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Auditory neuropathy: a report on three cases with early onsets and major neonatal illnesses

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Abstract

We report 3 children without any brainstem auditory evoked potential (BAEP) neural component who all retained isolated cochlear microphonic potentials as well as click-evoked otoacoustic emissions. Two of them demonstrated only moderately impaired audiometric thresholds. These features correspond to a peculiar pattern of auditory dysfunction recently coined 'auditory neuropathy'. In contrast with the published previous cases of auditory neuropathy presenting with an acquired hearing deficit as children or young adults, all 3 children had a history of major neonatal illness and the auditory neuropathy was already demonstrated in the first months of their lives.
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1. Introduction

The aim of the present paper is to report 3 new cases of a rather exceptional form of auditory dysfunction that is characterized by absent BAEPs with evidence of preserved cochlear outer hair cell function in the form of preserved cochlear microphonic potential and evoked otoacoustic emissions. This peculiar pattern of results from auditory physiological testing has recently been labelled 'auditory neuropathy' (Sininger et al., 1995). Ten such cases have recently been brought together from different North American laboratories (Starr et al., 1996). These subjects presented as children or young adults with an acquired hearing loss and several of them developed signs or symptoms of a peripheral neuropathy in the following years (Sininger et al., 1995; Starr et al., 1996). In contrast with the 10 subjects previously published as auditory neuropathy cases, the 3 patients reported here went through major neonatal health problems and the results of physiological testing already indicated a pattern of auditory neuropathy in the first few months of their lives.

2. Patients and methods

2.1. Patients

The 3 patients reported here shared the same major anomaly of their click-evoked BAEPs: no neural component could be identified, although they exhibited a prominent early fast oscillation identified as an isolated microphonic potential.

2.2. Case reports

Patient 1 was first seen at 2 months of life. She was the second born twin at an estimated post-conceptional age of 28 weeks. She went through a severe respiratory distress syndrome complicated by persistent pulmonary hypertension and bronchodysplasia. At day 11, a haemolytic hyperbilirubinaemia (maximum blood level 20.8 mg/dl) followed a blood transfusion and prompted an exchange

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transfusion. Her neurological status was abnormal (generalized hypotonia accompanying stereotyped repetitive movements) and despite gradual improvement, a mild global psycho-motor retardation was still present when last seen at 4 years of age. Two cerebral MRI scans performed at 3 months and 1 year of age were normal.

Patient 2 was born with a birthweight of 1200 gm at an estimated post conceptional age of 30 weeks, after a twin pregnancy. He had to be intubated for hyaline membrane disease, and was hospitalized several times for recurrent pulmonary problems. At 4 months he developed a pulmonary infection and was given a 10 day course of antibiotic therapy of daily amoxicillin 4×200 mg and clavulinic acid 4×20 mg; oxacilline 3×150 mg; erythromycin 3×40 mg. He was referred to the Evoked Potentials Laboratory at 1 year of age, because of insufficient reactivity to sound.

Patient 3 was born after an uneventful pregnancy of normal duration. Her neonatal examination was normal, and her first 3 days of life were uneventful until she was found lethargic, hypotonic and hypothermic (35.7°C). In the following hours, she developed several brief episodes of hypertonia of the 4 limbs and jaw accompanied by tachycardia. These episodes were interpreted as convulsive manifestations. The diagnostic work-up revealed a metabolic acidosis (arterial lactic acid level oscillating between 3.9 and 7.1 mEq/l). A diagnosis of deficit in the activity of the Cytochrome C Oxydase was reached from skin and muscle biopsy specimens. This deficit was attributed to a non-inherited mutation of the mitochondrial DNA. Two cerebral MRI examinations performed at 5 days and 16 months of age were normal. She was referred to the Evoked Potentials Laboratory at 4 and again at 21 months of age.

With the exception of patient 2, none of the infants was exposed to antibiotics and none of the family histories revealed any neurological or otological disease.

2.3. Audiological assessment

2.3.1. Middle ear function

Behavioural and physiological data from the 3 patients were gathered after normal middle ear status had been ascertained by otomicroscopic and tympanometric examinations.

2.3.2. Behavioural thresholds

Each child was repeatedly assessed by a team of experienced and skilled child audiologists using conditioned play audiometry and selecting for each child the most appropriate method for their age and capability.

2.3.3. Acoustic reflex

The presence of a contralateral acoustic reflex was sought by applying pure tone bursts at 250, 500, 1000, 2000 and 4000 Hz.

