■ ORIGINAL ARTICLE

Prevalence of Auditory Neuropathy: Prospective Study in a Tertiary-Care Center

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Objective: The primary goal of this study is to determine the frequency of onset of this disorder in our infant population. Its clinical importance is due, among other reasons, to the fact that idiopathic cases constitute false negatives in the auditory screening programmes based on the performance of otoacoustic emissions to all newborn children and brainstem auditory evoked response only to those presenting these risk factors, for which reason another goal is to establish the prevalence of these pure cases and the diagnostic delay they cause.
Patients and method: Prospective study of all newborn children at the Virgen de la Arrixaca Mother and Child Hospital (Murcia, Spain) in the period between June 1, 2000 and June 30, 2006.
Results: Our screening programme, with a coverage of 95.68%, detected 114 patients with unilateral or bilateral sensorineural hearing loss, with 6 presenting hearing loss attributable to auditory neuropathy.
Conclusions: The estimated prevalence of auditory neuropathy in our infant population turned out to be 1.406 for every 10 000 children, ie 5.26% of all sensorineural hearing loss diagnosed. Another significant finding was the delay in diagnosis, since the mean age at the moment of diagnosis was of 11.5 months, mainly due to idiopathic cases not detected during neonatal screening. Two clear conclusions can be inferred from these data: *a)* auditory neuropathy does not constitute an extraordinarily rare disorder, and *b)* idiopathic cases constitute false negatives in the universal auditory screening programmes based on the performance of otoacoustic emissions, which habitually leads to a delay in diagnosis and treatment.

Key words: Auditory neuropathy. Prevalence. Screening.

Prevalencia de la neuropatía auditiva: estudio prospectivo en un hospital de tercer nivel
Objetivo: El objetivo principal de este estudio es determinar la frecuencia de aparición de este trastorno en nuestra población infantil. Su importancia clínica se debe, entre otros motivos, a que sus casos idiopáticos son falsos negativos de los programas de cribado auditivo basados en la realización de otoemisiones acústicas a todos los recién nacidos y potenciales evocados auditivos de tronco cerebral sólo de los que presentan dichos factores de riesgo, por lo que otro objetivo es la prevalencia de estos casos puros y el retraso diagnóstico que ocasionan.
Pacientes y método: Estudio prospectivo de todos los recién nacidos del Hospital Materno-Infantil Virgen de la Arrixaca (Murcia) en el período comprendido entre el 1 de junio del 2000 y el 30 de junio del 2006.
Resultados: Nuestro programa de cribado, con un índice de cobertura del 95,68 %, detectó a 114 niños con hipoacusia neurosensorial unilateral o bilateral, de los que 6 presentaron una hipoacusia neurosensorial atribuible a la neuropatía auditiva.
Conclusiones: La prevalencia estimada de la neuropatía auditiva en nuestra población infantil resultó ser de 1,406 cada 10.000 niños, es decir, un 5,26 % de todas las hipoacusias neurosensoriales diagnosticadas. Otro dato relevante es el retraso diagnóstico, ya que la media de edad al momento del diagnóstico fue de 11,5 meses, fundamentalmente por los casos idiopáticos que pasaron el cribado neonatal. De estos datos podemos deducir 2 claras conclusiones: *a)* la neuropatía auditiva no es un trastorno extraordinariamente raro, y *b)* los casos idiopáticos son falsos negativos de los programas de cribado auditivo universal basados en la realización de otoemisiones acústicas, lo que habitualmente conduce a un retraso diagnóstico y, por lo tanto, terapéutico.

Palabras claves: Neuropatía auditiva. Prevalencia. Cribado.

INTRODUCTION

The development of electro-physiological methods for detecting otoacoustic emissions and their application, mainly in programmes for early deafness detection, allowed Starr's group[1,2] to identify a new audiological entity known as auditory neuropathy.

