Auditory maturation and congenital hearing loss in NICU infants

Saskia Coenraad

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Auditory maturation and congenital hearing loss in NICU infants

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Chapter 1

General introduction

The number of preterm births has increased over the past decades as a result of increasing maternal age and in vitro fertilization (1). At the same time the survival of preterm infants has increased due to advances in perinatal and neonatal care. For example, antenatal corticosteroids for women with threatened preterm delivery, high-frequency oscillatory ventilation and inhaled nitric oxide have now become standard therapy (1). Unfortunately, these improvements sometimes come at a price. Neonatal intensive care unit (NICU) survivors have an increased risk of neurodevelopmental impairment, such as cerebral palsy, cognitive delay, blindness and deafness (2). Infants admitted to the NICU have an increased risk of congenital (present at birth) and acquired hearing loss compared to infants admitted to the well-baby nursery (3). Multiple risk factors have been associated with congenital hearing loss (Table 1) (4). Many of these risk factors occur in daily NICU care. The increased knowledge of the etiology of congenital hearing loss has put the emphasis not only on treating, but also on preventing congenital hearing loss. For example, bilirubin serum levels are kept within a very strict range in NICU infants. While prevention may not always be possible, the increased awareness has resulted in earlier diagnosis and careful counseling. Between 2002 and 2006 the universal newborn hearing screening (UNHS) program was introduced in the Netherlands. This has resulted in earlier identification and referral of infants with congenital hearing loss. Several studies have shown that early and adequate intervention of infants with congenital hearing loss minimizes future problems with speech and language development (5-6). Treatment before the age of six months results in better speech and language development at school age.

Table 1

Risk indicators associated with permanent congenital, delayed-onset, or progressive hearing loss in childhood	
1	Caregiver concern regarding hearing, speech, language, or developmental delay
2	Family history of permanent childhood hearing loss
3	Neonatal intensive care of more than 5 days or any of the following regardless of length of stay: ECMO, assisted ventilation, exposure to ototoxic medications (gentamycin and tobramycin) or loop diuretics (furosemide/Lasix), and hyperbilirubinemia that requires exchange transfusion
4	In utero infections, such as CMV, herpes, rubella, syphilis, and toxoplasmosis
5	Craniofacial anomalies, including those that involve the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies
6	Physical findings, such as white forelock, that are associated with a syndrome known to include a sensorineural or permanent conductive hearing loss
7	Syndromes associated with hearing loss or progressive or late-onset hearing loss, such as neurofibromatosis, osteopetrosis, and Usher syndrome; other frequently identified syndromes include Waardenburg, Alport, Pendred, and Jervell and Lange-Nielson
8	Neurodegenerative disorders, such as Hunter syndrome, or sensory motor neuropathies, such as Friedreich ataxia and Charcot-Marie-Tooth syndrome
9	Culture-positive postnatal infections associated with sensorineural hearing loss, including confirmed bacterial and viral (especially herpes viruses and varicella) meningitis
10	Head trauma, especially basal skull/temporal bone fracture that requires hospitalization
11	Chemotherapy

In Table 1 the risk indicators of permanent congenital, delayed-onset, or progressive hearing loss in childhood, as defined by the 2007 JCIH position statement are listed.

Normal hearing function

Normal hearing requires proper functioning of the external ear, middle ear, inner ear (cochlea) and ascending auditory pathways in the brainstem (Figure 1).

Figure 1

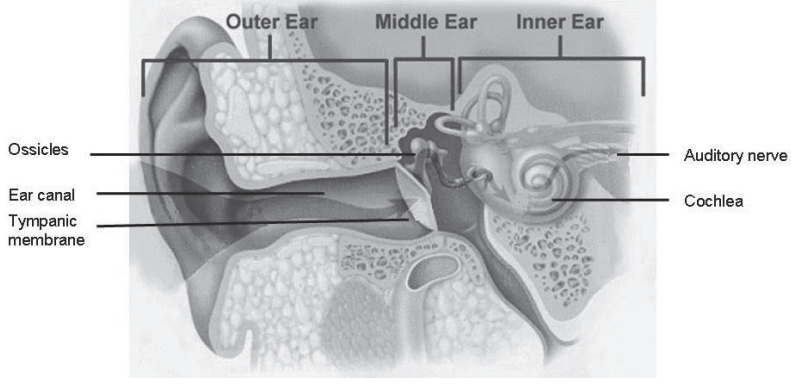

Figure 1 describes the anatomy of the human ear.

The external ear transports the sound pressure waves through the ear canal to the tympanic membrane. Vibration of the tympanic membrane and the ossicular chain amplifies the sound stimulus and transmits the signal to the cochlea. The cochlea is a spiralled, conical chamber of bone. The cochlea contains three fluid compartments, the scala tympani, scala vestibuli and scala media (Figure 2).

Figure 2

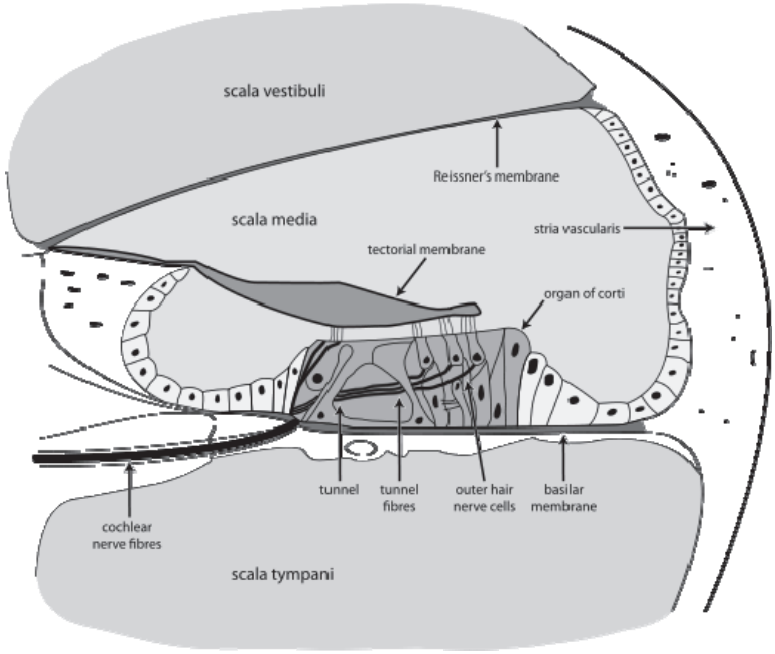

Figure 2 describes the anatomy of the cochlea.

The basilar membrane separates the scala tympani and scala media and is the base of the sensory cells within the cochlea. The scala tympani and scala vestibuli contain perilymph, the scala media contains endolymph. The perilymph and endolymph contain different electrical and chemical gradients. The organ of Corti is lined along the length of the cochlea and contains sensory epithelium. The sensory cells are arranged in one line of inner hair cells and three lines of outer hair cells. The tectorial membrane covers the hair cells in the organ of Corti. The basilar membrane and tectorial membrane are connected with each other through the outer and inner hair cells. Vibration of the basilar membrane and movement of the tectorial membrane results in deflection of the hair cells which transforms the fluid waves into nerve signals. Bending of the hair cells opens mechanosensitive channels that allow the influx of cations from the endolymph into the hair cell. In inner hair cells the depolarization triggers synaptic neurotransmission to afferent auditory neurons.

The afferent nerve signal travels through the auditory nerve and different levels of the brainstem until it reaches the auditory cortex in the brain (7). Outer hair cells are predominantly innervated by efferent neurons. The efferent system provides a feedback system from the brainstem to the cochlea. For example, it protects the cochlea from noise-induced injury. Outer hair cells generate unique forces that modify the organ of Corti and lead to frequency selective amplification of inner hair cell response.

Development and maturation of the human auditory pathway

To understand the mechanism behind congenital hearing loss, knowledge of normal embryologic development of the auditory system is essential. During the first trimester of pregnancy the basic structures develop at all levels of the auditory system i.e. the cochlea, brainstem and cortex. The cochlea develops from the otic placode, a thickening of the ectoderm on the outer surface of a developing embryo. The otic placode folds inwards forming a depression, then pinches off entirely from the surface forming a fluid-filled sac or vesicle (otic vesicle, otocyst). From the otic vesicle, branches are formed that generate an endolymphatic duct and sac from which the cochlea and vestibulum develop. The cochlear duct coils as it lengthens. Around the 9th week the organ of Corti appears. Development of the inner ear is paralleled by development of the cochlear nerve, which will ultimately transmit cochlear activity to the central auditory system. In return the efferent fibres provide a feedback system form the brainstem to the cochlea. The cochlear nerve cells also originate from the otic vesicle. The axons of the immature neurons extend towards the organ of Corti and towards the brainstem. Within the brainstem, all of the auditory centres and pathways are identifiable by the 7th to 8th foetal weeks. After this period the structures increase in size but retain the same basic configuration (8).

