Auditory Neuropathy: Clinical Evaluation and Diagnostic Approach

Neuropatia Auditiva: Avaliação Clínica e Abordagem Diagnóstica

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Acta Med Port 2016 Jun;29(6):353-359 ▪ http://dx.doi.org/10.20344/amp.6942

ABSTRACT

Introduction: Auditory neuropathy is a condition in which there is a change in the neuronal transmission of the auditory stimuli. Our objective was to describe the patients' series within the clinical spectrum of auditory neuropathy.

Material and Methods: We designed a transversal, retrospective study, with a description of a consecutive case series. Auditory neuropathy was defined by the presence of acoustic otoemissions plus absent/abnormal auditory brainstem responses with cochlear microphonism.

Results: 34 patients with bilateral hearing loss, 23 males and 11 females, were included in the study. Eighty percent of the cases had congenital onset of hearing loss. Acoustic otoemissions were absent in 67% of them. Cochlear microfonism was present in 79% of all cases. Prenatal, perinatal or ambiental factors were present in 35.2% of the cases.

Discussion: Medical literature shows great variability in findings related to auditory neuropathy, both in its etiology and epidemiological data.

Conclusion: Auditory neuropathy presents a broad spectrum of changes that may result from mild to severe changes in the functioning of the auditory pathway, and in our sample we observed that 80% of Auditory neuropathy have congenital onset of hearing loss and/or with cochlear microphonism identified. 91% of patients experience significant hearing impairment and 53% suffer from severe or profound deafness.

Keywords: Auditory Neuropathy; Evoked Potentials, Auditory, Brain Stem; Hair Cells, Auditory; Hair Cells, Auditory, Inner; Hair Cells, Auditory, Outer; Mononeuropathies.

RESUMO

Introdução: A neuropatia auditiva é uma condição na qual há alteração na condução neuronal do estímulo sonoro. Este trabalho pretende descrever e caracterizar a casuística de doentes com neuropatia auditiva.

Material e Métodos: Realizámos um estudo transversal, retrospetivo, com descrição de uma série de casos consecutivos. O diagnóstico da neuropatia auditiva foi definido nas seguintes situações: Presença de otoemissões acústicas com potenciais auditivos de tronco encefálico ausente ou anormal e presença do microfonismo coclear independentemente da presença de otoemissões acústicas.

Resultados: Foram avaliados 34 doentes com perda auditiva bilateral, 67% deles do sexo masculino. O aparecimento dos sintomas foi congênito em 80% dos casos. Na pesquisa das otoemissões acústicas, a resposta foi ausente em 67% dos doentes. O microfonismo coclear foi detetado em 79% dos doentes. Antecedentes gestacionais, perinatais ou ambientais relevantes estiveram presentes em 35,3% dos casos.

Discussão: A literatura médica ainda apresenta grande variabilidade nos achados relacionados com a neuropatia auditiva, tanto na sua etiologia quanto nos dados epidemiológicos.

Conclusão: A neuropatia auditiva apresenta um amplo espectro de alterações que podem resultar em disfunções leves a severas no funcionamento da via auditiva. Na nossa amostra, observámos que 80% das neuropatias auditivas terão tido origem congênita e/ou apresenta microfonismo coclear, 91% dos doentes apresenta défice auditivo significativo e 53% sofrem de surdez severa ou profunda.

Palavras-chave: Células Ciliadas Auditivas; Células Ciliadas Auditivas Externas; Células Ciliadas Auditivas Internas; Potenciais Evocados Auditivos do Tronco Encefálico; Neuropatia Auditiva.

INTRODUCTION

Auditory neuropathy (AN) or auditory dyssynchrony (AD) is a hearing disorder showing normal outer hair cell and abnormal inner hair cell function and/or with auditory nerve fibre damage and impaired nerve conduction.[1,2]

Patients of any age group may be affected, with 0.23 to 2% prevalence in children and has been considered as a risk factor for hearing impairment. It is estimated that around 8% of new patients each year with hearing impairment in children were related to AN.[3]

Data on the prevalence and incidence of AN in Brazilian population are scarce. In a recent study with 2,292 patients with hearing impairment, a 1.2% prevalence of AN was found.[4]

Pathophysiology of the disease is not well known and is currently considered as a single disease with a range of pathologies affecting auditory pathway.