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It is currently known as auditory or discordant neuropathy,[3,4] and is defined by 3 basic characteristics: *a)* the presence, either now or at some other time, of otoacoustic emissions indicating a conserved function of the external ciliate cells (ECC); *b)* absent or notably altered brainstem evoked response audiometry, demonstrating a disorder localized in the VIII pair or in the brainstem; and *c)* a normal tympanogram with absence of stapedial reflexes, thus discarding a dysfunction of the middle ear that would alter the otoacoustic emissions. Along with these main characteristics, these patients also show conserved cochlear microphonics, in the absence of the action potential in the electrocochleogram and are particularly noteworthy for their highly impaired perception of language, above all in noisy environments, in contrast on occasions with tonal audiometric thresholds that are not as deteriorated.

The exact location of the injury is currently still unknown, and one cannot determine with any precision if it is a cochlear or retro-cochlear injury owing to a lack of methods allowing for the determination of the functional state of the internal ciliate cells (ICC), and their synaptic bonds with the auditory nerve fibres. Damage can be found in the internal ciliate cells, in the synaptic bonds between these cells and the dendrites of the afferent nerve fibres, in the neurons of the spiral node on the nerve stem of the VIII pair itself, while the function of the external ciliate cells is retained intact.[6,7] What does seem clear is that, at any of these levels, dys-synchronization is produced in the transmission of the auditory impulse nerve.

Epidemiologically, studies on the prevalence of this condition, mainly in the United States and Hong Kong, have been carried out retrospectively on a series of patients with risk factors for hearing loss or with already established sensorineural hearing loss of between 3% and 11%.

From an aetiological viewpoint, the causes are very varied. During the initial years, in most of the cases described, the patient's hearing condition was one more symptom within a motor-sensory peripheral neuropathy.[2,6-9] At the present time, it is common to find publications on patients who suffered foetal distress or a toxic-metabolic alteration during the pre-natal period, with hyperbilirubinaemia[7,10,11] warranting a special mention. Genetic studies have allowed for the detection of various genes implicated in the development of some cases of auditory neuropathy and open the possibility of future gene therapy, although at the moment the use of this information is limited to eugenetic advice for relatives and family members.[12-14]

PATIENTS AND METHOD

A prospective study was performed between June 1, 2000, and June 30, 2006 at the Infant Ear, Nose and Throat Department of the "Virgen de la Arrixaca" Children's and Maternity Hospital (Murcia, Spain) with the aim of identifying all children suffering from auditory neuropathy. The study, forming part of our programme for the early detection of hearing difficulties, included all children born in our hospital as well as those referred for study from other centres.

For all the children entering our universal hearing screening programme, demographic details were taken on gender, age, family, and personal history, and the following tests were carried out: general paediatric, neurological, and ENT examination, transitory otoacoustic emissions, undertaken by nurses using a Eurocheck or an ILO 88, and tympanometry recorded using a GSI 37 paediatric tympanometer in the first 48-72 hours of life. During the first 3 months, newborn babies with hearing loss risk factors (as defined by the Commission for Early Detection of Hearing Loss [CODEPEH in its Spanish acronym])[8] are studied with BEAP, undertaken by the Neuro-Physiological Service and/or auditory steady state evoked response (ssER) performed by ENT specialists from the children's section using a GSI Audera device; these later tests were performed from December 2005 on, after this equipment was acquired. Once the sensorineural hearing loss had been diagnosed, various tests were performed, including computerized tomography and magnetic resonance of both ears, cerebellopontine, and cerebral angles; in addition, blood samples were taken from the patients and their parents for genetic tests on the family.

Otoacoustic Emissions Registered on ILO 88 Equipment

With a stimulus intensity of 86 dB SPL, 260 stimuli were averaged using an analysis time of 20 ms. The presence of transitory otoacoustic emissions was considered normal in a period lasting between 2.5 and 20 ms after the stimulus, determined to be when the response was 4 dB higher than the background noise and its reproducibility was >75% in at least 3 tested frequencies.

