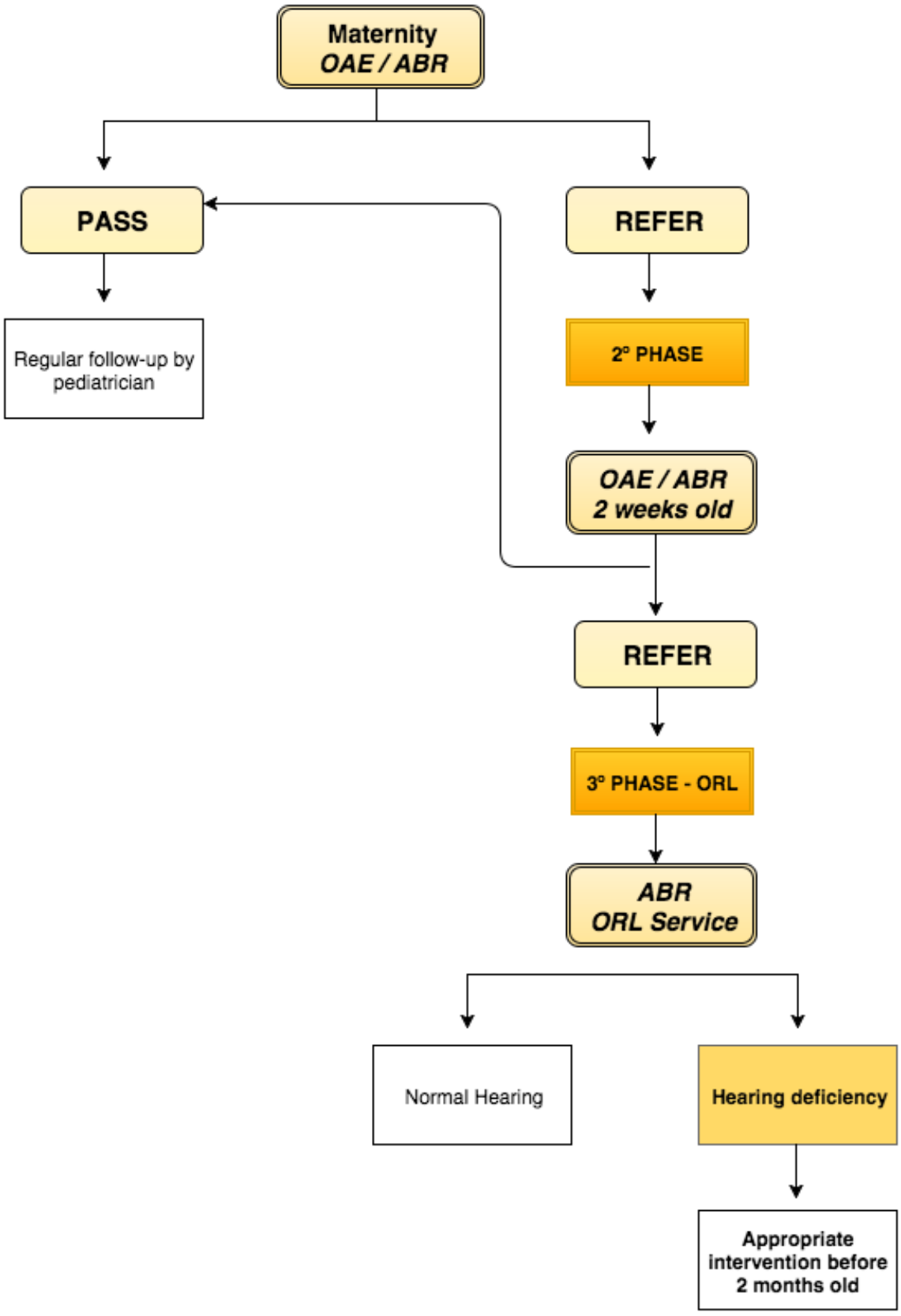


Figure 4 (28): Organization of the NHS in Portugal

No:	Test Type	Ear	Test Date	Test Time	Result
1	TEOAE	Left	28-10-2015	10:54:10	Pass
2	TEOAE	Right	28-10-2015	10:54:44	Pass

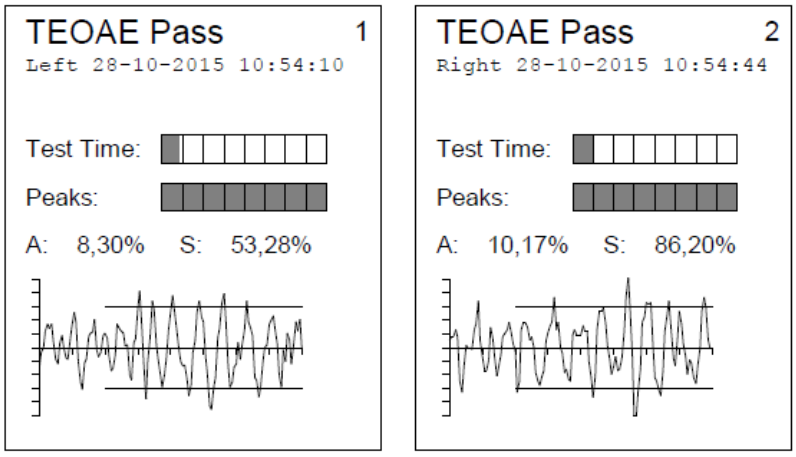


Figure 5: Normal OEA from NHS from audiology department CHP

OAE: Evoked otoacoustic emission echoes the activity of cochlea's response to sound stimulation (1). These emissions, produced by the cochlea, are low intensity sounds, related with the primary stimulus frequencies in a healthy ear, which are then transmitted back to the recording microphone by the outer and middle ear as well (16).

This exam can play an important role in ASD children especially in regard to their auditory sensitivity (14). Some studies have shown that an altered response to this stimuli can be present in children with an ASD diagnose (16,18).

Types of OAE (19)***:***

- ***SOAE:*** spontaneous otoacoustic emissions are otoacoustic emissions that can be captured in the absence of any stimulus, in 72% of ears with average hearing thresholds better than 25 dB. Sounds are very narrow bandwidth which can be detected in one or both ears, and can coexist to 4 AOES the same ear at frequencies situated between 3000 and 4000 Hz in children.

- ***TEOAE:*** transiently evoked otoacoustic emissions are OAE that are observed after sound stimulation of the cochlea by a short-term stimulus and mimicking, in frequencies characteristics, the initial stimulus. The stimuli that are used are the click stimuli, that stimulates the entire length of the cochlea and is therefore the most used, and the tone bursts. It is the type most commonly used in neonatal screening.
- ***DPOAE:*** Otoacoustic emissions by distortion product are sounds produced by the cochlea in response to two simultaneous stimuli composed of pure tones with different frequency. The resulting frequency otoacoustic emission does not correspond to any of stimuli, whereby the cochlear response is termed distortion.

Presentation (36): 1 - morphology of wave corresponding to the stimulus obtained by the probe microphone before the start of the collection process; 2 - Stimulus characteristics, ClickN (nonlinear click); 3 - stimulus intensity over the frequencies, uniform and regular; 4 - the intensity of the stimulus value, equivalent peak; 5 - wave response morphology, captured in the first 20 ms after the onset of the stimulus, the first 4 ms should be ignored in order to eliminate the influence of the stroke of the stimulus response.