In the second trimester rapid maturation of the cochlea and cochlear nerve occurs. By the end of the second trimester the cochlea has a mature appearance, with the exception that synaptic terminals formed by efferent brainstem axons are smaller and less numerous than in the adult cochlea. The myelin formatting cells are present along the cochlear nerve at this stage, but myelin formation has not yet begun. The auditory nuclei in the brainstem increase rapidly in size during the second trimester. The efferent system, that protects the cochlea from noise-induced injury, has begun to exert a trophic influence (by means of neurotransmitter substances and hair cell contact) on the developing cochlea by mid-gestation (8). At the beginning of the third trimester the first myelination occurs in the cochlear nerve and the brainstem. Myelin formation is of great importance for rapid and synchronized nerve conduction. Movement of the foetus in response to sound occurs for the first time around 25 weeks gestation and becomes more consistent around 28 weeks. This is the time when in preterm infants a recordable auditory brainstem response (ABR) appears (8-10).

Final maturation of the auditory system continues from the perinatal period until six to twelve months of age (8). Full functional cochlear maturity is achieved a few weeks before term birth.

During the perinatal months rapid growth occurs in the brainstem. Auditory neurons reach about 50-60% of their adult size at time of birth. The axonal myelin density in the cochlear nerve and brainstem increase rapidly and become adult like by six to twelve months of age (8). In figure 3 a schematic overview of the embryologic development of the auditory system and ABR maturation is presented.

Figure 3

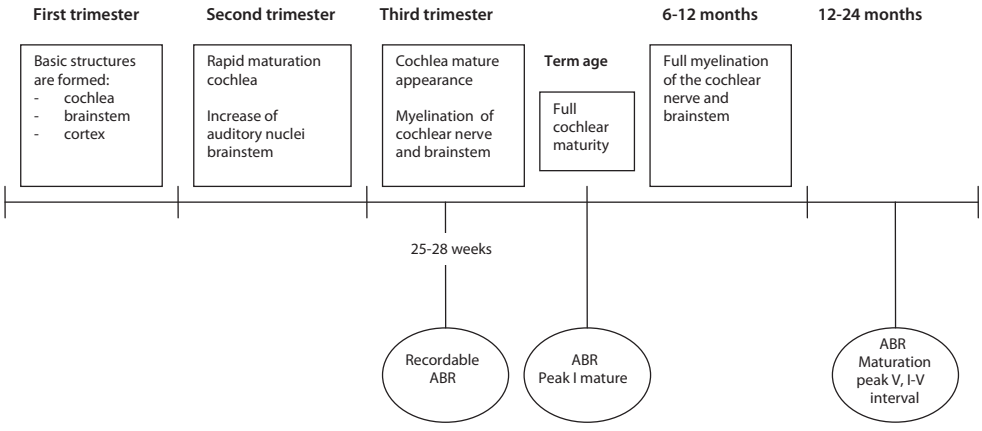

Figure 3 is a schematic overview of the embryologic development of the auditory system. The development of auditory brainstem response (ABR) measurement is also presented.

Types of hearing loss

Hearing loss may occur due to abnormal development or pathology in different parts of the auditory system. Two main types of hearing loss can be distinguished. A conductive hearing loss is located somewhere in the external or middle ear. A sensorineural hearing loss (SNHL) is located in the cochlea or the auditory pathway to the brain. A combination of both conductive and sensorineural hearing loss can also be found.

Table 2

Conductive hearing loss		Sensorineural hearing loss
Outer ear	*Middle ear*	*Inner ear*
Congenital atresia	Congenital atresia, ossicular chain malformation	Hereditary
Cerumen/debris	Otitis media	Congenital malformations
Exostosis	Otosclerosis	Infection: viral (CMV), bacterial (meningitis)
External otitis	Cholesteatoma	Ototoxic medication
	Tympanic membrane perforation	Noise trauma
	Temporal bone trauma	Trauma (noise, fracture)
	Glomus tumors	Autoimmune disease
		Tumors (meningeoma, acoustic neuroma)

Table 2 shows the most common causes of conductive and sensorineural hearing loss.

In infants, permanent hearing loss is usually of sensorineural origin, whereas temporary hearing loss is usually of conductive (middle ear effusion) origin. Table 2 shows the most common causes of different types of hearing loss at all ages. Some of these conditions are acquired, whereas others have a genetic origin. Morton et al. estimated the genetic and non-genetic causes of congenital hearing loss in the United States (Table 3) (11). They estimated that 65% of congenital hearing loss has a genetic origin. The genetic types of congenital hearing loss can be divided in syndromic and non-syndromic disorders. Examples of syndromic congenital hearing loss are Down's syndrome, CHARGE, Jervell Lange-Nielsen or Pendred's syndrome. The majority of non-syndromic congenital hearing loss is caused by a mutation in the GJB2 gene.

Table 3

Causes of deafness at birth		Incidence at birth
Genetic		
	Pendred's syndrome	3%
	GJB2 mutation	20%
	Syndromic	14%
	Non-syndromic	28%
Non genetic		
	Clinically apparent infection	10%
	Clinically unapparent infection	11%
	Other environmental causes	14%

Table 3 shows the estimated causes of deafness at birth as established by Morton CC, Nance WE. Newborn hearing screening--a silent revolution. N Engl J Med 2006;354(20):2151-64.

Congenital hearing loss

Infants admitted to the NICU have a relatively high incidence of perinatal complications and risk factors associated with congenital and acquired hearing loss (12). In the Netherlands the incidence of congenital hearing loss is 0.1% for the well-baby population and around 3.2% for NICU infants (13). The risk indicators for congenital hearing loss, as formulated by the Joint Committee on Infant Hearing (JCIH), include a large number of conditions that occur in daily NICU care (Table 1). Physicians are challenged among other things with the balance between optimizing the overall clinical condition of the infant, while trying to minimize the risk of congenital hearing loss.

Diagnosing hearing loss in infants

There are several different tests available to diagnose and evaluate hearing loss in infants. The challenge is to evaluate hearing without cooperation of the infant, which is required in conventional audiometry such as pure tone audiometry. The following tests can be used to diagnose hearing loss in infants: otoacoustic emission (OAE), tympanometry and auditory brainstem response (ABR) measurement.

Otoacoustic emissions

An otoacoustic emission is a low intensity sound, which is generated within the inner ear. These sounds are produced by the cochlea, most likely the outer hair cells, as a result of cochlear amplification. The mechanism behind cochlear amplification is the same hair-bundle mechanism that detects sound vibrations which actively "vibrates back" and thereby mechanically amplifies weak incoming sound. In the absence of external sound stimulation, the activity of the cochlear amplifier increases, leading to the spontaneous production of sound. Otoacoustic emissions can occur spontaneously, or as a result of an external sound stimulus.

OAEs measure only the peripheral auditory system, which includes the outer ear, middle ear, and cochlea. The response originates from the cochlea, but the middle and outer ear must be able to transmit the emitted sound to the recording microphone introduced in the ear canal.

OAEs are often used to screen hearing in infants and can partially estimate hearing sensitivity within a limited range. In general, the presence of an OAE suggests that hearing sensitivity should be below 30 dB nHL.

OAEs can also be used to differentiate between the sensory and neural components of sensorineural hearing loss. For example, in auditory neuropathy spectrum disorder (ANSD) transmission of sound from the cochlea to the brain is abnormal. ANSD is characterised by normal OAEs (outer hair cell function) and severe abnormalities on ABR measurement. The normal function of the outer hair cells, in combination with severe abnormalities on ABR measurement, indicates neural dysfunction.

Tympanometry

Tympanometry is an examination used to evaluate the mobility of the tympanic membrane and the ossicular chain. It describes the relation between the air pressure in the external ear and movement of the tympanic membrane and ossicular chain. A tympanogram provides information on the compliance of the middle ear, ear canal volume and middle ear pressure. In infants it is typically used to diagnose otitis media with effusion, which is a common cause of temporary conductive hearing loss.

Auditory Brainstem Response measurement

ABR measurement is the most important tool in diagnosing hearing impairment in infants. It provides an accurate evaluation of the type and degree of hearing loss.

Figure 4

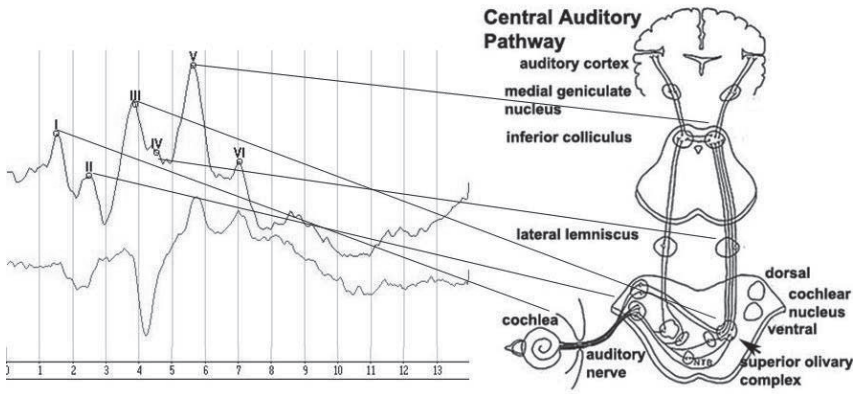

Figure 4 shows a typical ABR response wave recorded in an adult at our clinic. The response peaks are connected to their probable localization along the auditory pathway.