2.3.4. Sedation

All evoked potentials recordings were performed under sedation. The sedation regimen consisted of intrarectal pentobarbital and oral promazine. Patients were monitored for apneas using continuous intranasal capnography (Datex Normocap).

2.3.5. BAEP recordings

All recordings were performed in an electromagnetically and acoustically shielded booth. The BAEPs were obtained on a Nicolet Pathfinder Electrodiagnosis system running an in-house developed interactive software. Differential recordings were made between the vertex (non-inverting input) and the earlobe ipsilateral to the stimulated side (inverting input). The forehead served as ground. Bandpass analog filtering of the amplified signal was performed between 100 and 3000 Hz (−3 dB points, roll-off 12 dB/octave) before analog to digital conversion. Automatic artifact rejection based on a near amplifier saturation criterion (96%) was constantly applied.

Further technical details about BAEP recording conditions can be found in a previous report from our laboratory (Deltenre and Mansbach, 1995). For the patients reported here, BAEPs were also obtained using the Nicolet Tubal Insert Phone that introduces an acoustic delay of 0.9 ms between the stimulus electrical pulse and the actual sound delivery at the entrance of the ear canal, as a means to temporally separate the electromagnetic artifact from cochlear potentials.

In order to ensure discrimination between genuine auditory neurophysiological responses and artifactual signals, the click was systematically applied at high intensity to the 3 patients, with the sound delivery tube occluded by clamping in order to prevent the acoustic stimulus from reaching the ear canal, with all other stimulating and recording conditions unchanged (Fig. 1).

2.3.6. Otoacoustic emissions

Click-evoked otoacoustic emissions were recorded according to the method described by Bray and Kemp (1987), using an ILO88 system for stimulation, emission recording, averaging, reproductibility assessment and spectral analysis. The clicks (80 μs duration) were delivered in the non-linear mode at an intensity of 81 ± 4 dB SPL. An emission was considered to be present if the test-retest reproducibility was better than 50%, and if the comparison between the spectra of the averaged signal and of the residual noise demonstrated a signal to noise ratio greater than one.

3. Results

3.1. BAEPs

No standard neural component of the BAEP could be identified in all patients and their BAEPs were limited to

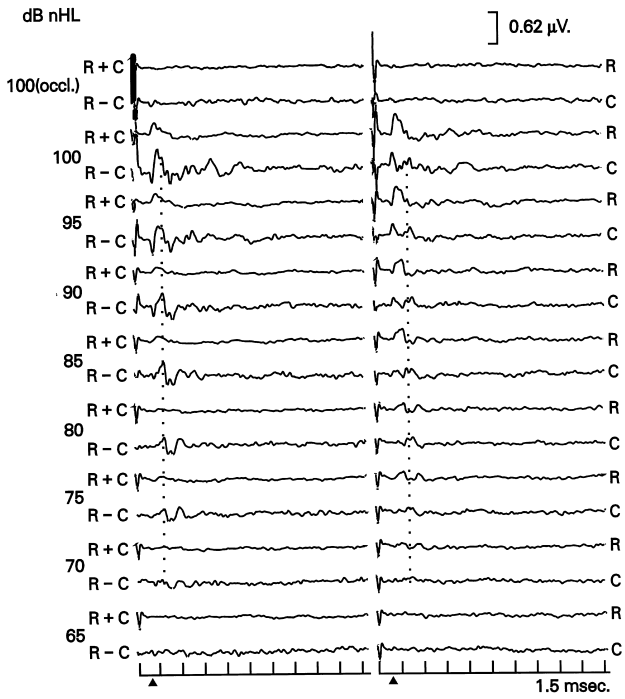

Fig. 1. BAEP recordings from the left ear of patient 1. In this and subsequent figures, the black triangle indicates the time of actual stimulus delivery at the entrance of the ear canal due to the use of an acoustic delay. The BAEPs evoked by single polarity clicks are restricted to an early oscillation that exhibits phase reversal with click polarity. This abnormal evoked activity is enhanced by subtraction of condensation from rarefaction response and incompletely cancelled by addition. The dotted vertical line drawn through the major peaks demonstrates the absence of latency increase at lower click intensities. When the tube delivering the sound is occluded by clamping (two upper rows), the response is no longer evoked.