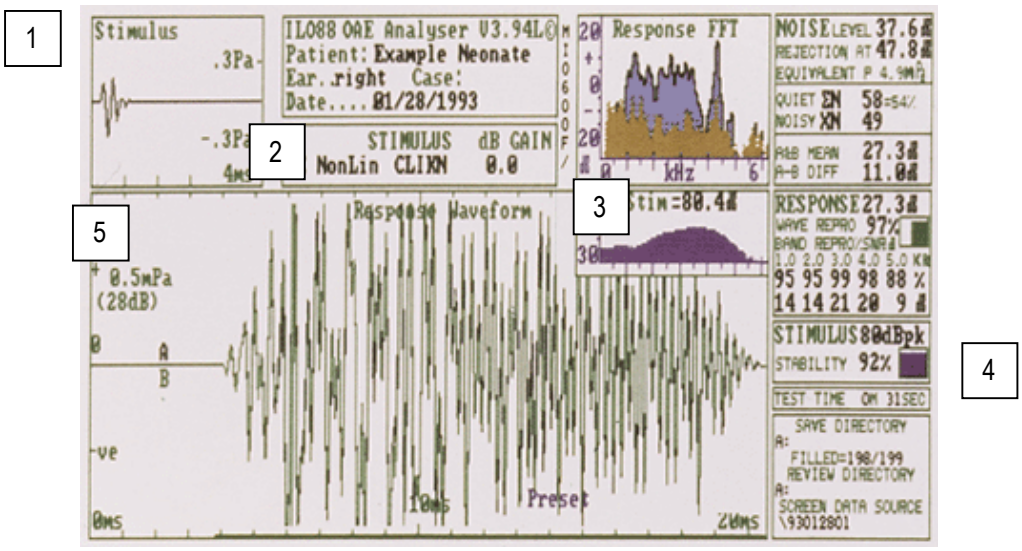


Figure 6 (19): OEA graphic

AccuScreen Madsen was used to perform OEA at the NHS. *See technical characteristics ANNEX III.I*

> ***TEOAE Parameters***: Noise-weighted averaging, counting of significant signal peaks Stimulus: Non-linear click sequence Stimulus level: 70-84 dB SPL (45-60 dB HL), self calibration depending on ear canal volume Click rate: Approx. 60 Hz Frequency range: 1.5 to 4.5 kHz Display: Statistical waveform, measurement progress, TEOAE detection level, noise level

TYMPANOGRAM: Tympanometry can be measured without demanding a behavioral response (9). This exam uses the physical properties of the middle ear in order to access the varied air pressure through the middle ear canal. One of these properties is the mobility of the tympanic membrane. The appraisal of the test also appraises the volume of the ear canal (16). The tympanometric curves obtained makes possible the recognition of problems in the external and middle ear (3) such as middle ear tumor, fluid in the middle ear, impacted ear wax, lack of contact between the conduction bones of the middle ear, perforated ear drum, scarring of the tympanic membrane (16). Types B or C2 curves can be most frequently observed in chronic otitis media with effusion being this one of the main causes of conductive hearing loss in pediatric ORL (3). ASD children have been reported as having a higher incidence of middle ear effusions (5).To perform tympanometry it is not required a behavioral response from the patient, so it can be used in children who lack the language or cognitive abilities to participate in other audiological exams (16).

Presentation (19,30): On the graph, the pressure falls on the abscissa: positive to the right and negative to the left; the ordinate are part of the increasing values of compliance. The maximum deviation is obtained as soon as the pressures are balanced, which corresponds to the pressure 0 mmH_2O, i.e. the normal atmospheric pressure, to an individual without pathology. In the normal

individual to have a symmetrical curve obtained from the peak height, normally situated to 0 mmH2O, tympanogram type A.

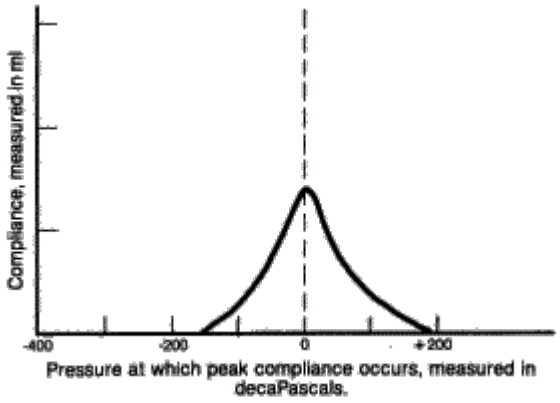


Figure 7 (19): Normal tympanogram

GSI TympStar version 1 was used to perform tympanometry to all the subjects of the study. *See technical characteristics ANNEX III.II*

> ***Parameters:*** automatic auditory stimuli at 226 Hz tympanometry in each ear performed using an olive. Sensitivity scales are automatically determined based on the peak amplitude of the tympanogram.

ABR: Auditory Evoked Potencial Device CENTOR USB was used in this study. This diagnostic device is based on biopotentials or short latency evoked potentials, allowing performing all investigations in the hearing field. This equipment is built around a standard PC and consists of two amplification and acquisition channels, and auditory stimulator, and runs under Windows. *See technical characteristics ANNEX III.III*

> ***Parameters:*** 50 µV 12.5 ms 160 Hz(1) 1.6 kHz (2) 1330A. Clic 100 µs Alterno 90 dB with mask (- 40 dB) 19.111 ps

Electrodes: To perform the exam the patient will be connected to the equipment through 4 electrodes, placed in the scalp, according to Figure 8, using disposable self-adhesive electrodes that must be destroyed after being used. The skin that will touch the electrode must be prepared once the exam can take until one hour to be complete. The electrodes will be connected to the inputs of the headbox by the correspondent cables.

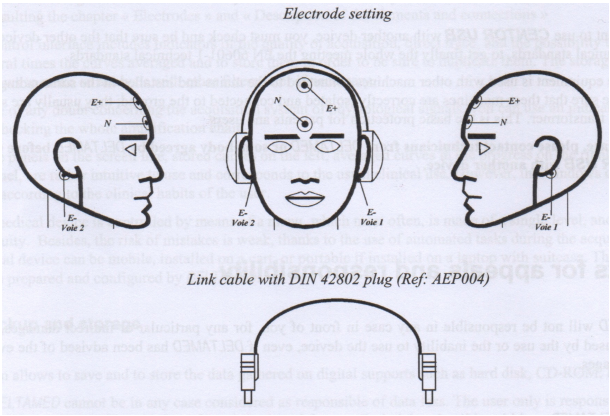


Figure 8: position of the ABR electrodes

Signal: In order to get correct analyses the user will have to take all the measures allowing improving the quality of the signal. To do so, a suitable filter must be used, the electrodes much be put on with much care, the conductive part of the electrodes and their cables should not be in contact either with other conductive parts or the ground, the electric interferences and interferences collecting should be reduced to the minimum. Even though, we must consider the possible influence of filtering and digitalization on the latencies and amplitudes registered.

Presentation: the presentation, which is standard (figure 9) shows face to face the right ear curves and those of the left ear, classifying them according to decreasing intensity levels. Two curves will be obtained at the intensity level of 90 dB to see if the obtained results are reproducible, same latencies and peaks. Markers will be put to mark waves I to V as far as possible. With a high stimulation levels the waves are clear and easily identifiable, then lose

amplitude progressively with the level decrease until it is impossible to separate them from the background noise – patient "auditory threshold" has been reached. The values of latencies I to V, variations I-III and I-V and amplitudes will be presented in tables. A diagram L=f(I) (figure 10) represents the latency of the I, III and V waves as a function of the stimulation intensity, the diagram also presents a grey part representing the normality zones for waves I and V.