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Recebido: 26 de agosto de 2015 - Aceite: 15 de fevereiro de 2016 | Copyright © Ordem dos Médicos 2016

Different factors including prematurity, hyperbilirubinemia, hypercholesterolemia, hypoxia, CNS immaturity, low birth weight, idiopathic conditions, genetic factors and others have been suggested as contributing factors (isolated or in combination) for the development of AN in newborn babies.[3-6]

Different theories on the sites of lesion in patients with AN have been suggested, including tectorial membrane, inner hair cells (IHC), outer hair cells (OHC), abnormal release of neurotransmitters in synapses between inner hair cells and auditory nerve fibres in the spiral ganglion, disrupted electrical transmission in auditory nerve fibres, different axonal disorders or even related to myelin content of the cochlear nerve.[7]

An approximately 13.4% prevalence of AN in paediatric patients with severe-to-profound hearing loss has been described.[8] Among widely studied genetic factors, mutations in classically described genes and associated with AN, such as OTOF and PJVAK, have been established.[4] It is believed that such genes may be responsible for disorders related to ICC.[9]

Four loci have already been mapped and have been considered in medical literature as responsible for non-syndromic AN, including (i) DFNB9 (*OTOF*) and DFNB59 (*PJVK*) consistent with autosomal recessive inheritance, (ii) AUNA1 (*DIAPH3*) with autosomal dominant inheritance and (iii) AUNX1 with X-linked inheritance. According with some authors, mutations in GJB2 gene and mitochondrial mutations (12S rRNA) may also be associated with AN.[10-15] Despite classical cases of AN have been described in patients diagnosed with a homozygous 35delG mutation in GJB2 gene, the association between GJB2 mutations and AN was only described in a small number of studies and no correlation having been already established.[4,16]

Hearing impairment will show different progressions, frequently with poor speech-perception abilities associated with abnormal results in electrophysiological testing.

Present otoacoustic emissions (OAE) with normal or abnormal brainstem auditory evoked response (BAER) test results is classically found in AN. Present cochlear microphonic (CM) and absent acoustic reflexes are normally found.[17,18]

Some patients concomitantly present with other peripheral neuropathies, mainly with Guillain-Barré syndrome and Charcot-Marie-Tooth disease.[14,15]

Rehabilitation therapy of patients with AN either with speech therapy alone, with cochlear implantation or with individual sound amplification auditory devices must be performed at the earliest possible stage in order to improve outcome.[18]

Our study aimed to describe the epidemiologic and audiological characteristics of paediatric patients having attended the Audiology Department at a tertiary referral university hospital and having been diagnosed with AN.

MATERIAL AND METHODS

This was a retrospective, cross-sectional study describing a series of consecutive patients based on the analysis of clinical records of patients diagnosed with bilateral hearing impairment and suspected AN having attended the Audiology Department at a university hospital.

The variables analysed included patient's age, gender, age of onset of hearing impairment (congenital, in childhood, in adolescence or in the adult stage), gestational, perinatal and genetic history and results from electrophysiological testing (including BAER, transient and distortion product OAE and cochlear microphonic testing [CM]).

Any situation described in patient's clinical history such as prematurity, jaundice, *kernicterus*, admission to neonatal ICU, meningitis, severe neonatal infection (including sepsis and pneumonia), genetic syndromes, concomitant neurological disorders (including rubella and toxoplasmosis), systemic clinical comorbidities (including high blood pressure, diabetes mellitus) was considered. Any family history of hearing impairment was also looked for and identified.

Age groups were defined according to age of symptom onset as congenital (up to one year of life), childhood (aged 1-10), adolescent (aged 11-18) or adult (over 18).

Clinical diagnosis of AN was established with (i) present OAE and/or (ii) CM and (iii) BAER with absent or abnormal response, with imaging tests excluding any anatomical disorder of the cranial nerve VIII.

Group of patients

Our study involved patients having attended our department over the last three years (2011 to 2014) and having been diagnosed with AN.

Only patients that underwent audiological and electrophysiological tests performed by our phonoaudiology team (audiologists and speech therapists) were included in our group of patients and the same equipment was used in all the patients.