an early and fast oscillation exhibiting complete phase reversal between rarefaction and condensation stimuli. The latency of these early components did not increase when click levels were reduced. Both ears produced similar responses in all 3 subjects. Fig. 1 illustrates typical responses as observed from the left ear of patient 1. No such pattern of responses was found in the many children that we have seen for audiological assessment, and who have proven to be profoundly or completely deaf. In such cases, neither the neural BAEP components nor the Cochlear Microphonic potential can be recorded. The 4 upper tracings from Fig. 1 demonstrate that the early response is evoked by the acoustic stimulus since it disappears when the sound delivering tube is occluded. The nature of this suspected isolated microphonic potential was assessed in all patients by adaptation studies that revealed (Fig. 2) the absence of any amplitude reduction of the early waveform when click rate was raised from 21.7 to 99.9 Hz, thus confirming a preneural origin, since in contrast with neural potentials, presynaptic potentials do not adapt (Sabin et al., 1987).

3.2. Click-evoked otoacoustic emissions

All 3 patients retained at least some portion of their click-evoked otoacoustic emissions with various extensions of the frequency spectrum (Fig. 3b, Fig. 4b, Fig. 5b).

3.3. Behavioural audiograms

The behavioural thresholds of patient 2 could not be determined because of his associated neurological and behavioural deficits. Reliable pure tone thresholds showing substantial residual functional hearing could be obtained in patients 1 and 3 (Fig. 3a, Fig. 4a, Fig. 5a).

3.4. Acoustic reflex

These measurements were performed in all 3 patients. No acoustic reflex could be elicited at maximal stimulation level (110 dB HL) from patients 1 and 2, whereas patient 3 produced acoustic reflexes from both ears, although with an elevated threshold (Fig. 5a).

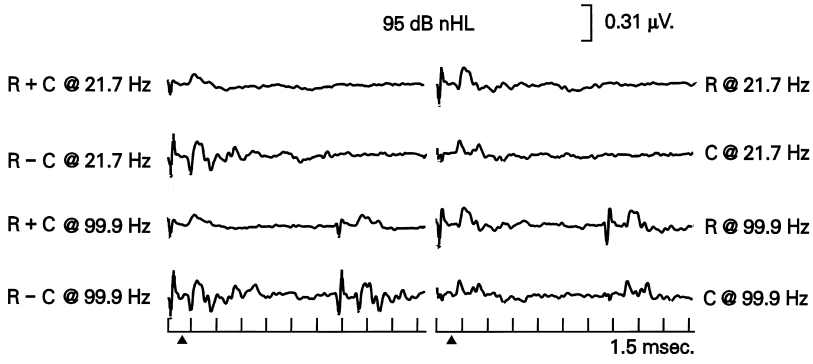

Fig. 2. Adaptation study from the left ear of patient 1. The preneural origin of the evoked activity is confirmed by the lack of any significant adaptation when the stimulation rate is increased from 21.7 to 99.9 Hz.

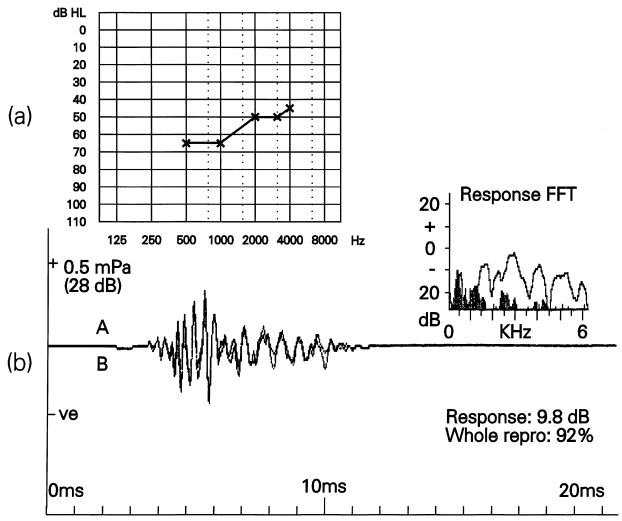

Fig. 3. Data from the left ear of patient 1. (a) The pure tone audiogram shows a moderate to moderately severe threshold elevation. (b) Preserved click-evoked otoacoustic emissions with a fairly wide frequency spectrum (the black spectrum is computed from the residual noise of the measurement, the white spectrum describes the energy distribution of the emission.)