ABR peaks reflect the conduction of a neural signal as a result of a sound stimulus along the auditory nerve and different levels of the brainstem (Figure 4). It is generally agreed that peak I and II reflect the cochlea and auditory nerve (peripheral response) and that peaks III, IV, and V are generated more centrally, i.e. by brainstem structures. It is assumed that peak III reflects the ascending auditory pathway or the cochlear nuclei in the ventral acoustic striae. Peak V reflects activity towards the inferior colliculus, most likely the lateral lemniscus (14-17).

The ABR response in human development first appears around 25 weeks gestational age (9-10). This response matures during the first years of life, resulting in decreased latencies of most of the response peaks. In full term infants the peripheral response, reflected in peak I, is reported to show no signs of maturation or development as a function of age (9-10, 17-19). The central conduction time, reflected by I-V interval, is reported to mature (i.e. shorten) until 11 to 18 months (17) up to

three to five years of age (20). This maturation effect differs for preterm and term infants (9, 19, 21-22). Preterm infants are reported to have increased latencies compared to term infants up to two years of age (18).

The degree of hearing loss is estimated with the ABR response threshold. The response threshold is determined by the lowest level at which a response is found. Peak V has the highest amplitude and can be clearly identified near threshold level and is consequently used to identify the response threshold. The degree of hearing loss is generally agreed to be 10 dB below threshold level.

The type of hearing loss can be estimated from the latency-intensity curves. A conductive hearing loss is characterized by an elevated response threshold and increased peak latencies. Peak I latency, reflecting the peripheral response and further peaks latencies are equally increased. In case of sensorineural hearing loss elevated response thresholds are found in combination with normal peak latencies. A prolonged I-V interval is often used as a measure of delayed or abnormal auditory maturation. In these cases, as described earlier, the combination of OAE and ABR measurement is used to diagnose neurological pathology, such as ANSD. Absent or abnormal ABR results are found in combination with normal OAEs. This reflects normal cochlear (outer hair cell) activity, but abnormal transmission of sound from the cochlea to the brain.

In infants ABR latencies are age-dependent, therefore age-adjusted normal values are required. Fitting models are often used to provide normal values corrected for maturational changes. In very preterm infants interpreting the results of ABR measurement is a special challenge since various peaks of the ABR response are poorly detectable. The normal evaluation system based on age-adjusted normal values of peak latencies may not be sufficient. Amin et al. proposed a system that categorizes ABR waveform responses in infants younger than 32 weeks postconceptional age (23). This system can be used to evaluate the morphology of the ABR response, but it gives little detailed information on the functioning of the auditory system.

Neonatal hearing screening

Since 1965 the hearing of children in the Netherlands has been tested through a nation wide screening program aimed at early detection of hearing impairment. The 'Compact Amsterdam Pedo-Audiometric Screener' (CAPAS) or Ewing-test, which is a behavioral observation test, was used. This test had several disadvantages. First, the test could not be conducted before the age of nine months. Second, it could not be used in infants with developmental retardation or visual impairment. Third and fourth, it could not test the ears separately and predictive values for sensorineural hearing loss were low.

A new and improved test became available as part of the UNHS program in 2002. It was implemented in the Netherlands between 2002 and 2006. The aim of the UNHS is to identify a conductive or sensorineural hearing loss with an average hearing loss of at least 40 dB in one or both ears before the age of three months. Intervention and counseling are aimed to start before the age of six months in accordance with the screening guideline of the Joint Committee on Infant Hearing (JCIH)

to prevent future problems with speech and language development (4).
The screening procedures for the well-baby nursery and NICU infants are different in the Netherlands. Infants from the well-baby nursery are screened by a three-stage screening method. First a two-stage OAE screening is conducted in the first week of life. A failure on OAE screening is followed by automated auditory brainstem response (AABR) testing.
Infants admitted to the NICU longer than 24 hours undergo standard hearing screening by means of AABR (Figure 5). The first AABR screening is usually conducted upon discharge from the NICU. In case of unilateral or bilateral failure on AABR screening, AABR measurement should be repeated before the corrected age of six weeks.

Figure 5

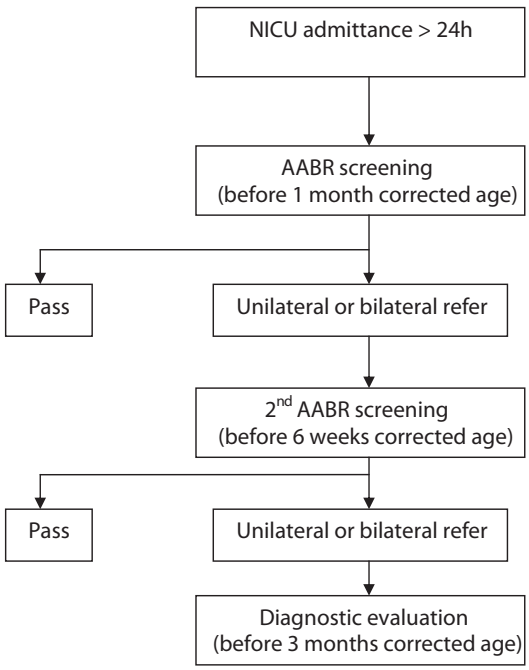

Figure 5 presents a schematic overview of the neonatal hearing screening in the Netherlands for infants admitted to the NICU > 24 hours.

The higher incidence of neural pathology, such as ANSD, in NICU infants has resulted in a screening program with AABR measurement. In infants from the well-baby nursery, cases of ANSD may be missed due to primary OAE screening. An infant who fails two (NICU) or three (well-baby clinic) unilateral or bilateral tests is referred to an audiologic centre for further diagnostic assessment. In our clinic, all infants are seen at the outpatient clinic by an experienced audiologist and otorhinolaryngologist. Diagnostic audiologic evaluation consists of ABR, OAE and tympanometry measurement to determine the type and degree of hearing loss and to start an adequate treatment.

Overall aim of the study

The main focus of this study was to identify the presence, type and course of hearing loss in NICU infants. First, to adequately diagnose hearing loss, age-adjusted normal values for ABR measurement are required. This is a special challenge since maturation of the auditory system is still in full progress during the perinatal period. Second, the course of hearing loss can chance over time. The degree and type of hearing loss are fundamental to the treatment and prognosis of hearing loss. Finally, to be able to prevent congenital hearing loss knowledge of the etiologic background is essential.

The outline of the thesis is as follows. In chapter two a fitting model is presented that describes age-dependent changes of ABR latencies in normal hearing infants. This model can be used to analyze ABR results in daily clinical practice. In chapter three the characteristic morphology of ABR measurement in very preterm infants is presented. Analysis is challenging since various peaks of the ABR response are often poorly detectable. We introduce an extended assessment system.

The remainder of this thesis focuses on a group of NICU infants who failed neonatal hearing screening between 2004 and 2009. In chapter four we studied the audiologic diagnoses and follow-up of NICU infants who failed neonatal hearing screening. In chapter five we present the prevalence of prolonged I-V interval as a measure of delayed auditory maturation and the correlation with ABR response threshold. In chapter six and seven we analyze the etiologic factors associated with auditory neuropathy spectrum disorder and sensorineural hearing loss respectively. Finally, in chapter eight and nine we present a general discussion and summary of our results.

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Chapter 2

Fitting model of ABR age-dependency in a clinical population of normal hearing children

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Abstract

The purpose of this study was to present a simple and powerful fitting model that describes age-dependent changes of auditory brainstem responses (ABR) in a clinical population of normal hearing children. A total of 175 children (younger than 200 weeks postconceptional age) were referred for audiologic assessment with normal ABR results. ABR parameters of normal hearing children between 2003 and 2008 were included. The results of the right ears recorded at 90 dB nHL were analyzed. A simple and accurate fitting model was formulated based on these data. A very similar age-dependent effect was found for peaks III and V, and I–III and I–V intervals; latencies decrease as postconceptional age increases. It shows that the total age-dependent effect will be completed after 1.5– 2 years. The age-dependent effect can be modelled by a relatively simple and accurate exponential function. This fitting model can be easily implemented to analyze ABR results of infants in daily clinical practice. We speculate about the underlying physiological processes.

Introduction

Auditory Brainstem Responses (ABR) were first reported by Jewett et al. (1) and also by Sohmer and Feinmesser (2). ABR response waves reflect the conduction of a neural signal as a result of a sound stimulus along the auditory nerve and different levels of the brainstem. Several authors studied the location of the waves (3-6). Most authors agree that wave I and II reflect the auditory nerve and cochlea (peripheral response) and that waves III, IV, and V are generated more centrally, i.e. by brain stem structures. It is assumed that wave III reflects the ascending auditory pathway or the cochlear nuclei in the ventral acoustic striae. Wave V reflects activity towards the inferior colliculus, most likely the lateral lemniscus.
The ABR response in human development first appears around 25 weeks gestational age (7-8). This response matures during the first years of life, resulting in decreased latencies of most of the response peaks. In full term infants the peripheral response, reflected in wave I, is reported to show no signs of maturation or development as a function of age (6, 9-11). The central conduction time, reflected by I-V interval, is reported to mature from 11-18 months (6) up to three to five years of age (7). This maturation effect differs for preterm and term infants (7, 10, 12-13). Preterm infants are reported to have increased absolute latencies compared to term infants up to two years of age (9).