Inclusion criteria

Inclusion criteria included the presence of sensorineural hearing impairment, absence of any middle-ear disorder, presence of the vestibulocochlear nerve shown in imaging tests (MRI or CT-scan) and absence of any retrocochlear disorder, absent acoustic reflexes, audiological tests

consistent with auditory neuropathy spectrum disorder:

a) present OAE and absent BAER, or

b) absent OAE, absent BAER and present cochlear microphonic, or

c) absent OAE and BAER with present tonal thresholds and clinical suspicion of auditory neuropathy.

Audiological Evaluation

Audiological tests were performed, including impedance testing, tonal and vocal audiometry.

Testing was performed using an AC30-SD25 audiometer, calibrated according to ISO 389/64 standards and an AT-235 (Interacoustics) device for OAE and BAER (these tests were repeated at least twice).

Distortion product OAE in the 700-8,000 Hz frequency range were obtained, stimulated at 65 to 55 dBNPS stimulation and using a 1.22 frequency ratio. A response was considered present when the difference between amplitude and noise was over 6dB, with a 70% reproducibility value or above.[19]

BAER was analysed as regards morphology, absolute and interpeak latencies, replicability, amplitude and intervals between waves I, III and V, with interpeak I-V intervals of 4.5ms or below being considered as normal. Latencies in waves I to V were considered as normal for values of 1.5, 2.5, 3.6, 4.9 and 5.6, at 100dB, respectively. The higher the intensity of the stimulation, the higher is the amplitude, considering that usually the amplitude of wave V is higher than wave I. Interaural latency differences between interpeak intervals was lower than 0.3 ms. Auditory threshold was considered when the least intensity of wave V was present. The electrophysiological evaluation was performed in the 12 ms upon audio stimulation.[19]

BAER and CM testing used insert ear phones. A 100 dBNA stimulus within a 250-8,000 Hz frequency range, 100 microsecond duration was used, with condensation and rarefaction polarity and 2,000 clicks for each series were performed and evaluation was repeated twice for all intensities. The test was considered as abnormal with absent wave formation or when a severe abnormality of wave morphology was found up to a 100 dBNA stimulus.[19]

Main BAER wave morphology abnormalities were associated to deformity or even non-formation of the wave at the expected period, as well as with lower of higher duration, wave prolongations, presence of more than one peak or absent peaks and non-reproducibility of waves. This was confirmed with up to 100 dB stimulus. Normal values of latency and amplitude were adjusted to patient's age for BAER's interpretation.[19]

CM was evaluated in BAER testing, using polarity inversion (condensation and rarefaction). The electrophysiological threshold was determined in patients with positive CM with 100 dBNA stimulus, following a descending procedure.[19]

Hearing impairment was ranked into mild, moderate, severe or profound.[20]

According to the professional interpretation of the speech therapists, patient's speech development was subjectively ranked into three categories (poor, acceptable or good).

Genetic Assessment

Genomic DNA was extracted from peripheral venous blood, according to standard protocols. Mutations were looked for through direct gene sequencing (GJB2).[4,6,9,10]

Statistical Analysis

A simple statistical analysis of data was carried out and mean, median and standard deviation were obtained.

Chi-square test was used for group comparison. Due to the small dimension of some variables, Fisher's exact test was also used to check for group correlation.

A 95% confidence interval has been used and a *p*-value <0.05 was considered as significant.

Ethics

Our study was approved by the Research Ethics Committee of the institution (report number 396/2006).

RESULTS

Upon careful revision of clinical records, quality data

Table 1 - Distribution of patients according to age of symptom onset of auditory symptoms and to patient's gender

		n
Gender	Male	23 (67%)
	Female	11 (33%)
Age of symptom onset	Congenital	27 (80%)
	Childhood	3 (9%)
	Adolescence	4 (11%)
	Adult stage	0 (0%)
Total		34

Table 2 - **Electrophysiological assessment**

Electrophysiological assessment	Present	Absent
Transient OAE	9 (26.5%)	25 (73,5%)
Distortion Product OAE	11 (33%)	23 (67%)
Cochlear Microphonic	27 (79%)	7 (21%)
BAER	0	34 (100%)

Table 3 - Speech development

Speech quality	n
Poor	21 (61.5%)
Acceptable	7 (21%)
Good	6 (17.5%)

were only available from 34 out of 49 patients and these were included in the study, in order to improve accuracy.

Main patient characteristics (67% male and 80% presenting with congenital disorder) are shown in Table 1.