Auditory Steady State Evoked Responses

These were obtained on a GSI Audera device containing specialist hardware connected to a laptop. The system operates using 32-bit software and a built-in patient database. Standard ASSR signals were at 250, 500, 750, 1000, 1500, 2000, 3000, 4000, and 6000 Hz, with simultaneous AM/FM modulation and 100% modulation depth. The intensity of the stimulus was varied seeking a threshold between –10 and 120 dB.

RESULTS

Since we began the universal hearing screening programme in 2000, out of the 44 592 children born in our hospital, screening has been conducted on 42 667, a coverage of 95.68%. Of all these cases, 114 children were diagnosed with sensorineural hearing loss and the affliction was bilateral in 97 of these, and unilateral in 17. Over these 6 years, the cases of auditory neuropathy diagnosed have been 6, 4 boys and 2 girls, which translates to a prevalence of 1.406 children every 10 000 births in our hospital, and 5.26% of the cases of sensorineural hearing loss diagnosed, a figure which rises to 6.18% if we consider only bilateral

cases. Table 1 presents these data and the cases are described in detail according to the level of hearing loss in Figure 1; in all cases it can be seen that auditory neuropathy was bilateral and severe. Table 2 presents the clinical and epidemiological details of the 6 cases and it can be concluded that our programme achieved early detection (μ=3.5 months) in cases which showed a hearing loss risk factor (cases 3 and 5) but not in the rest of the cases (μ=15.5 months). Case 3 was a very premature baby that we saw during its time in the Paediatric Intensive Care Unit with dyspnoea due to hyaline membrane disease and hyperbilirubinaemia which reached a maximum of 20 mg/dL and required phototherapy and a complete blood transfusion, while case number 5 was a brother of case number 1, who had been diagnosed 2 years earlier with congenital auditory neuropathy as a homozygote with mutation Q829X of the otoferlin gene, with the parents as heterozygote carriers (gene *OTOF*, Locus DFNB9 en the short arm of chromosome 2); the results of the genetic study confirming this are still pending. On the other hand, the 4 remaining cases were diagnosed late: in case 4, the delay was due to the fact that they child was born and observed in a different hospital, in which no screening process was in operation and was later referred to our hospital when hearing loss was suspected; in the cases of patients number 1, 2, and 6, who did not show any risk factors for hearing loss, the delay in the diagnosis was due to 1 of the flaws in using otoacoustic emissions as a screening test, since the result of the test is normal in cases of auditory neuropathy and the patients passed the test. Case 1 was initially considered to be of unknown aetiology, until the results of the genetic study were received, showing the mutation of the *OTOF* gene mentioned above. In cases 2 and 6, the genetic studies showed an absence of mutations in the genes normally implicated in hearing loss and are currently under investigation without any known cause. Therefore, the aetiologies involved are numerous and, in 50% of the cases in our series, they were initially found to be unknown. The audiological study showed profound bilateral sensorineural hearing loss with positive otoacoustic emissions in both ears (reproducibility >75% in all of them) and normal tympanograms (Figures 2 and 3).

DISCUSSION

At the beginning of the nineteen-eighties, some authors described a series of cases which showed paradoxical

Table 1. Coverage Data for the Neonatal Screening Programme for Hearing Loss and Sensorineural Problems Diagnosed in the Period 2000-2006

	n	*%*
Newborn babies	44 592	100
Newborn babies screened	42 667	95.68
Bilateral sensorineural hearing loss	97	0.227
Unilateral sensorineural hearing loss	17	0.039
Sensorineural hearing loss	114	0.267
Auditory neuropathy	6	0.014