ABR is the most important tool in diagnosing hearing impairment in infants. While ABR thresholds are important in establishing the degree of hearing loss, ABR latencies are important in differentiating between different types of hearing loss. In infants ABR latencies are important to identify delayed auditory maturation and neural pathology, such as auditory neuropathy. In addition, differentiation between conductive and cochlear hearing loss can be based on latencies, which should be corrected for age to obtain adequate classification of hearing loss. While ABR response thresholds only show a little age dependent effect, ABR latencies are age-dependent especially in young infants. To adequately diagnose hearing loss, age adjusted normal values are required. Several authors have reported average ABR normal values for infants of specific ages (7, 11-12, 14-17). No fitting model to analyze ABR results in daily clinical practice was reported in these studies.

Teas et al. first reported a fitting model to describe the time course in a quantative way (11). This fitting was derived from a statistical model rather than from modeling on physiological basis. Eggermont and Salamy proposed a fitting model based on maturational mechanisms (12). He used either a single exponential or the sum of two exponentials in his model. However it was not completely clear which of these two models was best suited to describe the data.
Issa and Ross established another normative dataset, including age dependent correction values for ABR latencies up to ten years of age (18). A fitting with a double exponential fitting model was used to compute these correction values. Gorga et al. presented a fitting model for wave V latency as a function of postconceptional age and stimulus level (15).
There is no consensus about a general model that can be easily implemented in daily clinical

practice to interpret ABR results in individual infants. Therefore, we would like to propose a simple and powerful fitting model that describes ABR age-dependency and may serve as a reference for daily clinical practice.

Material and methods

Subjects

We analyzed ABR parameters of children with normal ABR thresholds who were tested at the Sophia Children's Hospital between 2003 and 2008. This clinical population of normal hearing children was measured from term age onwards. A total number of 175 children were included. Both ears were sequentially tested, a strong correlation between the left and right ear can be expected. To prevent statistical overestimation, only the results of one ear, the right ear, were analysed. Postconceptional age at time of ABR measurement ranged from 38 to 194 weeks. Postconceptional age is defined as the period of time since conception. Postconceptional age is calculated as gestational age plus postnatal age. Sixty-nine girls and 106 boys were included.

Inclusion criteria to select these children were: presence of wave I, III and V at 90 dB measurement, infants measured in quiet or calm conditions and (sub)normal ABR thresholds (≤ 30 dB nHL). For children younger then 42 weeks postconceptional age an ABR threshold of 40 dB nHL was considered normal. Exclusion criteria were: ABR measured under general anesthesia, or known retrocochlear pathology.

To calculate the asymptote in our fitting model normal ABR results from 194 subjects older than 200 weeks postconceptional age were analyzed.

Apparatus and procedures

All ABR measurements were recorded at our out patient clinic in a sound proof room. All children were in natural sleep or in calm conditions throughout the assessment. Both ears were tested, but only the right ears were included for analysis. ABRs were recorded using the EUPHRA-1 system using a Toennies preamplifier. Responses were recorded using silver cup electrodes placed at both mastoids with a reference at the vertex and a ground electrode on the forehead and then band pass filtered (20 – 3000 Hz). These filter settings are commonly used in clinical practice. The repetition frequency was 23 Hz. Click stimuli were presented starting at a level of 90 dB nHL. With step sizes of 10 dB the level was decreased until no response was found.

Analysis of response

The response parameters studied were the absolute latencies of peak I, III and V, the I-III interval and I-V interval and the response thresholds. Experienced clinical specialists interpreted the ABR response waves. The response latencies in milliseconds were obtained by establishing the peak of the wave and reading out the digitally displayed time. The I-III interval and I-V interval were

obtained by subtracting the latency of peak I from peak III and peak V respectively. The threshold was estimated by the lowest level at which a response was found. The corresponding hearing loss was estimated as 10 dB below this level.

Fitting model

Our fitting model for the age dependency of the ABR latencies is based on a few assumptions. A nearly age independency of wave I is reported in the literature and is confirmed by our data (6, 9-11). Stimulus-level dependency is equally reflected in peak I and later peaks. Therefore our model assumes that the stimulus level dependency is realized solely in the first stage and age dependency is realized in the later peaks. Thus we can split the model in two parts; one for peak I, and another for peak III and V. The latency level model for peak I that can be used to generalize our fitting model for different stimulus levels is described in the appendix. Henceforth we will only focus on the age-dependent part of the fitting model.

Secondly, for reasons of simplicity, we assumed equal age-dependency for the I-III and III-V interval. A function with two age-dependent fitting parameters resulted in a simple and sufficiently accurate fitting of ABR interval latencies.

$$L_{III,V}(S,P) = L_I(S) + I_{I\_III,I\_V}\frac{1-e^{-\frac{P}{\tau_1}}}{1-e^{-\frac{P}{\tau_2}}} \tag{1}$$

Table 1 shows the explanations of the variables used in the different functions.

Table 1

Variable	Explanation	Value
L	Latency (ms)	
S	Stimulation level	90 dB
P	Postconceptional age (weeks)	
$L_I(90)$	I latency 90 dB (adults)	1.60 ms (SD 0.13 ms)
$L_{I\_III}(\infty)$	I-III interval (90 dB adults)	2.17 ms (SD 0.15ms)
$L_{I\_V}(\infty)$	I-V interval (90 dB adults)	4.04 ms (SD 0.18 ms)
τ_1	Time constant "nerve growth"	21.7 weeks (SE 2.1 weeks)
τ_2	Time constant "nerve maturation"	35.4 weeks (SE 1.8 weeks)

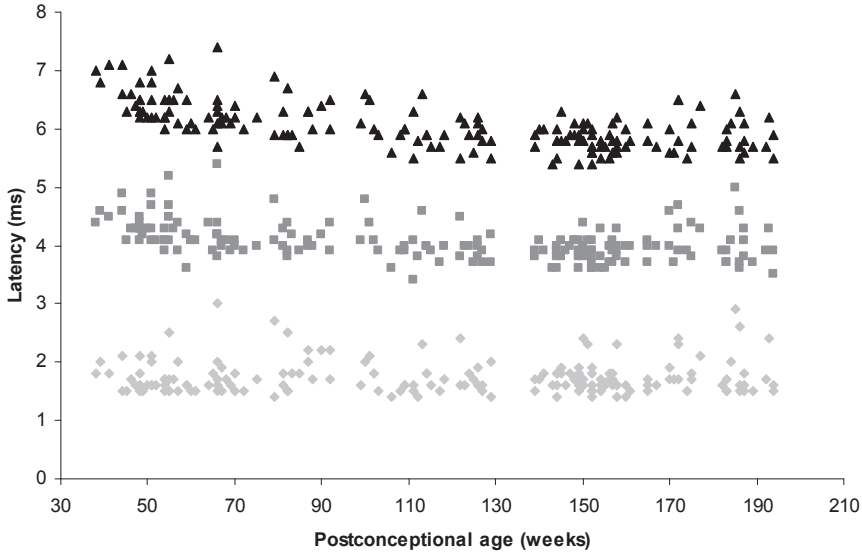
Table 1 shows the explanation and the values of the variables used in our fitting model. The time constants of 1 and τ2 can predict maturation from 38 weeks onwards. To use these time constants as a measure of postnatal maturation, 38 weeks should be added.

For larger age values the interval functions approach the adult values asymptotically. These values are calculated separately from the mean of an adult dataset.
Considering the intended use as normative curve the intervals were fitted directly (I-V and I-III together) instead of the reciprocal. Independent fitting was considered, but the results of combined fitting were equally reliable.

Results

Peak latencies are derived from the ABR recordings at 90 dB nHL of the 175 included normal hearing children as described in the method section of this paper. Since the earliest measurement in our dataset was conducted at 38 weeks postconceptional age, results are shown for 35-200 weeks postconceptional age. Between 38 and 45 weeks postconceptional age only limited data is available, as infants in our clinic are usually measured at later ages after they have completed the total neonatal screening pathway.
The individual data points for peak I, III and V from our dataset are shown in Figure 1. The age dependent changes are clear from these results. Peak I latency shows little or no age-dependency. Peak III and V latencies show a clear age-dependent decline, which is most evident up to 80 weeks.

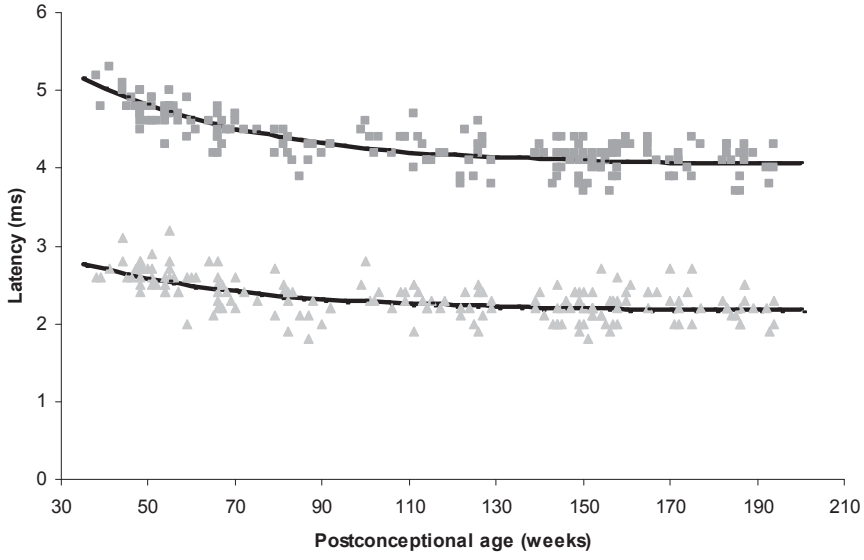
Figure 1



Latencies of peak I, III and V recorded at 90 dB nHL of 175 normal hearing right ears at different postconceptional ages.
The light grey diamonds represent peak I, the grey squares represent peak III and the black triangles represent peak V.