4. Discussion

The 3 patients reported here represent instances of a rare auditory dysfunction characterized by the absence of all BAEP neural components with physiological evidence of preserved cochlear hair cell function in the form of cochlear microphonic potentials and click-evoked otoacoustic emissions. Moreover, patients 1 and 3 produced behavioural evidence of sound perception, albeit with an elevated threshold, and patient 3 retained acoustic reflexes.

Although the overall incidence is low, cases of absent BAEP despite quantifiable hearing have been repeatedly reported in the literature (Davis and Hirsh, 1979; Chisin et al., 1979; Worthington and Peters, 1980; Stockard and Stockard, 1983; Kraus et al., 1984; Starr et al., 1991). Davis and Hirsh (1979) estimated the incidence of such paradoxical findings to be about 0.5% in their population of children referred for suspicion of hearing loss. The peculiar pattern of preserved hair cell function without any recordable BAEP has been found to be consistently observed in patients with hearing loss following neonatal jaundice (Sohmer, 1989), and with the advent of the evoked otoacoustic emissions technique, cases with absent BAEP and preserved mechanical outer hair cell function are beginning to appear in the literature (Berlin et al.,

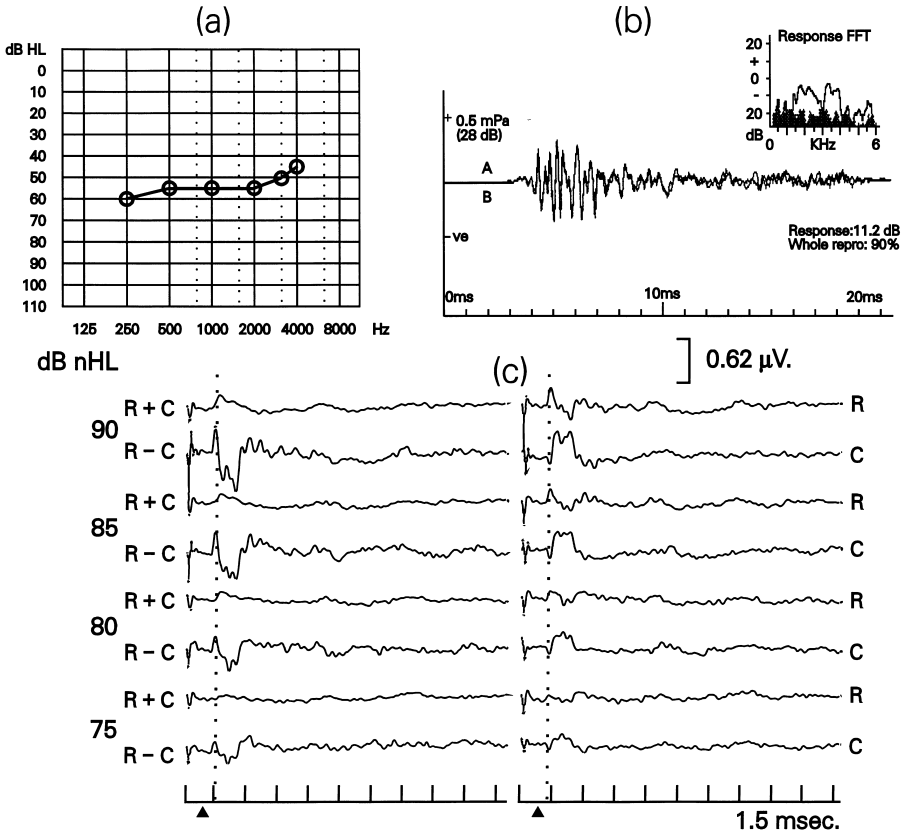

Fig. 4. Data from the right ear of patient 1, demonstrating the bilaterality of the findings. The audiogram (a), the otoacoustic emissions (b) and the BAEP recordings (c) show the same picture as that obtained from the opposite ear.