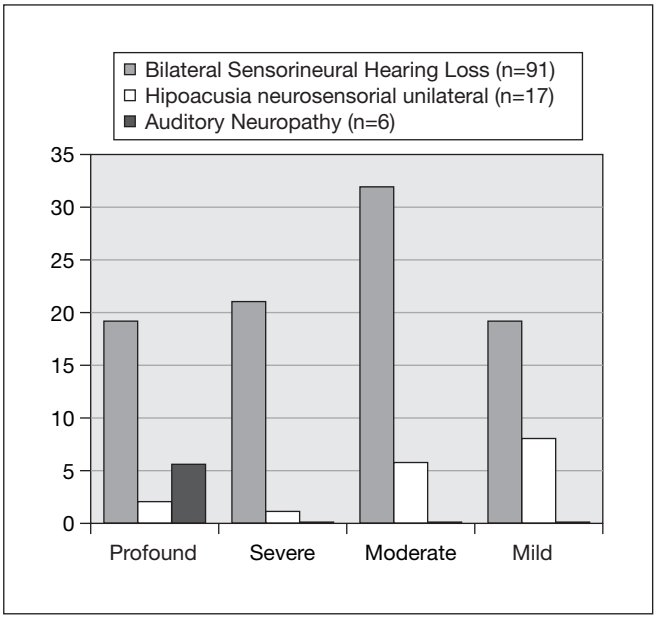

Figure 1. Graph showing the number of cases of bilateral and unilateral sensorineural hearing loss and auditory neuropathy detected in the period 2000-2006, classified by their severity.

Table 2. Clinical and Epidemiological Details of the 6 cases of Auditory Neuropathy*

Case, Year	*Gender*	*Age at Diagnosis*	*Aetiology*	*OAE*	*BEAP*	*Thresholds, dB*	*CT-MR*
1 (2002)	M	14 months	Congenital OTOF+	+	Anacusis	>130 dB	Normal
2 (2004)	F	13 months	Idiopathic	+	Anacusis	>105 dB	Normal
3 (2001)	M	4 months	Toxic metabolic, hyperbilirubinaemia, premature	+	Anacusis	>100 dB	Normal
4 (2002)	M	14 months	Toxic metabolic, hyperbilirubinaemia	+	Very Severe	>100 dB	Normal
5 (2005)	M	3 months	Congenital? Brother of case 1	+	Anacusis	103.3 (LE); 105 (RE) dB	Normal
6 (2006)	F	21 months	Idiopathic	+	Anacusis	95 (LE); 105 (RE) dB	Normal

*RE indicates right ear; LE, left ear.
In the first 4 cases, the thresholds were determined by BEAP, whereas in cases 5 and 6 these were calculated by the steady state potentials with the mean at 500, 1000, and 2000 Hz.

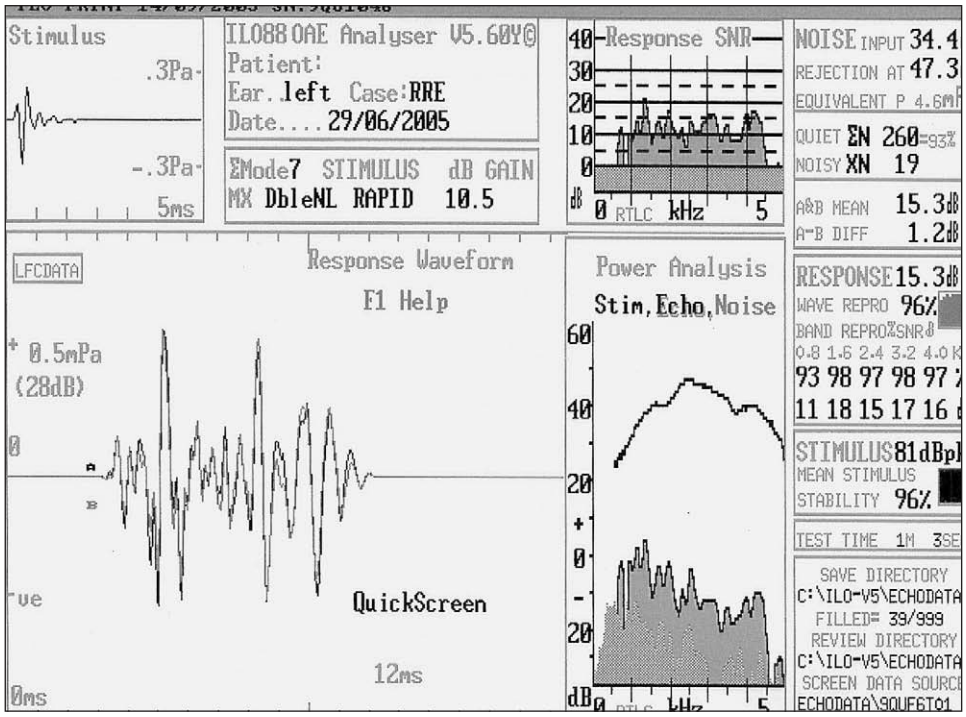

Figure 2. Register of positive transitory otoacoustic emissions in the left ear of case number 5, with a reproducibility and stability of 96%.