As regards the results of OAE bilateral testing (Table 2), abnormal BAER were considered whenever these were absent or when significant abnormalities in wave morphology were found. CM was identified in all the patients with absent OAE (transient or distortion product OAE) and was crucial for clinical suspicion.

Speech quality was ranked as poor, acceptable or good (Table 3) by the Audiology team and around 62% of the patients were ranked as presenting with poor speech quality.

Gestational, perinatal and environmental history was available in 12 patients (35.3%), as shown in Table 4.

Genetic assessment is shown in Table 5 and none of the results had any previously described association with AN. The 35delG mutation in GJB2 gene was the only homozygous mutation found and a relationship with AN has not yet been established. None of the patients with genetic abnormalities had any family history of hearing impairment.

Audiometric and electrophysiological testing of patients diagnosed with AN is shown in Table 6.

Most patients (53%) presented with severe-to-profound hearing impairment (severe in 11 patients and profound in seven), while moderate hearing impairment was found in 13 patients (38%) and mild in 3 patients (9%).

A correlation between the type of hearing impairment and electrophysiological data was not established ($p > 0.05$).

Table 4 - **Gestational, perinatal or environmental relevant history**

History	n
Admission to neonatal ICU	10 (29.4%)
Prematurity	6 (17.5%)
Family history of hearing impairment	4 (11%)
Jaundice	2 (6%)
Kernicterus	1 (3%)
Neonatal meningitis	1 (3%)
Gestational toxoplasmosis	1 (3%)
Neonatal pneumonia	1 (3%)
CHARGE syndrome	1 (3%)
Spinal muscular atrophy	1 (3%)
Systemic comorbidities	0 (0%)
Absent	22 (64.7%)

DISCUSSION

Auditory neuropathy has been differently studied over the last decade and electrophysiological testing is currently crucial for diagnosis.

In our group of patients, 35.3% of the patients presented with gestational, perinatal or environmental history of AN. Many recent studies have described the possible mechanisms involved in pathophysiology, regarding mainly genetic factors. Genetic abnormalities were found in five patients (14%) in genes potentially associated with AN, even though no clinical or laboratorial evidence of a cause-effect relationship was found in any of our patients.[19,21]

Both classic and recent studies have suggested that, in 42% of the patients, AN was associated to inherited neurological disorders, with different other situations (toxicity, metabolic and infectious situations) in 10% of the patients and idiopathic AN was found in the remaining 48% of the patients.[19,21-23]

In our group of patients, approximately 40% of the patients had relevant gestational, perinatal or environmental history and prematurity and admission to a neonatal ICU were most prevalent.

It is generally agreed that idiopathic AN is associated mostly with genetic abnormalities. Some authors have even

Table 5 - Genetic results

Location	Abnormality	Frequency (n)	Genotype	Clinical Meaning
Exon 2	p.D43D (c.129C > T)	1	Heterozygous	Probably non-pathogenic
Intron 2	IVS2 + 28T > G	1	Heterozygous	Unknown
Intron 4	IVS5 - 59T > C	1	Heterozygous	Unknown
Intron 5	IVS5 + 10A > G	1	Heterozygous	Probably non-pathogenic
GJB2	35delG / 35delG	1	Heterozygous	Pathogenic (related with AN?)
GJB2	35delG / N	1	Heterozygous	Probably non-pathogenic

Table 6 - Distribution of patients according to audiometric assessment[20]

Hearing impairment	OAE + BAER -	OAE - BAER - CM +	OAE + BAER - CM+	CM +	Total (n)
Mild	3	0	2	2	3 (8.8%)
Moderate	6	7	0	7	13 (38.2%)
Severe	1	10	1	11	11 (32.4%)
Profound	1	6	1	7	7 (20.6%)
Total (n)	11 (32.4%)	23 (67.6%)	4 (11.8%)	27 (79.4%)	34 (100%)

considered that auditory neuropathy spectrum disorders are based in syndromic, non-syndromic or mitochondrial genetic disorders.[22]

Widely different results may be obtained in the audiometric assessment of patients with AN, ranging from patients with normal thresholds up to severe hearing impairment. Therefore, no audiometric standard pattern exist, due to a wide interpersonal variability.[19,21,22]

Our study showed that most patients (53%) presented with severe or profound hearing impairment, while 38% presented with moderate and 9% with mild impairment, showing a great variability, in line with literature.