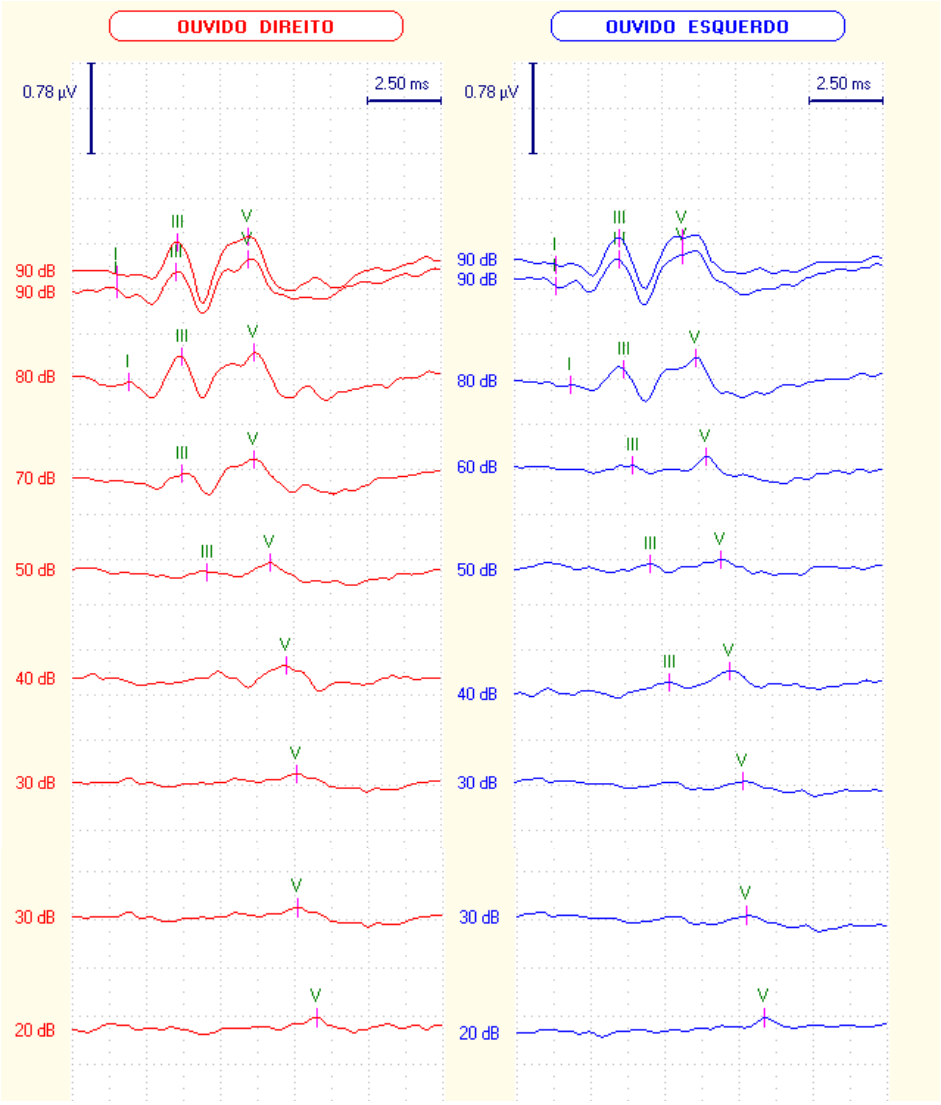


Figure 9 (19): Normal ABR waves, with normal hearing

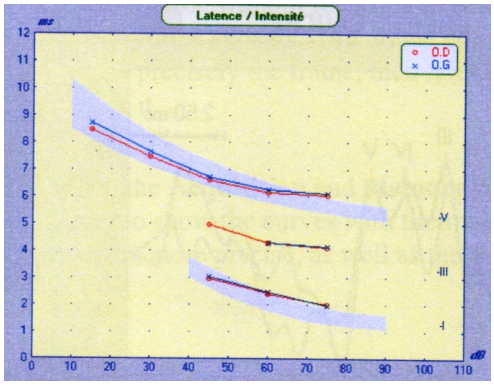


Figure 10: L=f(I) Diagram

Normal values (36, 32):

Latency	I	1,50 msec +/- 0,25 msec
	III	3,70 msec +/- 0,25 msec
	V	5,50 msec +/- 0,50 msec
Interpeak	I-III	2,20 msec +/- 0,50 msec
	III-V	1,80 msec +/- 0,30 msec
	I-V	4,00 msec +/- 0,50 msec
Amplitude	Amplitude I/ Amplitude V < 1	

Methods of data collection

The data will be collected from the clinical medical records of each participating patient, will be collected using the "Patient Sheet" (Annex II.I) and will then be gather on the study database. In order to protect the patient confidentiality a code will be given to all the patients.

STATISTICAL ANALISIS

In order to make the description between the categorical variables, it will be planted a frequency table, allowing thus, estimate the proportions. An Odds Ratio association form will be calculated, and the expected values with a confidence interval of 95% is equal or higher than 5.

Once this study comports both variables as categorical nominal, chi-square test will be used to compare them. Considered the possible intervention of confounding factors (age and sex), an individually impairment technique was used in our sample. The descriptive co-variables will be accessed using means and medians.

P values less than 0,05 were considered statistically significant. To perform the statistical analysis, SPSS will be used.

ETHICAL CONSIDERATION

During the realization of this study, we will act according to the medical ethics requirements defined in the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (revised in October 2013). The following protocol was also been approved by the Comissão Ética para a Saúde from the Centro Hospitalar do Porto, in Oporto, Portugal. The European Biomedical Research law will also be respected (95/46/CE).

All the participants in our study will be informed about the study (Annex II.I) and the patient's parents or caregiver will sign a consent form (Annex II.II) before they could be included on it. The confidentiality rules will be respected, guaranteeing the anonymity of the involved children, and

allowing the access, modification or destruction of the collected data, according to National Data Protection Commission in Portugal, in particular those related to Law 67/98 from 26 of October 1998 - Protection of Personal Information.

LIMITATIONS

Once we are selecting cases and controls from the ORL consult this could be non-representative of the population once patients are followed in a hospital environment.

To try to minimize alterations and erroneous readings of the ABR exam results, an assessment including the otoscopy and tympanogram will be performed to exclude those who have associated pathology at the time of the ABR exam.

Relatively to the controls as we are trying to reach healthy peers with suspected language delay requirement to perform the ABR test this could result in a selection bias of the sample and once this are pediatric patients an unknown pathology related to the results obtained in the ABR exam could be diagnose in the future resulting in an error of selection. This selection bias could result in some errors in the analysis and discussion of the results.

An information bias related to the diagnosis of autism could be make (soft endpoint), although we try to minimize this by only including patients with ASD that are followed in the child and adolescent psychiatric or pedopsychiatric consultation where the diagnosis was made.

A limitation of this study is the small number of participants (small N), which could result in a random bias that can affect the precision of the study. This limitation is related with the fact that being a single center study it could be difficult to have a larger sample. A way to resolve this

study would be to make this a multicenter study or enlarge the time period of the data used. Even though it would increase the cost of the present study.

Once the patient's parents or caregiver will be contact by letter or phone call it could be possible that no answer will be obtained, resulting in a loss of possible subjects in the study. To compensate this we will try to reach the patients parents or caregivers in our center appointments and be available to answer any questions.

As a case-control study, there are only some statistical data that we could obtain, such as associations instead of prevalence or incidence that would be more reliable in order to continue and be able to extrapolate the data.