audiological results, with an absence of BEAP, highly impaired verbal discrimination and audiometric tones with normal thresholds or with moderate hearing loss; these authors considered that the origin came from a possible dual cochlear and troncoencephalic lesion.[15] However, it was necessary to wait until halfway through the nineties, when the clinical use of otoacoustic emissions became commonplace, for the Starr[1,2] group to describe auditory neuropathy in a series of 10 cases (5 adults and 5 children). Berlin et al,[3,4] at the beginning of the 21st century, considering a synchronization deficit in the transmission of the auditory nerve impulse as the most coherent theory explaining this pathogeny, complemented the term neuropathy with *auditory dyssynchrony*.

This can now be recognized when the 3 main characteristics are shown: positive otoacoustic emissions (or at least positive in the past, as in some cases they can disappear over time or after using auditory prostheses); absent or highly altered BEAP; and the absence of muscle reflexes in the middle ear.[2,4] To these characteristics we must add the fact that these patients present highly impaired verbal discrimination in noisy environments and on many occasions this does not correspond to the audiometric tonal thresholds which are not so badly deteriorated.

Epidemiologically, the data relative on incidence vary from one series to another; in series of patients with sensorineural hearing loss, it ranges between 3% and 11%. In 1999, Rance et al[10] obtained results showing that 0.23% of children with familial or neonatal risk factors for hearing loss and 11.09% of those with permanent sensorineural hearing loss had auditory neuropathy. Later, in 2000, Berlin et al, and, in 2002, Madden et al[11,12] obtained similar results in their tests on children with permanent hearing loss and, finally, Lee et al[16] in 2001, and Tang Tang et al[17] in 2004 performed 2 studies at deaf schools in Hong Kong and respectively obtained 3% and 2.44% of children with auditory neuropathy. It is very likely that the incidence will increase in future, due to the reduction in the mortality rate among premature and low birth weight babies presenting important auditory neuropathy risk factors.

In the years following its description, this clinical entity was described as an early manifestation of certain motor-sensory peripheral polyneuropathies such as Type I Charcot-Marie-Tooth disease or multiple sclerosis.[2,6,9] The latter association was what led to the hypothesis of a myelinization of the auditory fibres which would lead to an asynchrony in the transmission of the auditory impulse nerve in the afferent portion of the VIII pair between the internal ciliate cells ICC and the cochlear neurons.

This neural-based pathogenic model proposed in 1991[18] was to find support in post mortem histological studies[19,20] performed on patients with these conditions that described the existence of an intact cochlea, degenerated VIII pair, and spiral ganglion, with a loss of myelin in the Type I afferent nerve fibres, as well as in experimental models with ouabain in gerbils where the destruction of Type I neurons is induced in the spiral ganglion due to the alteration of the Na-K ATP-ase pump.[21] In 2001, Starr[22] observed that 27% of his patients showed evidence of motor-sensory peripheral neuropathy. Alongside this model, there are experimental studies defending a possible cochlear origin for the ICC, based on the experimental studies performed on Bronx-Waltzer strain mice showing agenesia or dysgenesia of the ICC after inducing the selective destruction of the ICC with carboplatin or via hypoxia,[23] with results in the audiological tests similar to