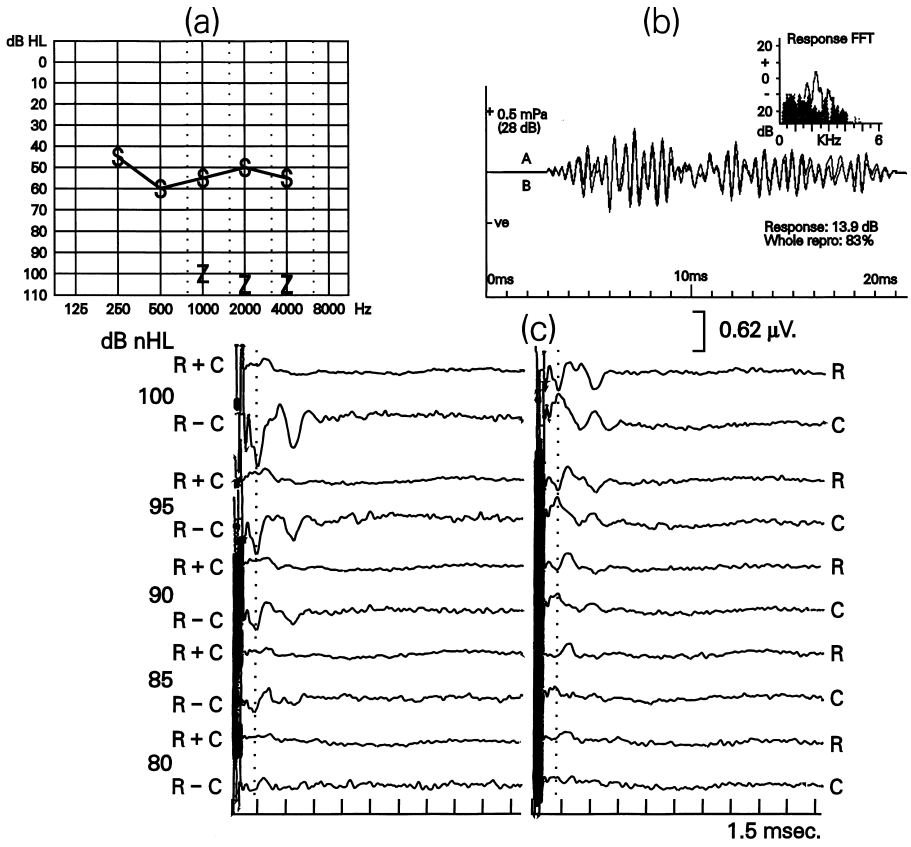

Fig. 5. Data from patient 3. (a) The pure tone free-field audiometric thresholds (S symbols) show a moderate to moderately severe elevation; the contralateral acoustic reflex thresholds (Z symbols) obtained after stimulation of the left ear are present at 1, 2 and 4 KHz, but could not be elicited at 250 and 500 Hz. (b) Preserved click-evoked otoacoustic emissions from the left ear with a moderately wide frequency spectrum. (c) BAEP recordings from the left ear after stimulation with a standard TDH transducer. The absence of acoustic delay helps to emphasize the short latency of the early cochlear microphonic response.

1993; Katona et al., 1993; Sininger et al., 1995). Following the extensive physiological and psychophysical evaluation of one such case by Starr et al. (1991), the concept of 'auditory neural synchrony disorder' later called 'auditory neuropathy' (Sininger et al., 1995) has been suggested as a broad diagnostic label. A pathophysiological model proposing defective synchronisation of the cochlear nerve action potentials has been conceived (Starr et al., 1991). According to the most recent review of the first 10 original cases of auditory neuropathy (Starr et al., 1996), the typical patient presents as a child or young adult with difficulty in understanding speech out of proportion with the hearing threshold impairment. No particular medical history is recorded, and several years after the onset of the hearing impairment, a peripheral neuropathy is likely to appear. The same authors suggest that it would seem appropriate to designate as auditory neuropathy cases, various patients retaining normal otoacoustic emissions despite absent or severely distorted BAEPs and hearing loss. They further hypothesize that kernicterus, uremia, diabetes and platinum compounds toxicity might induce such a picture. In these various circumstances, the brunt of the damage can be exerted to the neural elements or to the Inner Hair Cells (Dublin, 1986; Takeno et al., 1994).

It is therefore proposed that the 3 patients reported here represent such instances of auditory neuropathy secondary to their major neonatal illnesses as the auditory neuropathy pattern was already demonstrated in the first year of their lives.

To the best of our knowledge, this is the first time that a pattern of auditory neuropathy is reported in a case of mitochondrial enzymatic defect (patient 3), thus further expanding the spectrum of entities in which such a type of auditory impairment can be found.

These cases also raise a concern about the risk of false-negative findings when neonatal screening for hearing loss is restricted to otoacoustic emissions (Probst et al., 1991). Until more is known about the true incidence of such cases, it may be wise to record BAEPs in babies who have suffered a major illness in their neonatal period, even though their otoacoustic emissions are normal.