FEASIBILITY

In order to do so, all the involved personal will be trained in order to be capable of understanding the objective we aim to reach. Once established the goal of this project, a list of the data that should be collected was made. According to the analysis of published studies, and taking into account the experience of CHP specialist, we decided to focus our project on the study on the collection of: neonatal screening, otoscopy, control tympanogram and ABR tests.

For each examination, we selected the parameters that could be of interest to the study (see Annex alpha and "Methods of data collection"). All parameters chosen are already analyzed in patient care, so that the coordination with the audiologist technician that had performed the exams in our patients in order to facilitate the results of the OEA and ABR exams collected.

WORK PLAN

Personnnel

- Investigators: ORL specialist, ORL resident from CHP
- Collaborators: audiological technicians, ORL secretaries, CHP aquiver personnel
- Statistical consultant

This study will be designed in 4 main stages:

- STAGE 1: Preparation phase (2 months)

  During this period the protocol of the study will be prepared. Additionally, the investigators, collaborators and statistical consultant will have meetings, in order to clarify all the objectives aimed by this study as well as to develop the timeline and plan the methods of data collection.

- STAGE 2: Selection of the possible patients of the study (1 months)

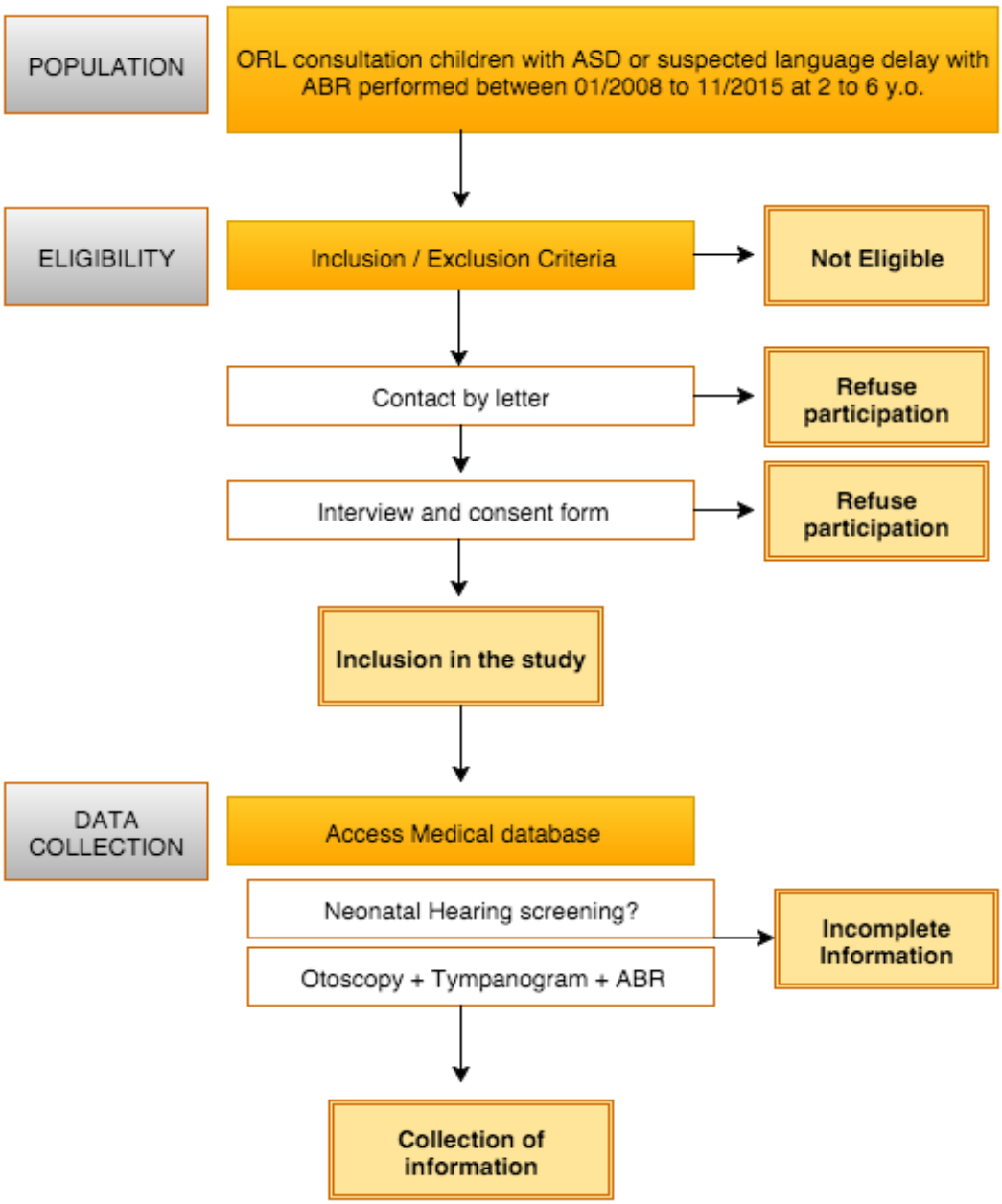
  During this stage patients from the ORL service, who fulfill the inclusion criteria will be asked to join the study. In order to do that a letter will be sent with all the information required. An interview will be set to sign the consent form and explain possible doubts.

- STAGE 3: Data collection (1 month)

  After the inclusion of the patient in our study, information of each patient will be retrieved from the medical database, such as gender, age, medical history, preformed of neonatal screening, results from ABR, control tympanogram, otoscopy and associated pathology. The patients information will be collect in ANNEX ALPHA and previously transferred to the study database.

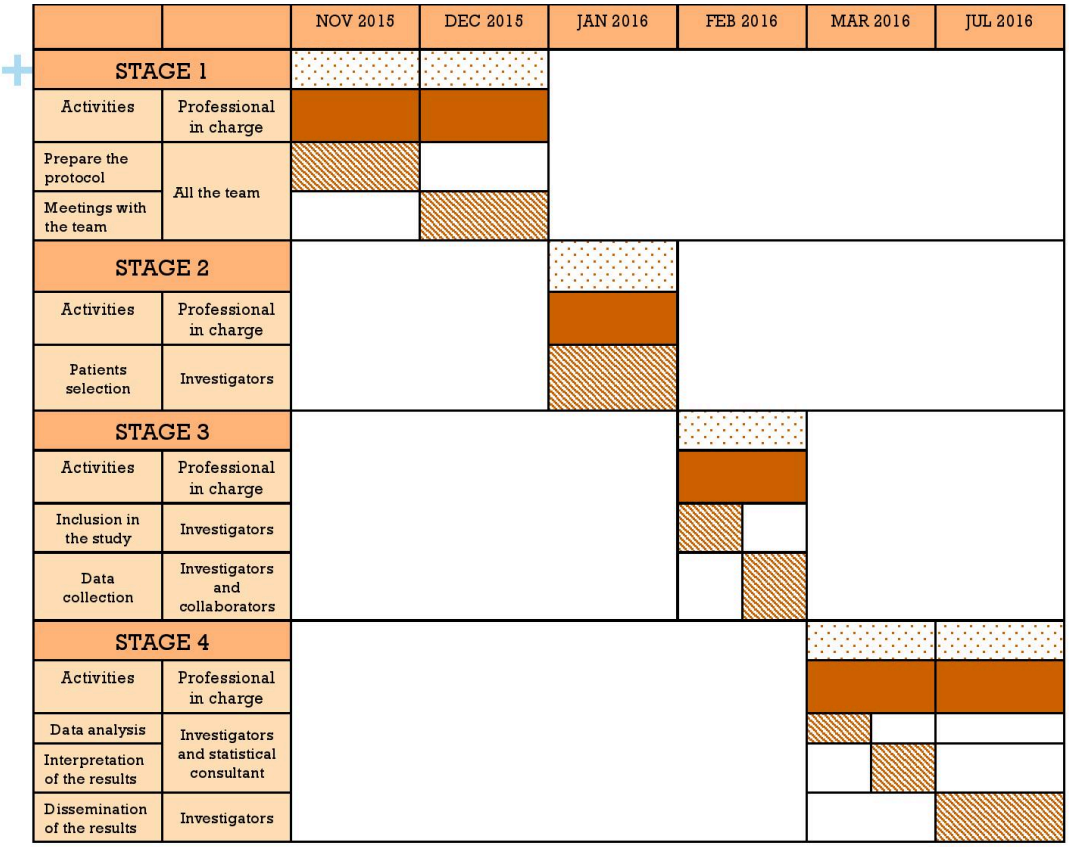
- STAGE 4: Data analysis and interpretation of the results (1 months)