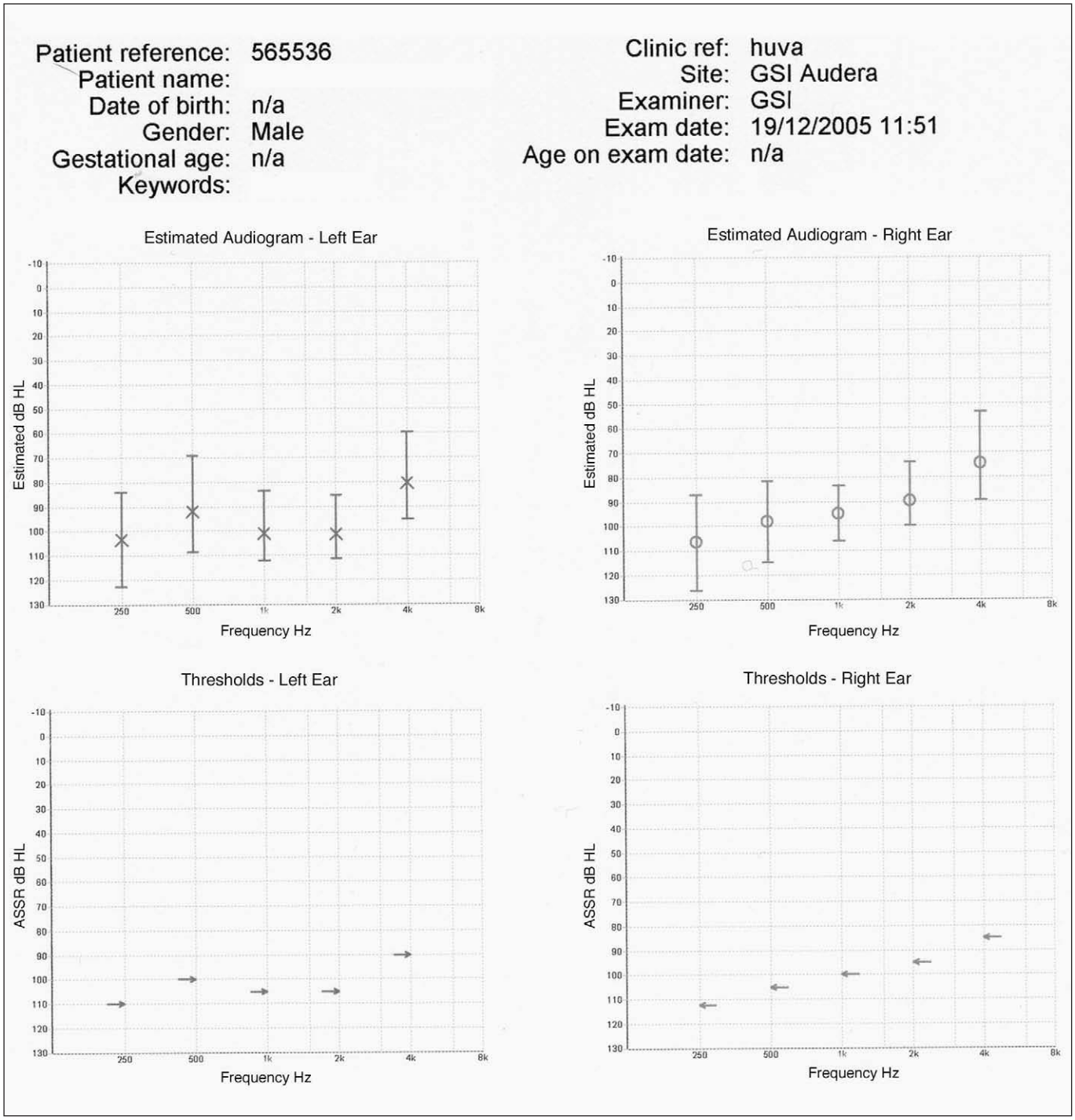

Figure 3. Register of steady state evoked response audiometry of case number 5, showing a mean threshold of 103.3 dB in the left ear and 100 dB in the right ear at 500, 1000, and 2000 Hz.

those of auditory neuropathy. So far, there has only been 1 study done on the temporal bones of premature babies arriving from the Neonatal Intensive Care Unit and it has shown selective damage to the ICC with a normal number of ECC.[24] In conclusion, and with respect to its pathogeny, the origin is still unknown and may be found on 1 or more of the following levels, respecting the function of the ECC: in the ICC of the cochlea, in the synaptic bonds between the ICC and the dendrites of afferent fibres, Type I neurons of the spiral ganglion, and the VIII pair itself, either due to demyelinization or to fibre lesions.