Finally, it should be noted that although the otoacoustic emissions and behavioural threshold data provided a major contribution to the delineation of the auditory disorder of these children, the BAEPs alone had already indicated the presence of a highly unusual situation. It is indeed the BAEP finding of an isolated microphonic potential that prompted further specific testing. The recognition of an

isolated microphonic potential from routine recordings has been greatly facilitated by the systematic use of both rarefaction and condensation clicks, a stimulation paradigm that has already been found to be highly valuable for the neurophysiological assessment of the auditory periphery and is therefore strongly recommended (Deltenre and Mansbach, 1995).

5. Note added in proof

While this manuscript was being processed, 4 instances of a unilateral auditory neuropathy pattern have been reported in otherwise healthy children (Konrádsson, 1996).

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References

Berlin, C.I., Hood, L.J., Cecola, R.P., Jackson, D.F. and Szabo, P. Does type I afferent neuron dysfunction reveal itself through lack of efferent suppression? Hear. Res., 1993, 65: 40–50.

Bray, P. and Kemp, D.T. An advanced cochlear echotechnique suitable for infant screening. Br. J. Audiol., 1987, 21: 191–204.

Chisin, R., Perlman, M. and Sohmer, H. Cochlear and brain stem responses in hearing loss following neonatal hyperbilirubinemia. Ann. Otol., 1979, 88: 352–357.

Davis, H. and Hirsh, S.K. A slow brainstem response for low-frequency audiometry. Audiology, 1979, 18: 445–461.

Deltenre, P. and Mansbach, A.L. Effects of click polarity on the brainstem auditory evoked potentials in cochlear hearing loss: a working hypothesis. Audiology, 1995, 34: 17–35.

Dublin, W. Central auditory pathology. Otolaryngol. Head Neck Surg., 1986, 95: 363–424.

Katona, G., Büki, B., Farkas, Z., Pytel, J., Simon-Nagy, E. and Hirschberg, J. Transitory evoked otoacoustic emissions (TEOAE) in a child with profound hearing loss. Int. J. Pediatr. Otorhinolaryngol., 1993, 26: 263–267.

Konrádsson, K.S. Bilaterally presented otoacoustic emissions in four children with profound idiopathic unilateral sensorineural hearing loss. Audiology, 1996, 35: 217–227.

Kraus, N., Özdamar, Ö., Stein, L. and Reed, N. Absent auditory brain stem response: peripheral hearing loss or brain stem dysfunction? Laryngoscope, 1984, 94: 400–406.

Probst, R., Lonsbury-Martin, B.L. and Martin, G.K. A review of otoacoustic emissions. J. Acoust. Soc. Am., 1991, 89: 2027–2067.

Sabin, H.I., Prasher, D., Bentivoglio, P. and Symon, L. Preservation of cochlear potentials in a deaf patient fifteen months after excision of an acoustic neuroma. Scand. Audiol., 1987, 16: 109–111.

Sininger, Y.S., Hood, L.J., Starr, A., Berlin, C.I. and Picton, T.W. Hearing loss due to auditory neuropathy. Audiol. Today, 1995, 7: 10–13.

Sohmer, H. Auditory nerve and brainstem responses (ABR): physiological bases and clinical uses. In: J.E. Desmedt (Ed.), Neuromonitoring in Surgery. Elsevier, Amsterdam, 1989, pp. 23–47.

Starr, A., McPherson, D., Patterson, J., Don, M., Luxford, W., Shannon, R., Sininger, Y., Tokanawa, L. and Waring, M. Absence of both auditory evoked potentials and auditory percepts dependent on timing cues. Brain, 1991, 114: 1157–1180.

Starr, A., Picton, T.W., Sininger, Y., Hood, L.J. and Berlin, C.I. Auditory neuropathy. Brain, 1996, 119: 741–753.

Stockard, J.E. and Stockard, J.J. Recording and analysing. In: E.J. Moore (Ed.), Bases of Auditory Brain-stem Evoked Responses, Ch. 10. Grune and Stratton, New York, 1983, pp. 255–286.

Takeno, S., Harrison, R.V., Ibrahim, D., Wake, M. and Mount, R.J. Cochlear function after selective inner hair cell degeneration induced by carboplatin. Hear. Res., 1994, 75: 93–102.

Worthington, D.W. and Peters, J.F. Quantifiable hearing and no ABR: paradox or error? Ear Hear., 1980, 5: 281–285.