  The investigators and statistical analyst using the proper statistical test will analyze the data collected during the stage 3. Posteriorly, a correct interpretation of the outcomes of the study will be made, and with the results an article will be written. To disseminate the accessed information, the investigators will be participating in some ORL conferences.



Scheme 1 Patient Participation

Chronogram



AVAILABLE MEANS TO CARRY OUT THE PROJECT

This study will take place in the CHP, a terciary hospitalar center, where we can guarantee the quality of the infrastructures and clinical care, suitable for all the activities necessary to the accuracy of this study (appointments, information about the study, informed consent, collection of clinical data, attend to patients doubts). All the patients are or have been followed in the ORL consult in CHP and had criteria to perform the ABR test.

Within the normal management and care of patients possibly presenting hearing/audiological problems all data needed for this retrospective study has already been accurately collected in the

personal medical history, which greatly facilitates its fulfillment, without any additional monetary weight.

BUDGET

	CATEGORY	COST
PERSONNEL COSTS	Statistical consultant (10h/1week)	10 x 40€
RESOURCE COST	Letters	250 x 1,5€
	Paperwork	800 x 0,05€
DISSEMINATION OF THE RESULTS	Article Publication – International Journal of Pediatric Otorhinolaringology	0€
	Conference – ESPO European Society of Pediatric Otorhinology - Travel and Accomodation - Inscription	 200€ 500€
TOTAL AMOUNT CLAIMED		**1,515€**

Regarding the costs associated with audiological exams and treatments, those should not be included in the budget, since they are not an imposition of the investigation; they are used in the care given to the patient by the hospital itself, to monitor and treat possible hearing deficits.

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ANNEXES

ANNEX ALPHA: PATIENT SHEET

centro hospitalar do Porto

Universitat de Girona

PATIENT SHEET: AUTISM AND THE AMPLITUDE OF THE ABR WAVE I

NAME: _____

PROCESS Nº: _____ BIRTH DATE : ___ / ___ / ___

ADRESS: _____

CONTACT: _____

1- OTOCOSPY:

- LE: _____
- RE: _____

2- HEARING SCREENING:

- YES: ___ NO: ___ DATE: ___ / ___ / ___
- PASS: ___ REFER: ___

3- TYMPANOGRAM:

- YES: ___ NO:___
- TYPE OF TYMPANOGRAM: _____

4- STAPEDIAL REFLEX:

- YES: ___ NO: ___

5- ABR:

- SPONTANEOUS SLEEP: ____ SEDATION: ____

WAVE LATENCY	RE			LE		
	I	III	V	I	III	V

WAVE AMPLITUDE	RE	LE

INTERWAVE LATENCY	RE			LE		
	I-III	I-V	III-V	I-III	I-V	III-V

6- ASSOCIATED COMORBIDITIES:

- YES: ___ NO: ___

7- DIAGNOSIS OF AUTISM SPECTRUM DISORDER:

- YES: ___ NO: ___
- DATE OF DIAGNOSE: __ / __ / __ AGE OF DIAGNOSIS: _____
- DIAGNOSIS RESPONSIBLE: _____

8- DELAY LANGUAGE DEVELOPMENT:

- YES: ___ NO: ___

OPORTO, _____

RESPONSIBLE: _____

ANNEX I: DSM-V CRITERIA

Autism Spectrum Disorder Diagnostic Criteria 299.00 (F84.0)

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive; see text):

   1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
   2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures: to a total lack of facial expressions and nonverbal communication.
   3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Specify current severity: Severity is based on social communication impairments and restricted, repetitive patterns of behavior (see Table 2).

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):

   1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining on toys or flipping objects, echolalia, idiosyncratic phrases).
   2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).
   3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or

perseverative interests).

4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Specify current severity: Severity is based on social communication impairments and restricted, repetitive patterns of behavior (see Table 2).

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals, who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Specify if;

- With or without accompanying intellectual impairment
- With or without accompanying language impairment

- Associated with a known medical or genetic condition or environmental factor (Coding note: Use additional code to identify the associated medical or genetic condition.)
- Associated with another neurodevelopmental, mental, or behavioral disorder (Coding note: Use additional code[s] to identify the associated neurodevelopmental, mental, or behavioral disorder[s].)
- With catatonia (refer to the criteria for catatonia associated with another mental disorder, pp. 119-120, for definition) (Coding note: Use additional code 293.89 [F06.1] catatonia associated with autism spectrum disorder to indicate the presence of the comorbid catatonia.)

ANNEX II.I: PATIENT INFORMATION SHEET

PATIENT INFORMATION SHEET

"AUTISM AND THE AMPLITUDE OF THE ABR WAVE I: A RETROSPECTIVE STUDY"

We are inviting you to take part in a research study which will be performed in the ORL service in Centro Hospitalar do Porto, in Oporto. We are proposing you to allow your child to enter this study once he was diagnosed with an autistic disorder spectrum.

Thanks for your cooperation in our study, which contributes significantly to improve the knowledge we have of ADS and its associations with hearing alterations.

Before you decide whether or not to participate in this study, please carefully read the following information. Remember that your decision is voluntary, and if you decide not to take part on the study, it will not affect in any aspect your medical care in this centre. Besides, you can exit this study any time you desire.

The aim of our study is to correlate the alterations in ABR test already performed in your medical care in our service with ADS. Autism disorder spectrum is a behaviorally diagnosed disorder of early onset characterized by an impairment of social and communication deficit. These children usually have a failure to develop non-verbal and verbal communication skills, mannerisms and great distress over minor changes in the daily routines or in immediate environment. Hearing disorders are common among children with ADS, ranging from hypersensitivity to sensorineural hearing deficit.

What will be your participating in this study?

The collaboration we are requesting you is based on the access of your medical information saved in the Centro Hospitalar do Porto medical database. It is important for you to know that we will access your information about your ADS diagnose (age of diagnose and responsible for the diagnosis) and your ORL information, such as the ABR exams results, otoscopy and tympanogram done at the time of the ABR exam, and your neonatal hearing screening. It is also possible that we will require an interview by phone to fulfill our doubts about your personal and family medical history. All the information collected will be collected by our investigators.

After obtaining all the data we need all this information will be saved in the study database. Your privacy will be guaranteed by the National Data Protection Commission in Portugal - Law 67/98 from 26 of October 1998 - Protection of Personal Information and by the law. The following study was also approved by the Comissão Ética para a Saúde from the Centro Hospitalar do Porto, in Oporto, Portugal. The European Biomedical Research law will also be respected (95/46/CE).

Any relevant findings related to your medical condition will be reported to you, although you can demand access to the results or new information anytime you want.