Figure 2 shows the absolute data for the I-III and I-V interval and the corresponding fitting curves. A similar age-dependent effect as described for peak III and V is observed for I-III interval and I-V interval.

Figure 2



The I-III and I-V interval recorded at 90 dB nHL of 175 normal hearing right ears and corresponding fitting curves at different postconceptional ages.
The light grey triangles represent the I-III interval, the black line represents the corresponding fitting curve. The grey squares represents the I-V interval, the black line represents the corresponding fitting curve.

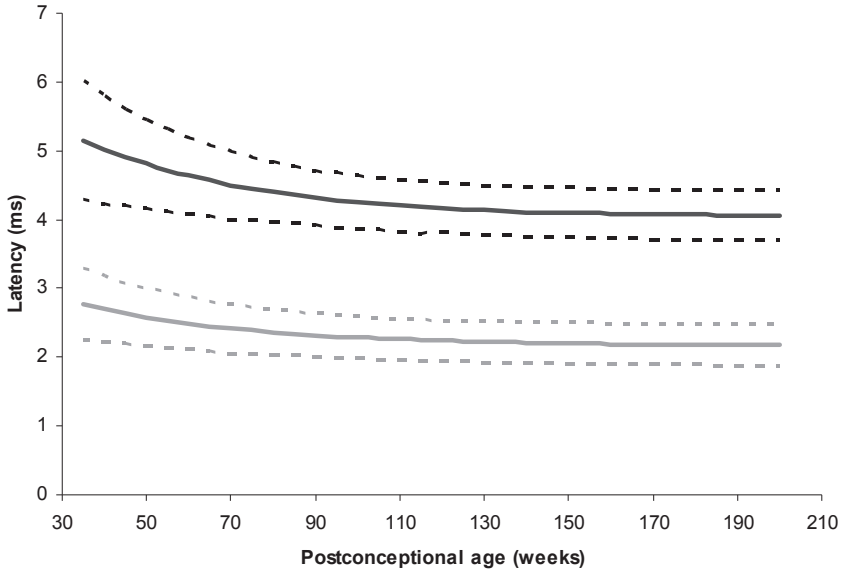
Table 2 shows the average values and standard deviations derived from our fitting model for peak I, III, V, I-III interval and I-V interval for different postconceptional ages. The standard deviations decrease with increasing postconceptional age. The overall standard deviations are small, which implies accurate measurement that can be rightfully implemented in our fitting model. Figure 3 shows the fitting curves for I-III and I-V interval including the standard deviations. As a reference of normal results a cut-off of two standard deviations is used.

Table 2

	Peak I		Peak III		Peak V		I-III interval		I-V interval	
PCA (weeks)	latency (ms)	SD	latency (ms)	SD	latency (ms)	SD	latency (ms)	SD	latency (ms)	SD
35	1,60	0,23	4.37	0,27	6.75	0,44	2.77	0,26	5.15	0,43
40	1,60	0,23	4.30	0,25	6.63	0,39	2.70	0,24	5.02	0,39
45	1,60	0,23	4.24	0,23	6.51	0,36	2.64	0,22	4.91	0,35
50	1,60	0,23	4.19	0,22	6.41	0,33	2.58	0,21	4.81	0,32
55	1,60	0,23	4.14	0,21	6.32	0,31	2.54	0,20	4.72	0,30
60	1,60	0,23	4.10	0,20	6.24	0,29	2.49	0,19	4.64	0,28
65	1,60	0,23	4.06	0,19	6.17	0,27	2.45	0,18	4.57	0,26
70	1,60	0,23	4.02	0,19	6.11	0,25	2.42	0,18	4.50	0,25
75	1,60	0,23	3.99	0,18	6.05	0,24	2.39	0,17	4.45	0,23
80	1,60	0,23	3.97	0,18	6.00	0,23	2.36	0,17	4.40	0,22
85	1,60	0,23	3.94	0,18	5.96	0,23	2.34	0,16	4.36	0,21
90	1,60	0,23	3.92	0,18	5.92	0,22	2.32	0,16	4.32	0,20
95	1,60	0,23	3.91	0,17	5.89	0,21	2.30	0,16	4.28	0,20
100	1,60	0,23	3.89	0,17	5.86	0,21	2.29	0,15	4.25	0,20
105	1,60	0,23	3.88	0,17	5.83	0,20	2.27	0,15	4.23	0,19
110	1,60	0,23	3.86	0,17	5.81	0,20	2.26	0,15	4.20	0,19
115	1,60	0,23	3.85	0,17	5.79	0,20	2.25	0,15	4.18	0,19
120	1,60	0,23	3.84	0,17	5.77	0,20	2.24	0,15	4.17	0,18
125	1,60	0,23	3.83	0,17	5.76	0,19	2.23	0,15	4.15	0,18
130	1,60	0,23	3.83	0,16	5.74	0,19	2.22	0,15	4.14	0,18
135	1,60	0,23	3.82	0,16	5.73	0,19	2.22	0,15	4.13	0,18
140	1,60	0,23	3.82	0,16	5.72	0,19	2.21	0,15	4.11	0,18
145	1,60	0,23	3.81	0,16	5.71	0,19	2.21	0,15	4.11	0,18
150	1,60	0,23	3.81	0,16	5.70	0,19	2.20	0,15	4.10	0,18
155	1,60	0,23	3.80	0,16	5.69	0,19	2.20	0,15	4.09	0,18
160	1,60	0,23	3.80	0,16	5.69	0,19	2.19	0,15	4.08	0,18
165	1,60	0,23	3.80	0,16	5.68	0,19	2.19	0,15	4.08	0,18
170	1,60	0,23	3.79	0,16	5.68	0,19	2.19	0,15	4.07	0,18
175	1,60	0,23	3.79	0,16	5.67	0,19	2.19	0,15	4.07	0,18
180	1,60	0,23	3.79	0,16	5.67	0,19	2.19	0,15	4.07	0,18
185	1,60	0,23	3.79	0,16	5.67	0,19	2.18	0,15	4.06	0,18
190	1,60	0,23	3.79	0,16	5.66	0,19	2.18	0,15	4.06	0,18
195	1,60	0,23	3.78	0,16	5.66	0,19	2.18	0,15	4.06	0,18
200	1,60	0,23	3.78	0,16	5.66	0,19	2.18	0,15	4.06	0,18

Table 2 shows the derivative values of peak I, III and V and the average derivative values of the fitting of the I-III and I-V interval at 90 dB nHL for different postconceptional ages. The standard deviations of the I-III and I-V fittings were also fitted.

Figure 3



Fitting curves of the I-III and I-V interval. The grey line represents the I-III interval, the dotted grey lines indicate the I-III interval plus or mines two standard deviations (considered cut off of normal). The black line represents the I-V interval, the dotted black lines indicate the I-V interval plus or minus two standard deviations. Data were recorded at 90 dB nHL stimulation intensity.

Discussion

We present a simple and accurate fitting model that describes the age-dependent effect found for ABR latencies and can be easily implemented to serve as a reference for daily clinical practice. Our model is based on a clinical population of normal hearing children. An age-dependent effect of ABR latencies for peak III and V and I-III interval and I-V interval can be concluded from our results. The latencies of peak III, V, I-III interval and I-V interval decrease as postconceptional age increases. For peak I no clear age-dependent effect was found. The age-dependent effect we found for peak III, peak V, I-III interval and I-V interval is concurrent with other studies (11-12).

Only one variable (postconceptional age) is used in our fitting model. Our fitting model contains two fitting parameters with an opposite effect. The fitting parameters represent time constants in an exponential function. The time constant in the denominator (τ_2) results in decreased ABR latency intervals with increasing age. A plausible explanation for this effect is nerve maturation caused by a combination of increased myelination and synaptic efficacy. The time constant in the numerator (τ_1), which was introduced to improve the accuracy of the fit for the youngest infants, results in increased ABR latency intervals with increasing age. This effect could be explained by growth of the nerve, a

longer pathway results in increased conduction time. Moore et al. demonstrate that both of these theoretical principals are involved in ABR maturation (19). The effect of nerve maturation is reported to be stronger than the effect of nerve growth (19).

There are a few basic assumptions underlying our model. First of all we assume the latency of peak I to be constant. This is based on the literature as well as our own results (6, 11, 20). However it must be noted that before 55 weeks postconceptional age peak I latency may show a small decline with age, but no sufficient data is available.