At the present time, the most numerous group of patients developing auditory neuropathy are those who have a history of toxic-metabolic illnesses, considered to be risk factors in neonatal hearing loss. Of these, hyperbilirubinaemia stands out significantly yet we must not overlook perinatal anoxia,

neonatal meningoencephalitis, excessively premature birth, ototoxic drugs, or mitochondrial disorders, which in many of these children occur simultaneously.[7,10-12,25-28] Until now, no directly proportional relationship has been established between the level of hearing loss and the concentration of bilirubin in the blood, although in 2001 Yilmaz et al[29] made a study of 22 children with indirect neonatal hyperbilirubinaemia, of whom 2 developed auditory neuropathy. They showed that these 2 patients were the only ones who had shown maximum levels of bilirubin in their blood >28 mg/dL. Despite these studies, there is still no explanation as to why, while jaundice appears in a high percentage of newborn babies (60% at term and 80% of those premature), only a few develop auditory neuropathy, even at concentrations <28 mg/dL as happens in our study where cases 3 and 4 reached maximum levels of 20 and 15 mg/dL, respectively. Because of this and to try to answer this last question, in 1998 Berlin[30] put forward the theory that these children have a genetic predisposition for hypersensitivity to bilirubin. Finally, there is a group of patients in whom we do not find any accompanying alteration nor any of the risk factors mentioned previously.[7,11] In some of these cases, considered idiopathic or pure, a genetic origin has been suspected due to the cases in twins and siblings[12]; it has been possible to show this origin in some patients presenting a non-syndromic autosomal recessive hereditary pattern due to different mutations of the otoferlin gene (*OTOF*), which would cause an altered *OTOF* protein and a loss of viability in the ICC or their synaptic stability.[13,14] Approximately 3.5% of the patients suffering from non-syndromic pre-lingual hearing loss in the Spanish population show mutations of this gene, some with symptoms of auditory neuropathy and some without. Thus, in 2003, Rodríguez-Ballesteros et al[13] collected data from a series of 37 patients with early sensorineural hearing loss and mutations of the *OTOF* gene, of which 11 showed symptoms of auditory neuropathy. In addition, they also revealed that a significant number of cases of neuropathy are characterized by having 2 mutations in the *OTOF* gene, unlike the rest of the cases with neuropathy. Although most of the non-syndromic cases occur as recessive forms, as in the previous case, a dominant non-syndromic form of auditory neuropathy was described[31] in 2004 at a new locus, AUNA 1, found in 13q14-21.

Clinically, except for those included among the neurological disorders already mentioned, these patients present normal general paediatric and ENT examinations, with the absence of pathological findings in the imaging tests. The audiological tests provide us with the diagnostic criteria for auditory neuropathy, fundamentally in the otoacoustic emissions, the BEAP and tympanometry with stapedial reflexes. These tests, applicable to all patients, can be complemented in adults and in children consenting to take them by tonal threshold audiometry and in children under 18, whenever possible, by audiometry of the canal. In some cases of auditory neuropathy (between 7% and 10%), patients had no other objective symptoms of deafness, apart from some absent or highly altered BEAP, and show such minimal hearing loss so low that some of these patients are able to develop normal speech.[3]