Your participation in this study will not result in any economic benefit either for patients or clinical staff. If you accept to sign the informed consent, you will be accepting the above mentioned conditions.

Thank you for reading this, if you still have any doubts or would like more information please contact any physician from our team.

PATIENT INFORMATION SHEET

"AUTISM AND THE AMPLITUDE OF THE ABR WAVE I: A RETROSPECTIVE STUDY"

We are inviting you to take part in a research study which will be performed in the ORL service in Centro Hospitalar do Porto, in Oporto. We are proposing you to allow your child to enter this study once he followed in our ORL consult because of a suspicious language delay. We are comparing the results of ABR exam in children with language delay and children with an autistic disorder spectrum.

Thanks for your cooperation in our study, which contributes significantly to improve the knowledge we have of ADS and its associations with hearing alterations.

Before you decide whether or not to participate in this study, please carefully read the following information. Remember that your decision is voluntary, and if you decide not to take part on the study, it will not affect in any aspect your medical care in this centre. Besides, you can exit this study any time you desire.

The aim of our study is to correlate the alterations in ABR test already performed in your medical care in our service with ADS. Autism disorder spectrum is a behaviorally diagnosed disorder of early onset characterized by an impairment of social and communication deficit. These children usually have a failure to develop non-verbal and verbal communication skills, mannerisms and great distress over minor changes in the daily routines or in immediate environment. Hearing disorders are common among children with ADS, ranging from hypersensitivity to sensorineural hearing deficit.

What will be your participating in this study?

The collaboration we are requesting you is based on the access of your medical information saved in the Centro Hospitalar do Porto medical database. It is important for you to know that we will access your information about your ADS diagnose (age of diagnose and responsible for the diagnosis) and your ORL information, such as the ABR exams results, otoscopy and tympanogram done at the time of the ABR exam, and your neonatal hearing screening. It is also possible that we will require an interview by phone to fulfill our doubts about your personal and family medical history. All the information collected will be collected by our investigators.

After obtaining all the data we need all this information will be saved in the study database. Your privacy will be guaranteed by the National Data Protection Commission in Portugal - Law 67/98 from 26 of October 1998 - Protection of Personal Information and by the law. The following study was also approved by the Comissão Ética para a Saúde from the Centro Hospitalar do Porto, in Oporto, Portugal. The European Biomedical Research law will also be respected (95/46/CE).

Any relevant findings related to your medical condition will be reported to you, although you can demand access to the results or new information anytime you want.

Your participation in this study will not result in any economic benefit either patients or clinical staff. If you accept to sign the informed consent, you will be accepting the above mentioned conditions.

Thank you for reading this, if you still have any doubts or would like more information please contact any physician from our team.

ANNEX II.II: CONSENT FORM

centro hospitalar do Porto

Universitat de Girona

INFORMED CONSENT FOR MEDICAL RESEARCH

"AUTISM AND THE ALTERATIONS OF THE ABR WAVES"

NAME: _____

PROCESS Nº: _____ BIRTH DATE : ___/ ___/ ___

ADRESS: _____

CONTACT: _____

I, _____ , declare that I agree with, and realized what I was proposed and explained by the doctor who signs the document. I declare, I have been given the opportunity to ask any questions about it and for all of them have obtained illuminating answer. I have been given enough time to reflect on this proposal. I declare to have received the information sheet for the patient. In addiction I confirm that my participation is voluntary and I can exit any time I want. I endorse my participation in this study.

OPORTO, _____

SIGNATURE: _____

DOCTOR SIGNATURE: _____ DOCTOR Nº: _____

ANNEX III: TECHNICAL CHARACTERISTICS

III. I: OEA

MADSEN AccuScreen®

Technical specifications:

Measurement techniques
TEOAE
Evaluation method: Noise-weighted averaging, counting of significant signal peaks
Stimulus: Non-linear click sequence
Stimulus level: 70-84 dB SPL (45-60 dB HL), self calibration depending on ear canal volume
Click rate: Approx. 60 Hz
Frequency range: 1.5 to 4.5 kHz
Display: Statistical waveform, measurement progress, TEOAE detection level, noise level
DPOAE
Evaluation method: Noise-weighted phase statistics
Stimulus: Primary tone pair, f2/f1 = 1.24
Available test frequencies: Configurable, f2 range 1 to 6 kHz
Range of protocols (default: 5, 4, 3, 2 kHz (PASS at 3 out of 4))
Test level: L1/L2 = 60/50 or 65/55 dB SPL
Display: DPOAE level, test progress, noise level, DP-Gram
Result display: Overall PASS/REFER, DP-Gram with DPOAE and noise level
ABR
Evaluation method: Noise-weighted averaging and template matching
Stimulus: 30, 35, 40 or 45 dB nHL click
Click rate: Approx. 80 Hz
Impedance sense signal: 1 kHz square wave
Impedance test range: 1 to 99 kΩ
Impedance accepted for test: < 12 kΩ
Impedance control:
Before test, periodically during test, stimulus continues during impedance control
Display: Statistical graph, test progress, EEG-level, ABR detection probability
Electrodes: Disposable hydrogel electrodes
Dimensions
Approx. 202 x 73 x 30 mm (8 x 2.8 x 1.2 inches)
Weight
Approx. 240 g (8.5 oz) excluding battery
280 g (9.9 oz) including battery
Display
Type: Color, TFT, touch screen with adjustable LED backlight
Dimensions: 71,5 x 53,6 mm (28.1 x 21.1 inches)
Resolution: 240 x 320 pixels
Keystroke durability: min. 1 million repetitive strokes per screen point
Keypad
Resistive Touch Screen (can be used with gloves)
Memory
Patient memory capacity: Max. 250 patients / Min. 500 tests
Connectors
OAE probe connector: 14 pin ODU Medisnap - For OAE Probe or ABR ear coupler cable
ABR (ABR version only): 4 pin ODU Medisnap - For ABR electrode cable
Real time clock
Integrated real-time clock for time-stamping of measurements.
The clock is automatically synchronized with PC clock when docked.
Backup: Min. 5 days, when battery is removed from unit
Data interfaces
PC: IR data transmission to Docking Station - USB interface from Docking Station to PC
Transport and storage environment
Temperature range: -20 - +60°C (-4 - 140 °F)
Humidity range: 20-80 % rel., non-condensing
Air pressure 500 hPa to 1060 hPa
Operating environment
Temperature range: 10 - 40°C (50 - 104°F)
Humidity range: 30-80 % rel., non-condensing
Air pressure 600 hPa to 1060 hPa