Since we assume peak I to be constant, the age-dependent effect can be found in the I-III and III-V intervals. Secondly, we assume this effect to be uniform for both intervals. However, some authors suggest that this effect is not completely the same for the I-III and III-V intervals (12, 18, 21). Eggermont and Salamy did find some degree of association between I-III and III-V intervals. For simplicity reasons and because the extent of this effect is not well known we argue an equal age-dependent effect for I-III and III-V interval in our model. Also, separate fitting parameters for I-III and III-V did not produce a more accurate fitting model. The standard deviations originating from our fitting are at least as accurate as values given by other authors (11-12, 18).

For age-dependency, we only analyzed latencies obtained at 90 dB nHL stimulation level. A stimulus intensity level dependent effect cannot be obtained from these results. We assume age-dependency to be independent of intensity level, as stimulus dependency takes place in the cochlea (i.e. peripherally) and therefore does not influence the maturation effect, which is located more centrally. This is supported by Teas et al. who found that age related latencies are similar for two intensities (50 dB and 30 dB) (11)

Some authors suggest that this central maturation effect is caused by increased myelination of axions, thereby reducing axonal conduction time (6-7, 13, 17-19). This is in line with our assumption that age-dependency is equally distributed along the total I-V interval. Other theories include a mild conductive hearing loss and tuning of the cochlea to lower frequencies located in the apical part of the cochlea, resulting in an elevated threshold and latency delay (20). However, this does not explain the maturation of the I-V interval. Also increased synaptic efficacy is mentioned as a cause of the maturation effect (6, 11, 18).

As a general rule for exponential fitting functions, 95% of the total maturation effect can be expected to end after three times τ. From our data a total age-dependent effect of 103.1 weeks and 144.2 weeks for τ_1 and τ_2 respectively can be computed. After 2 to 2.5 years this effect will be completed. This is in line with earlier reports of a maturation effect for I-V interval of 4-5 months (6) up to 3-5 years of age (7).

Our data are obtained from a large number of infants and were fitted towards adult results (>200 weeks postconceptional age). Whether our model is suitable to fit data for preterm infants cannot be concluded from our results. It may be possible that the time constants that describe the age-dependent effect are different for preterm infants.

A separate function for each gender has been considered. This was abandoned for the sake of

simplicity since the inter sex differences in time constants were negligible (men; τ_1 20.2, τ_2 33.7 women; τ_1 20.6, τ_2 33.4). Sleifer et al. also found no gender differences for ABR latencies (10).

We chose to analyze only the results obtained from right ears. Since we expect a strong correlation between left and right ears, inclusion of both ears could lead to statistical over interpretation of the age-dependent effect. However small left to right latency differences are found in ABR results of neonates (22-24). Since the inter-aural differences are very small we feel that our results can be extrapolated to left ears.

We studied results obtained at 90 dB nHL stimulation level to optimise quality and ensure presence of peak I responses (especially in the younger infants). We experienced no problems with the interpretation of the results due to acoustic reflexes. ABR results are analyzed by two experts in our clinic. However we are unable to provide data on interrater-reliability

A selection bias may have occurred in our study because all included children were referred for auditory assessment to our tertiary care clinic. Therefore the chance that they have a condition altering ABR results is higher than in the normal population. We tried to minimize this effect by applying strict inclusion and exclusion criteria. On the other hand, by deriving our fitting model from a clinical population of normal hearing children it is a true reflection of the population it is intended for.

The strength of our fitting model compared to the current fitting models proposed by Eggermont, Issa and Teas is that it is a relatively simple model that leads to accurate fitting of the data. Furthermore, the model reflects physiological processes of myelination and nerve growth. Teas et al. based his fitting model on statistical analysis of the ABR results, resulting in a non-linear equation with four parameters for latencies of peak III and V (11). For peak I a linear model was used. Peak I showed similar results compared to adults, except for 2 kHz, where peak I latencies decreased with age. Peak V showed a larger age dependent decrease in latency, but did not reach adult values yet at 60 weeks of age. He also found a frequency dependent immaturity at rostral sites for higher frequencies (8kHz). Eggermont and Salamy proposed two models, with either one or two exponential parameters (12). The I-V interval is always fitted with one exponential, but it is not completely clear how the other latencies should be fitted. Peak I latencies are nearly mature at term age. Issa and Ross used an exponential function with two time constants to derive age dependent correction values (18). They fitted the latencies and intervals of peak I, III and V (measured at 70 dB nHL) individually. The two time constants resulting from their fitting are surprisingly diverse, which is difficult to explain. Children were not equally divided along different age groups and they did not use threshold criteria to exclude conductive hearing losses.

The present study introduces a simple and powerful fitting model that can be easily implemented in daily clinical practice to be used as a reference for ABR results in infants. We speculate about the underlying physiological processes.

Since our data are based on mostly full term infants it is unsure whether our model is suitable to fit data from preterm infants.

Appendix

The model is constructed for values measured at 90 dB nHL only as it is primarily meant to describe age-dependent changes. To be used generally by including stimulus intensity level dependency, the model had to be substituted to a latency-level model for peak I using;

$$L_I(S) = A + Be^{-\frac{S}{C}} \qquad L_I(S) = L_I(\infty) + Be^{-\frac{S}{C}} \tag{2}$$

The complete result latency as a function of stimulation level and postconceptional age which reflects a "mathematical surface";

$$L_{III,V}(S,P) = L_I(S) + I_{I\_III,I\_V}\frac{1-e^{-\frac{P}{\tau_1}}}{1-e^{-\frac{P}{\tau_2}}} \tag{3}$$

S = stimulation level (dB), P= postconceptional age (weeks). We use the following variables derived from fitting of our own data: A=1.46, B=1.10 ms, C 43 dB.

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chapter 3

ABR morphology and analysis in very preterm NICU infants

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Abstract

Objectives: Analysis of auditory brainstem response (ABR) in very preterm infants can be difficult due to the poor detectability of the various components of the ABR. We evaluated the ABR morphology and tried to extend the current assessment system.

Study design: Prospective cohort study

Methods: We included 28 preterm very low birth weight infants admitted to the neonatal intensive care unit (NICU) of Sophia Children's Hospital. ABRs were measured between 26 and 34 weeks postconceptional age. The presence of the following ABR parameters was recorded: the ipsilateral peaks I, III and V, the contralateral peaks III and V and the response threshold.

Results: In 82% of our population a typical "bow tie" response pattern is present as a sign of early auditory development. This "bow tie" pattern is the narrowest part of the response wave and is predominantly characterized by the ipsilateral negative peak III, this effect may be emphasized by the contralateral peak III. The "bow tie" pattern is seen approximately 0.1 ms before the ipsilateral peak III. From 30 weeks postconceptional age onwards a more extensive morphological pattern is recorded in 90% of the infants. A flowchart was designed to analyze the ABR morphology of preterm infants in an unambiguous stepwise fashion.

Conclusion: A typical "bow tie" pattern preceding peak III seems to be the earliest characteristic of the developing ABR morphology in preterm infants. As ABR characteristics will improve with increasing age neonatal hearing screening should be postponed until after 34 weeks.

Introduction

Auditory brainstem response (ABR) measurement is an important tool in diagnosing hearing impairment in infants. ABR waves reflect the conduction of a neural signal as a result of a sound stimulus along the auditory nerve and different levels of the brainstem.
The auditory system matures from the periphery to the cortex (1). Cochlear maturity is achieved around term birth. The central conduction time, reflected by the I-V interval, is reported to mature from 11 to 18 months (2) up to three to five years of age (3).

To adequately diagnose hearing impairment in infants age-adjusted normal values are required. Several fitting models have been described that correct ABR latencies for postconceptional age (4-8). In very preterm infants this may not be sufficient due to the poor detectability of various components of the ABR. Not much data is available for this group of infants. Only Amin et al. gathered a considerable amount of data. They proposed a system that categorizes the ABR waveforms in infants younger than 32 weeks postconceptional age (9). One limitation is that it is a rather basic system based on identifiable peaks III and V. They did not include contralateral response data in their analysis. Not much is reported about the presence and development of contralateral ABR traces at this very young age. Salamy et al. mention that the development of the contralateral response starts around 34 weeks postconceptional age (10). This suggests that the contralateral response cannot contribute to the analysis of wave morphology before this age. It also suggests a different maturational process of the contralateral pathways.

Secondly, Amin's system does not include information about the response threshold (9). Due to the poor detectability and smaller amplitudes of the peaks and poor measurement conditions, response thresholds are often difficult to determine. Yet, when a clear ABR waveform is present at lower stimulus intensities this provides valuable additional information. It may be an indication that the maturation of the auditory system is in a succeeding developmental stage.

The aim of our study was to describe the ABR morphology in very preterm infants in a more accurate way than is available until now. To extend the current assessment system by evaluating ABR response thresholds and the contralateral ABR traces, more specific information about presence and order of consequent peaks becomes available. This may provide new information about maturation of the ipsilateral and contralateral pathways and how to interpret ABR measurement in preterm neonates.

Material and methods

Subjects

Twenty-eight preterm infants admitted to the neonatal intensive care unit (NICU) of Sophia Children's Hospital were included between 1-3-2009 and 31-8-2010. Postconceptional age at time of ABR measurement ranged from 26 to 34 weeks. All very low birth weight (< 1500 grams) infants were eligible for this study unless they had congenital anomalies (including chromosomal disorders) or metabolic disease. All ABR measurements were recorded in the second or third postnatal week. Informed consent was obtained from the parents. The study was approved by the local ethics committee.