Congenital disorders were diagnosed in 80% of the patients and most of these were assessed in our department upon an abnormal neonatal auditory screening. Even though AN is mostly diagnosed in childhood, some authors believe that most patients with AN are only diagnosed in the adult stage.[21]

OAE testing provide information related to the function of outer external hair cells and represent preneural phenomena related to mechanical processes in the cochlea. Present OAE depends on an intact auditory system and showing the function of the Organ of Corti, which is represented in this specific situation by the inner hair cells and also of the auditory efferent system (outer hair cells).[23]

All or nearly all outer hair cells are affected with the progression of AN, leading to the absence of CM and OAE. This may occur in up to 30% of the patients with AN and that's the reason why absent OAE is not an exclusion criteria for the diagnosis of AN.[8,24]

CM testing is another way for checking cochlear function and integrity. This is an alternating current potential in response to an acoustic stimulation and reflects the movement of the basilar membrane. This is a preneural activity taking place before the synapse of hair cells with the auditory nerve terminals, i.e. before the wave I of BAER.[28]

In a way, the function of outer hair cells and the basilar membrane is also assessed by CM, making it crucial for the differential diagnosis of AN. As described, CM testing is also relevant in the absence of OAE.[8,24]

The presence of CM in BAER testing is included in some neonatal auditory screening programs, such as the Newborn Hearing Screening Programme, looking for cochlear pathologies, such as AN.[24]

It is known that outer hair cells are cochlear primary amplifiers and may help in the modulation of the sensitivity of inner hair cells. OHC's dysfunction leads to moderate hearing impairment (~50 dB). Apart from some degree of sound amplification, these patients need favourable acoustic environments (in silence, with no competing noises) in order to achieve satisfactory auditory performance.[25]

Patients with IHC disorders usually present with severe to profound hearing impairment. Speech intelligibility, as well as individual speech development will depend on the level of hearing impairment, on age of symptom onset (pre or post-lingual) and on time of auditory privation. Speech/sound discrimination in noise is frequently affected, as well as auditory processing.[25]

Present CM was found in 27 (79%) of our patients and absent OAE and BAER with present CM (OAE- BAER- CM+) was found in 23 patients (67%), showing some degree of cochlear integrity, making diagnosis of AN more difficult for non-specialized medical team. A classical OAE+ PEATE- situation is not always found in a patient with suspected AN, in line with literature.

Vocal discrimination is usually affected in patients with auditory neuropathy.[21-23] Speech development is clearly disrupted in patients with congenital hearing impairment. In our group, 61.6% of the patients with AN presented with poor speech quality and only 17.5% of the patients presented with acceptable development, which may be related to the fact that many of these patients presented with congenital hearing impairment.

Further studies will improve our understanding of AN. This manuscript is part of a project involving clinical, genetic and therapeutic aspects of AN, including cochlear implantation as well as other forms of rehabilitation and further studies will follow.

Genetic mapping of new mutations has been performed in the 49 initially selected patients, as well as other mutations already described as being associated with hearing impairment and auditory neuropathy (connexin 26 and 30

mutations, mutations in OTOF and PJVAC genes and also whole-genome sequencing). Further results and scientific conclusions are to be expected. As genetic assessment is more time-consuming and involves higher costs, mainly in our reality, this information is not yet available for publication.

Auditory neuropathy shows a wide range of mild to severe abnormalities of the auditory pathway, affecting neurological development, oral communication and language.

CONCLUSION

This was a case-study and therefore the conclusions regard the group of patients included in the study and may not be extrapolated to the entire population of patients with auditory neuropathy. Apart from what has been described, auditory neuropathy shows a wide clinical heterogeneity.

Most patients (80%) in our group presented with a congenital disorder and/or with CM. Most of our patients (91%) presented with significant hearing impairment and half of the patients (53%) with severe-to-profound hearing impairment.

Auditory neuropathy is still challenging as regards diagnosis and therapeutic approach, showing a wide range of abnormalities that may lead from mild to severe disorders in auditory pathway.

HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to the regulations established by the Research Ethics Committee and to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

FINANCIAL SUPPORT

The authors declare that there was no financial support in writing this manuscript.

This manuscript is part of a PhD project, which has been financed by the CAPES (*Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*, Health Minister, Brazil). The authors wish to acknowledge the institutional support of the CNPq (*Conselho Nacional de Desenvolvimento Científico e Tecnológico*).

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