Standards
Otoacoustic emissions: EN 60645-6, Type 2
Auditory evoked potentials: EN 60645-7, Type 2
Patient Safety:
• EN 60601-1, Internally Powered, Type BF, IPXO
• UL 60601-1
• IEC 60601-2-26
• IEC 60601-2-40
EMC: EN 60601-1-2
Power supply and battery
Battery type: Rechargeable Li-ion 3.7 V/1800 mAh (6.7 Wh), fully charged
Estimated battery life: 8 hours of continuous use (based on a typical use scenario
Actual use can influence the battery life time)
Battery level indicator: 5-step battery level indicator
Charge time in AccuScreen docking station: 80% charged 4½ hours. Fully charged 6 hours
PC interface
Interface type: USB 2.0, Full-speed
USB Power: Uses <100 mA of current from the USB interface
Printer interface
Interface type: RS232
Connector type: 6-pol Mini Din
DC power input
Input voltage: 5 V DC ±5%
Max. power consumption when AccuScreen is docked: 5VA (5V, 1.0 A)
Max. power consumption when AccuScreen is not docked: 0.25 VA (5V, 50 mA)
Power adapter
Input voltage/range: 100-240 V AC, 50-60 Hz
Output voltage: 5.0 V DC/min. 1.0A
Mains plug types: US, UK, Europe and Australia
Probe
Flexible, shielded cable, approx. length: 120 cm (approx. 55 inches)
Dimensions
Probe body: 20 mm Ø x 23 x 11 mm (0.8" Ø x 0.9" x 0.43")
Probe tip: 3.3 mm Ø x 10 mm (0.13" Ø x 0.4")
Weight
Probe incl. probe tip: Approx. 4.5 grams
Eartips
Standard (cylindrical): 4 sizes (3.7 - 5 mm)
Tree tip: 1 size (4 - 7 mm)
Foam tip: 1 size (13 mm)
ABR electrode cable
Flexible, shielded cable, approx. length: 140 cm (approx. 55 inches)
ABR ear coupler cable (optional)
Flexible, shielded cable, approx. length: 145 cm (approx. 57 inches)
Device class
IIa (according to Council Directive 93/42/EEC Appendix IX)

Standard accessories

The MADSEN AccuScreen comes with customized Carrying case, Docking station including Power Adaptor and USB Cable, Starter kit, OAE probe (DPOAE/TEOAE or TEOAE only), Battery, ABR electrode cable (ABR version only), ABR Tester (ABR version only), Cleaning cloth and User Manual.

Optional accessories

Label Printer with printer cable, ABR ear coupler cable and External battery charger. Standard accessories and optional accessories may vary from country to country - please consult your local distributor.

Specifications are subject to change without notice. Copyright © GN Otometrics. 2012/03. 7-26-8100-EN/03. Part no. 7-26-81000-EN.

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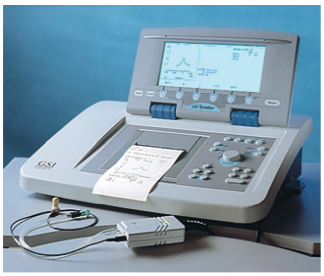
www.otometrics.com

otometrics
MADSEN · AURICAL · ICS

III.II: TYMPANOGRAM

GSI TYMPSTAR™

COMPREHENSIVE MIDDLE-EAR ANALYZER



No other middle-ear analyzer offers the advanced technology and complete flexibility of the GSI TympStar.

Product Specifications

The following specifications apply to both Version 1 and Version 2 of the GSI TympStar. *Italic type with an orange arrow (▸) indicates the additional capabilities of Version 2.*

General Specifications

- 20.47"(W) x 14.96"(D) x 12.59"(H)
- Weight: 16.53lb
- Shipping Weight: 29.54lb
- Power Consumption: 120 Watts maximum
- Test Types: Tympanometry, Acoustic Reflex Threshold, Reflex Decay, Eustachian Tube Function (Intact and Perforated)
- Protocols: Diagnostic, Screening, User-defined
- ▸ *Special Tests: Two-component Tympanometry, Multiple Frequency Tympanometry, Acoustic Reflex Latency Test, Reflex Sensitization*
- Display: Internal or External VGA Monitor
- Interface: RS232, parallel and keyboard output
- Printout: Internal or External Deskjet or Laserjet Printer

Probe Tone

- 226 Hz (85 dB SPL ± 1.5 dB)
- ▸ *678 Hz (85 dB SPL ± 3.0 dB)*
- ▸ *1000 Hz (75 dB SPL ± 3.0 dB)*
- Accuracy: ± 1%
- Harmonic Distortion: Less than 5%

Admittance Measurements

- Range: 226 Hz (-1.0 to +7.0)
- ▸ *678 Hz (-5.0 to +25)*
- ▸ *1000 Hz (-5.0 to +30)*
- Sensitivity Scale: Auto Scales to Appropriate Range, Manual selection also possible in Reflex Modes only
- Accuracy (226 Hz):
  - Tymp Mode: ± 5% of reading or ± 0.1 ml, whichever is greater
  - Reflex Mode: ± 5% of reading or ± 0.2 ml, whichever is greater

Pressure Measurements

(load volume of 0.2 to 7.0 ml)

- Range: Normal = +200 to -400 daPa
  Wide = +400 to -600 daPa
- Accuracy: ± 10% of reading or ± 10 daPa, whichever is greater
- Sweep Rate: 12.5, 50.0 and 600/200 daPa/sec,
- ▸ *200 daPa/sec.*
- Sweep Accuracy: 10% of nominal rate
- Maximum limits (in 0.5cc cavity): -800 daPa and +600 daPa

Reflex Measurements

- Stimuli: ▸ *250*, 500, 1k, 2k, 4k, BBN, LBN, HBN,
- ▸ *Click (100 microseconds pulse), External Input, Non-acoustic*
- Frequency Accuracy: ± 3%
- Harmonic Distortion (THD): Less than 5% (measured acoustically)
- Noise Signals: (3 dB bandwidths)
- Low Band: 125 -1,600 Hz
- High Band: 1,600 -4,000 Hz
- Broad Band: 125 -4,000 Hz
- Intensity Range: 35 to 120 dB HL
- Step Size: 5 dB, ▸ *1 dB and 2 dB*
- Calibration Accuracy: ± 3 dB
- Step Accuracy: ± 0.5 dB
- ON/OFF Ratio: 70 dB minimum

Environmental

- Temperature:
  - Storage: -40° F to +167° F
  - Operating: +59° F to +95° F
  - Humidity: 90% at 95° F (non-condensing)

Accessories Supplied

- Probe assembly (including contralateral insert phone)
- Eartips (1 pkg. each standard, special, screening)
- Printer paper, 2 rolls thermal, 1 roll self-adhesive
- Calibration test cavity, Cleaning kit, Probe mount kit (shoulder, clip, wrist band), Quick User Guide, Reference Instruction Manual, Remote (RS232 link)
- Dust Cover

Optional Accessories

- Deskjet printer 1700-9613
- External VGA monitor 1700-9614
- External keyboard 1700-9615
- Isolation Transformer 1700-9617
- Service Manual 2000-0110
- Conversion Kit (V1 to V2) 2000-9650

Language Kits

- GSI TympStar Version 1
  - English 2000-9645E
  - French 2000-9645F
  - German 2000-9645G
  - Spanish 2000-9645S
  - Italian 2000-9645I
- ▸ *GSI TympStar Version 2*
  - *English* *2000-9646E*
  - *French* *2000-9646F*
  - *German* *2000-9646G*
  - *Spanish* *2000-9646S*
  - *Italian* *2000-9646I*

Quality System

- Manufactured, designed, developed and marketed under an ISO 13485, ISO 9001 certified quality system

Compliance/Regulatory Standards

Designed, tested and manufactured to meet the following domestic (USA), Canadian, European and International Standards:

- UL 2601-1 American Standards for Medical Electrical Equipment
- IEC 601-1, EN 60601-1 International Standards for Medical Electrical Equipment
- CSA C22.2 # 601-1-M90
- ANSI S3.39, ANSI S3.6, IEC 645-1, IEC 1027, ISO 389
- Medical Device Directive (MDD) (ID No.: 0086) to comply with "EC Directive" 93/42/EEC

Setting The Clinical Standard www.grason-stadler.com

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800-700-2282 • 952-278-4402 • *fax* 952-278-4401 • *e-mail* info@grason-stadler.com

gsi Grason-Stadler

III.III: ABR

Technical characteristics

CENTOR USB is an equipment of electrical class I and type BF, for continuous service.