Study setting

The Sophia Children's Hospital is tertiary care centre in Rotterdam, the Netherlands. In 2008 the life birth number in the Netherlands was 184,634, of which 4,003 infants required NICU care of which 639 were admitted to the NICU at Sophia's Children Hospital (all deceased infants are excluded from these admittance numbers).

ABR measurement

ABR measurements were recorded in the NICU. All children were in natural sleep or in calm conditions throughout the assessment. Both ears were sequentially tested. ABRs were recorded using a Centor USB Racia-Alvar system. Responses were recorded using silver cup electrodes placed at both mastoids with a reference at the vertex and a ground electrode on the forehead and then band pass filtered. A band-filter was used with cut-off frequencies of 20 Hz and 3 kHz. The repetition frequency was 29 Hz. Click stimuli were used with alternating polarity. Click stimuli were presented starting at a level of 90 dB nHL. When no response was found stimulus level was increased to 100 dB nHL. The level was decreased with step sizes of 20 dB until no response was found. The response threshold was defined as the lowest level at which a replicable response was found. The response latencies in milliseconds were obtained by establishing the peak of the wave (at 90 dB nHL) and reading out the digitally displayed time. The inter-observer difference of peak latencies had to be ≤ 0.3 ms, the average of the two latencies was used. The response peaks were sometimes poorly reproducible; in that case the combination of traces at various stimulation intensities was used to establish the presence of a peak. The fact that a combination of traces was needed to establish the presence of a peak reflects a level of insecurity, which is common when analysing new data. When a peak can be confirmed in several traces this is an indication that the observation is no result of chance. Dealing with these aspects is an important process in understanding and analysing new data. The ipsilateral (stimulated side) and contralateral (not stimulated side) response traces were recorded. For each trace the test retest values are displayed, as a measure of recording accuracy. Two specialized audiologists independently interpreted the ABR waves, in case of disagreement the audiologists arrived at a consensus. For the analysis, only the results of the best ear of each infant

were included to prevent the negative influence of possible hearing loss on ABR morphology. Possible hearing loss was diagnosed consequently by neonatal hearing screening using automated auditory brainstem response (AABR). Otoacoustic emission (OAE) measurement was not conducted in the NICU for technical reasons, mechanical ventilation and surrounding noise made it impossible to obtain reliable OAE measurement.

Statistical analysis

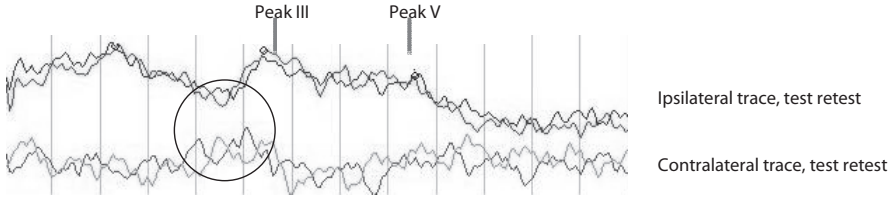
The SPSS 15 (SPSS Inc., Chicago, IL, USA) statistical package was used for the analysis. For dichotomous values the Pearson's χ^2 was used. P-values ≤ 0.05 were considered statistically significant.

Results

The 28 studied preterm infants had a median postconceptional age at birth of 28.3 weeks (interquartile range 26.6 to 29.4 weeks). The median birth weight was 878 grams (interquartile range 718 to 1010 grams). All ABR measurements were conducted in the NICU between the 7th and 23rd postnatal day when infants were stable enough to undergo the examination. The median postconceptional age at time of ABR measurement was 30.1 weeks (interquartile range 28.7 to 33 weeks). AABR hearing screening was conducted after 34 weeks postconceptional age in most infants. A few infants were tested between 31 and 33 weeks postconceptional age upon discharge. All except one infant passed the AABR neonatal hearing screening (96%). Hearing loss has been confirmed in this infant. ABR results improved from a maximum hearing loss in one ear and a sensorineural hearing loss in the other ear to a sensorineural hearing loss of 40 dB nHL in both ears with an additional conductive component. Two infants have unfortunately died during the course of follow-up.

Two specialized audiologists independently interpreted the ABR waves. When identifiable, the ipsilateral peaks I, III and V, the contralateral peaks III and V and the response threshold were established. In contrast to ABR measurement at later ages, peak III instead of V showed to be the most characteristic peak. A typical "bow tie" pattern is the earliest characteristic that appears just before peak III (Figure 1).

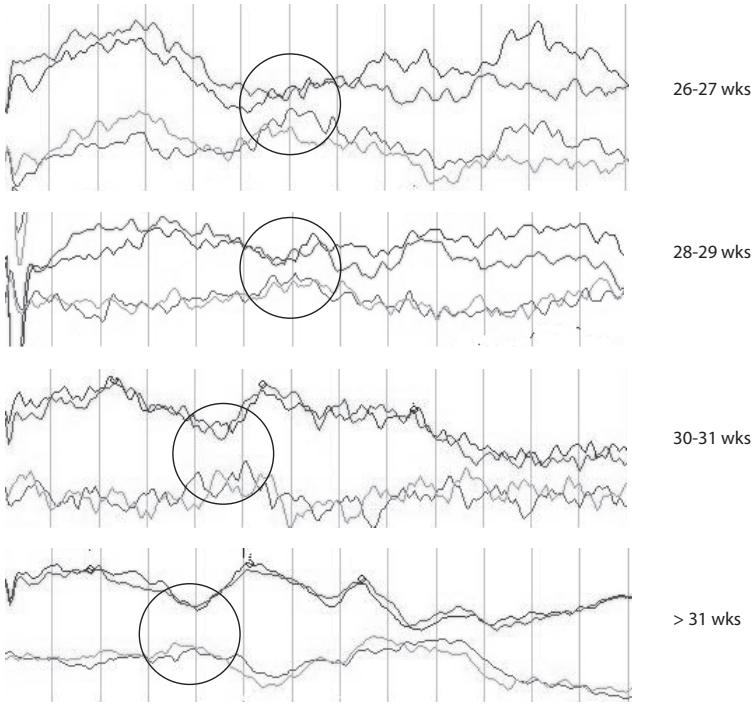
Figure 1



Typical "bow tie" pattern recorded at 90 dB, at 30 weeks postconceptional age. The first trace is the ipsilateral trace, showing test retest recordings. The second trace is the contralateral trace, showing test retest recordings. Peak III and V are indicated. The "bow tie" pattern is encircled. It appears just before peak III and is predominantly characterized by a negative wave III. It can be amplified by a positive peak III in the contralateral trace.

It is the narrowest distance between the ipsilateral and contralateral response waves with a characteristic appearance. The negative peak preceding peak III is the soundest characteristic of this pattern. The positive peak III, if present, follows after approximately 1 ms. The contralateral peak III can emphasize the "bow tie" pattern. In figure 2 typical ABR traces with a "bow tie" pattern are presented, for different postconceptional age groups.

Figure 2



Typical "bow tie" patterns are displayed of right ears of infants in different postconceptional age groups. The "bow tie" pattern is encircled. The ipsilateral and contralateral traces are presented, each trace showing test retest.

With increasing postconceptional age the latency of the "bow tie" shortens, while more peaks become identifiable. With increasing postconceptional age the latencies of the peaks also decrease. In the table the latencies of peaks III and V, the III-V interval and the threshold levels are presented for different postconceptional age groups. After primary analysis the inter observer concordance was 89%. The audiologists arrived at a full consensus at final analysis.

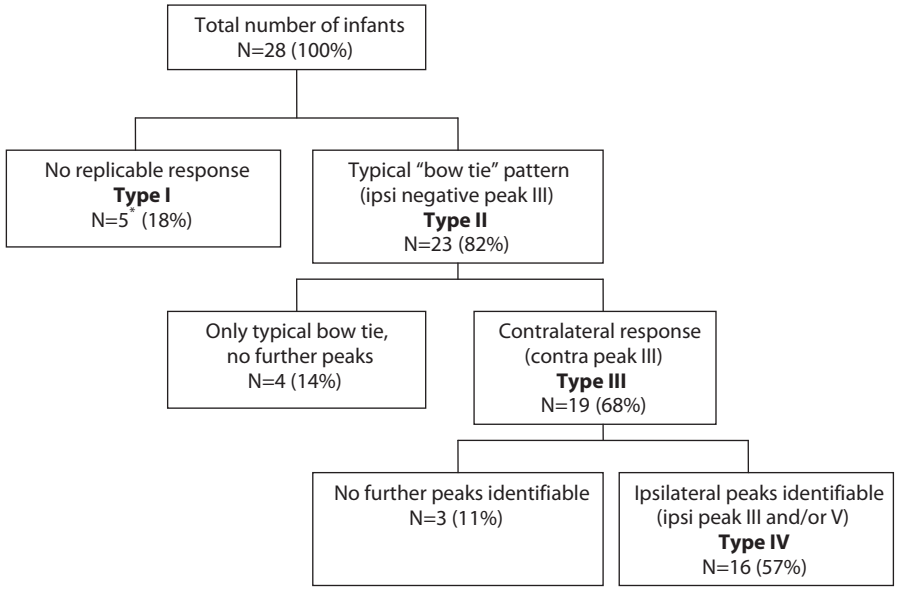
Table 1

	Postconceptional age 29-30 weeks Mean (Standard deviation)	Postconceptional age ≥ 30 weeks Mean (Standard deviation)
Negative peak III (ms)	5.5 (0.7)	4.1 (0.6)
Peak III (ms)	6.1 (0.5)	5.6 (0.9)
Peak V (ms)	10.1 (1.0)	8.9 (1.2)
III-V interval (ms)	3.8 (0.8)	3.4 (0.9)
Response threshold (dB)	68 (23)	51 (19)

Table 1. The mean values of the peak latencies, III-V interval and response threshold are presented. The results of the best ear of each infant are included. Before 29 weeks postconceptional age available data are too limited.