Otoacoustic emissions are positive, at least at the beginning, which implies the normal functioning of the ECC and an aerated middle ear, but these can become negative later on, without the cause for this being known, except when due to problems in the outer or middle ear.[25] This would hinder the identification of previously unknown cases of neuropathy, causing a mistaken diagnostic and therapeutic approach, as well as underestimating its prevalence. Some authors have observed that this negative reversal is produced after the placing of hearing aids, and consider that their origin in the over-stimulation of the ECC.[11,12] BEAP are found to be greatly altered or absent, with electro-cochleogram being reserved for cases in which auditory neuropathy is suspected and the otoacoustic emissions turn out be negative (diagnostic delays, mixed hearing losses with tympanus problems, etc) and in order to establish the differential diagnosis with other hearing losses localized in the brainstem, fundamentally immaturity of the auditory tract.[17] This is due to the fact that the electro-cochleogram allows for the determination of cochlear microphonic potential, which is the only constant data that indicates correct functioning of the ECC, even in the cases in which the otoacoustic emissions become negative.[25,26] However, the compound action potential is found to be missing, a sign of synchrony deficit in the nervous discharge between the ciliate cells and the nerve fibres.[4] Mason et al[26] consider promontory stimulation tests, although they are not necessary for the diagnosis of neuropathy, to have an important part to play in the evaluation of adult patients, albeit not in children. Impedanciometry gives normal or Jerger's Type A tympanometric curves with the absence of stapedial reflex. With respect to tonal audiometry, the great heterogeneity of the findings is worthy of mention, in terms of both the level of sensorineural hearing loss and in the audiometric configurations, and case reports have show gradual changes over time with both worsening and even improvement of the tonal thresholds, especially in cases with a history of hyperbilirubinaemia.[10,11,28] Thus, in a study by Madden et al,[11,12] it was possible to see that children with jaundice show a greater frequency of more profound initial hearing loss than children who did not suffer from this condition, but they show a greater tendency to present spontaneous recovery and often achieve better hearing than non-jaundice patients. This improvement could be seen up to 18 months of age, at which time the thresholds become stable, and for these authors this is valuable information in order to know the correct moment to place a cochlear implant in patients with hyperbilirubinaemia. On the other hand, those cases which had a genetic origin did not show a spontaneous improvement. With respect to logoaudiometry, there is poor verbal discrimination, disproportionately worse than their tonal thresholds would indicate and worse than children with cochlear hearing loss of the same intensity and the same age.[1,2,7,10,14]

At the present time, the majority of the screening programmes for hearing loss are based on the determination of otoacoustic emissions in newborn babies, due to the fact that this system is cheap, simple and painless to perform, complemented by BEAP in subjects presenting hearing loss

risk factors.[11,27] What is achieved with these programmes is an early diagnosis and an adequate therapeutic management of hearing loss, including those cases of auditory neuropathy with hearing loss risk factors, but they do not avoid the false negative findings that appear in idiopathic cases of auditory neuropathy (in our series, 50% of all cases), who pass through the screening despite suffering from an alteration in the synchrony of the neural transmission of the auditory stimulus with the corresponding hearing loss, and months pass before the parents detect any hearing difficulties in their children,[7] as happened in 4 of our cases, and the BEAP are then performed. In the same way, if the study were based solely on the handling of the BEAP, there would be a percentage of children with abnormal BEAP who would show normal otoacoustic emissions and would therefore not respond well to treatment with hearing aids, delaying a more appropriate diagnosis and therapeutic approach in such cases.

In conclusion, it must be pointed out, first of all, that auditory neuropathy is under constant investigation and its prevalence shows it is not extremely rare and represents a significant percentage of patients with sensorineural hearing loss, for which reason it must be considered in the differential diagnosis of this condition; secondly, diagnostic delays in the cases of idiopathic auditory neuropathy due to screening programmes based only on the study of otoacoustic emissions makes this even clearer. Our experience has helped us propose modifications to our programme, for example having all children tested with tympanometry and stapedial reflex, because, even though they may have positive otoacoustic emissions, the absence of reflexes with a normal tympanogram would lead us to suspect hearing loss, with subsequent performance of the BEAP (and/or ssEAP) tests and the early diagnosis of these idiopathic cases. Taking into account cost-benefit analysis, we do not believe in programmes based on the execution of BEAP tests on all children, as it is very expensive and difficult to implement in large-capacity children's and maternity hospitals.

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