It is not protected against:

- The liquids penetration
- The use in the presence of flammable gases
- Discharge of defibrillators

General

CENTOR USB is composed of the following elements:

- Computer base of PC type (central processing unit, keyboard, mouse, monitor, USB 2.0 connectors), desktop or laptop – eventually fixed on a mobile carriage –,
- Software compatible with Microsoft Windows® operating system,
- Headbox for the acquisition /amplification /conversion of physiologic signals,
- Interface box connected onto a computer's USB 2.0 port that ensures data transmission between the headbox and the computer, and generates the various stimulation types,
- Specific power-supply unit for the Interface box,
- Headphone or /and insert, referred for ***CENTOR USB***, the calibration of which was controlled by *DELTAMED*,
- Cables for the interconnections of the various elements,
- Insulation transformer for the powering of the elements, especially the computer if it is not powered by a battery (see *Installation manual DCTUSB_IA* for more details on using the insulation transformer)
- Options :
  - Bone vibrator
  - Neuromuscular stimulator
  - Video monitor for checkerboard stimulation
  - SLI Box for flash stimulation
  - GOGGLE glasses
  - Carriage
  - Headbox support

Interface box

Features:

- Specific power-supply unit in the form of an external adapter

- Connection to the computer: type USB 2.0 high speed
- Connection to the Headbox: serial, differential, type RJ45
- Auditory stimulator (integrated):
  - Optically isolated (BF), class I
  - Amplifier: 0 – 110 dB HL, step 1 dB
  - Output: for headset or auditory inserts
- Visual stimulator (integrated, valid only on option):
  - Output: for video monitor (checkerboard stimulation)
  - Output: for SLI box /GOGGLE glasses (flash stimulation)
- Triggering:
  - Internal: from 0.01 to 500 pps,
  - External: 2 trigger inputs for an external triggering signal
  - Footswitch
- 2 Trigger outputs, with pulse width and polarity adjustable
- 2 Trigger inputs, for an external triggering signal, triggering edge adjustable
- Analog outputs for physiologic input signals
- Output for loudspeaker
- Options :
- Amplifier and output for bone vibrator
- Command and output for neuromuscular stimulator 1

Headbox

Features :

- Amplifiers optically isolated (BF), class I
- Number of channels:
  - 2 channels, differential (2-channel Headbox); inputs for electrodes as individual sockets on the top cover
  - 4 channels, differential (4-channel Headbox); inputs for electrodes as a common connector to be connected to a cable of electrodes
  - Channels totally independent
- Input impedance: ~ 1GΩ
- Common mode rejection ratio: 1000000 (120 dB)
- Residual noise :
  < 5 µV peak to peak with the largest frequency band (0.13 Hz – 10 kHz)
  < 2 µV peak to peak with the AEP frequency band (160 Hz – 1.6 kHz)
- Conversion 14 bits, 200 kHz per channel (or 400 kHz 1 channel)
- Continuous data stream
- Analog hi-pass filter: 0.13 Hz /32 Hz (complemented by digital hi-pass filtering after conversion)

- Analog lo-pass filter: 10 kHz (complemented by digital lo-pass filtering after conversion)
- Amplifier sensitivity, full scale: 10 µV – 100 mV, by increasing of 1, 2, 5
- Notch 50/60 Hz, factory-adjusted
- Command for the measurement of the impedance of the collecting electrodes as a pushbutton on the top cover (measures on the computer screen)
- Checking signal to verify the amplifiers, software-commanded
- Connector "Patient event" with 2 inputs, allowing to take into account events

Neuromuscular stimulator (option)

Features:

- Isolated (BF) class II
- 2 ranges of current: 0 – 5 mA and 0 – 100 mA,
- Stimulation: alternated, normal, inverted
- Pulse width adjustable
- Intensity adjustable
- Manual stimulation triggering
- Notification for overloads and defects

Software

The software controls the following elements :

Acquisition parameters:

- 2 or 4 channels; direct corresponding of the channels to the amplifiers or redirection
- Amplifier sensitivity: 10 µV – 100 mV
- Hi-pass and lo-pass digital filters, type Butterworth :
  - Hi-pass: by list (0.16 Hz … 400 Hz) or editable, precision 1/100 Hz
  - Lo-pass: by list (16 Hz … 10 kHz) or editable, precision 1/100 Hz
  - Order: 1 à 4
- Number of points per buffer: 500 to 4000
- Analysis duration: 2.5 ms – 20 s
- Delay pre or post-analysis: -95 % to 95 % of the analysis duration
- Measures of the impedance of the electrodes on screen
- Rejection outline:

- Amplitude adjustable: 50 % up to 100 %
- Rejection-inhibition delay adjustable: 5 % up to 100 % of the analysis duration

- Preset of the number of sweeps for averaging.

Auditory stimulation parameters

- Stimulus :
  - CLICK: Width: by list (50 µs … 250 µs) or editable
  - LOGON : Number of cycles: by list (3 … 100) or editable
    Frequency: by list (125 Hz … 8 kHz) or editable
  - BURST : Duration: by list (50 ms … 500 ms) or editable
    Frequency: by list (125 Hz … 8 kHz) or editable
    Envelop: linear, sine, Hamming, Blackman, Gauss
    (rising time adjustable for linear: 0 …50 %)
  - WAVE (option): List of WAVE files customizable
- Stimulation intensity: by list (0 dB … 110 dB HL, step: 5 dB) or editable, step 1 dB
- Masking: contralateral white noise, enslaved to the stimulation level: 0 dB … -50 dB HL
- Polarity: Condensation, rarefaction, or alternating (with artefact-reject control: same reject number for positive and negative stimulations)
- Stimulation frequency: by list (0.1 pps … 50 pps) or editable up to 500 pps, precision 1/1000 pps
- Control of an external stimulator (input or output triggering)
- Earphone type: headset, insert (delay adjustable), bone vibrator
- Earphone output: right and /or left, always right, always left

Visual stimulation parameters (option)

- Checkerboard stimulation (video monitor) :
  - Contrast: 10 up to 100 %, step 10%
  - Type: checkerboard, vertical stripes, horizontal stripes
  - Field: total, right field, left field
  - Pattern per degree: 0,34 up to 5,34
  - Target: red square in the middle of the screen (removable)
  - Monitor resolution: VGA (640x480) or XGA (1024x768)
  - Triggering: enslaved to the monitor refreshing or not.
- Flash /GOGGLE stimulation:
  - Pulse duration: 10 up to 50 ms, editable, step 1 ms.

Electric stimulation parameters (option)

- Pulse : simple, double, train
- Pulse duration: 0.05 ms up to 0.6 ms, editable
- Pulse polarity: positive /negative
- Intensity: adjustable, displayed on the computer screen
- Range: 0 – 5 mA or 0 – 100 mA
- Remote control of the neuromuscular stimulator
- On-screen notification for overloads and defects

Data processing

- Several protocols (Threshold, EAEP 2 channels, etc.)
- Raw and averaged traces simultaneously displayed
- Superposition of isophonic curves
- Possibility to work with memorised curves during acquisition
- Measurements of latency, amplitude, etc. Mathematical operations on curves
- Diagram « Latency / Intensity » with normative graphs (adult and new-born)
- Report page setting: 2 layouts by default, possibility for new user-created layouts
- Report printing
- Acquisition-task chaining: automated acquisition protocols. 2 automated protocols by default, possibility for new user-created automated protocols
- Independent acquisition parameters for each protocol, adjustable.
- Insertion of comments in the examination record (that describe, for instance, the recording conditions)
- Pre-positioning of the markers for auditory threshold detection