Based on the observed characteristics of the ABR morphology a flow chart was designed to analyze the ABR morphology of preterm infants in an unambiguous stepwise fashion (figure 3). The best ear of each infant was included in the analysis. A classification was made based on the extensiveness of the response. In type I no response is found. In type II a typical "bow tie" pattern is observed. In type III a contralateral response can be found as well as a "bow tie pattern". In type IV clear ipsilateral peaks (often peaks III and / or V) are identified as well as a contralateral response. A contralateral response (type III) was identified in 68% of the infants, even before 30 week postconceptional age in some cases. A more extensive morphological pattern (type IV), with reproducible ipsilateral peaks was seen in 57% of the infants.

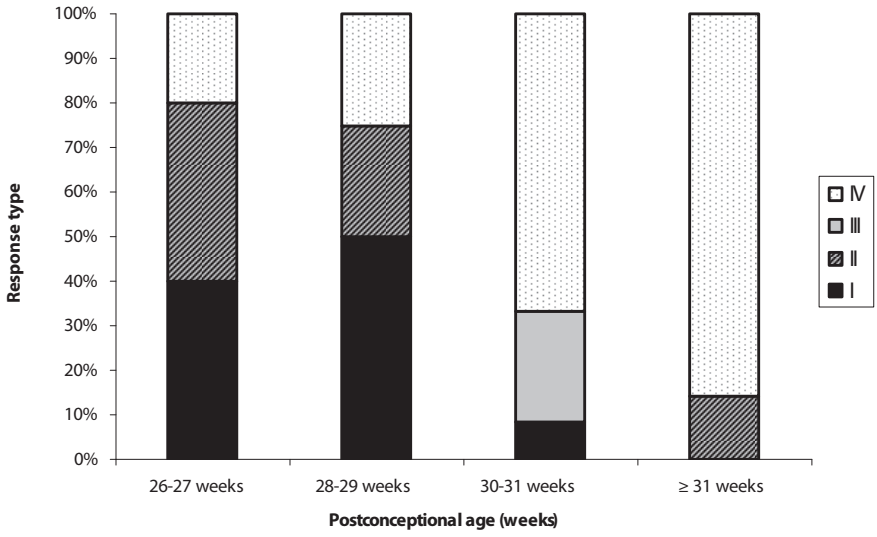
Figure 3



This flow chart was used to analyze the ABR responses. Infants were classified according to their best ear. The typical "bow tie" pattern is the narrowest point of the response wave. This is predominantly characterized by the ipsilateral negative wave III and can be amplified by the contralateral wave III when present.
* In 2 infants there seemed to be some kind of a replicable response, however this did not fit the "bow tie pattern" The responses are categorized (type I-IV), with type IV being the most extensive response type.

In figure 4 the division of the response types is described for different postconceptional age groups. A more extensive morphological pattern develops with increasing postconceptional age. Especially between 29 and 30 weeks postconceptional age a remarkable transition is observed. The ipsilateral and contralateral responses suddenly become more frequently detectable. From 30 weeks postconceptional age onwards both an ipsilateral and contralateral response is identifiable in 90% of infants. After 31 weeks postconceptional age peaks III and V are identifiable in almost 90% of infants. The difference in response type between infants younger than 30 weeks postconceptional age and infants who are 30 weeks postconceptional or older is statistically significant (P=0.004).

Figure 4



The ABR response types in different postconceptional age groups are presented. In type I no response is found. In type II a typical "bow tie" pattern is found. In type III a bow tie pattern and a clear contralateral response is found. Finally, in type IV clear ipsilateral and contralateral peaks are identifiable.

Discussion

We developed a flowchart to analyze the morphology of the ABR results of 28 preterm infants in an unambiguous way. We found that in 82% of infants a typical "bow tie" response pattern is present, dominated by a negative peak III. The presence of a more extensive morphological response type increases with increasing postconceptional age. From 30 weeks postconceptional age onwards an ipsilateral and / or contralateral response is present in 90% of the infants in their best ear.

Interpretation of ABR results in adults and older infants is largely dependent on peak V, which is the clearest and strongest peak. The peripheral to central maturation of the auditory system, results in a weaker projection of peak V in these preterm infants (1). This was even more clearly observed in our data. In stead of peak V a broad negative ipsilateral peak III response appeared to be the best identifiable and most consistent characteristic. Especially in combination with a contralateral peak this results in a typical "bow tie" pattern. The typical "bow tie" pattern can also be found in older infants or adults, but the clearer peaks III and V make it less easy to identify. In these preterm infants it seems to be the clearest and earliest characteristic of the ABR waveform and should be the first pattern to look for when measuring ABR in very young preterms.

Interpretation of ABR results using the flow chart results in a reliable ABR analysis at early developmental stage. The stepwise analysis from a basic ABR morphology to a more extensive response type ensures that no ABR characteristics will be missed. The analysis can be difficult due to the broader peaks and poorer reproducibility, however an unambiguous characterization was found for most infants. As a result of the immature auditory system a longer time span had to be considered to identify peak latencies. Sometimes the combination of traces at various stimulation intensities had to be used to establish the presence of a peak. We chose to report only the results of the best hearing ear to prevent the negative influence of possible hearing loss on ABR morphology. Absence of this pattern did not correlate with a hearing loss as 96% of infants passed the AABR screening.

The ABR peak latencies that we found are comparable to the results found by Amin et al (9). Before 29 weeks the number of infants with identifiable peaks was limited, therefore data of peak latencies and the III-V interval are presented beyond this age. A clear age-dependent decline of peak III and V latencies, III-V interval and ABR response threshold is observed. These results indicate the well known ongoing maturational processes of the auditory system in infants.
Since peak I is rarely identifiable in these infants, the III-V interval, instead of the I-V interval, was used as a measure of the central conduction time or auditory maturation. Interpeak intervals are not as much influenced by conductive hearing losses as individual peak latencies. Since tympanometry was not performed and peak I was often not identifiable, the degree of conductive hearing losses and its influence on peak latencies cannot be established.
Although peaks become identifiable around 30 week postconceptional age, threshold levels are still increased as a result of ongoing maturation or possible hearing loss. Threshold levels will decrease during the following weeks. In our data from 31 weeks postconceptional age thresholds become closer to the normal range. However, in certain cases no threshold can be established, suggesting a delayed maturation or congenital hearing loss. This confirms that neonatal hearing screening should be postponed until after 34 weeks.

The auditory system is known to develop in a peripheral to central fashion (1). Cochlear maturity is achieved a few weeks before term birth. Axonal myelin formation and synaptic efficacy result in maturation of the auditory pathways in the brainstem during the first months of life (1). When applied to the ABR response, this implies a small or absent age-dependency of peak I and large age-dependency of later peaks and intervals. The earlier and clearer identification of peak III compared to peak V in our preterm population is in line with the peripheral to central maturation of the auditory system. As peak V is generated in the colliculus inferior, around 30 weeks postconceptional age an important step in the maturation of the colliculus inferior takes place. The central conduction time, reflected in the I-V or III-V intervals is also known to decrease with increasing postconceptional age as a result of maturation.

Jiang et al. suggested that very preterm infants without perinatal complications have an advanced peripheral development of the brainstem but a retarded central development (11-12). Their findings were based on the fact that the III-V interval of preterm infants was much more prolonged than the I-III interval compared to term infants. This may be the result of early sound stimulation ex utero which could lead to accelerated myelination and peripheral auditory maturation. This may be another explanation for the strong expression of peak III in our population. Unfortunately we were unable to gather enough information on peak I latency in this population to study the various interpeak intervals.

In the 1980's the contralateral ABR response was reported to emerge around 34 weeks postconceptional age (10). However we found a contralateral response in 86% of infants from 29 weeks postconceptional age onwards. Even at 26 to 27 weeks postconceptional age a contralateral response is found in some cases. This implies development of contralateral pathways in a very early stage. Salamy et al. reported that the contralateral response develops in a rostro-caudal fashion, with peaks IV and V being the most pronounced in early life (10). In our population, similar to the ipsilateral response, peak III seems to be the earliest and most prominent of the contralateral response peaks. As a result of early measurement in the immature auditory system apparently peak V is not yet as strongly and clearly developed and therefore less frequently measurable in our population.

A limitation of our study may be that hearing loss may have influenced the interpretation of the ABR morphology. However 96% of the infants passed AABR neonatal hearing screening.

Conclusion

We developed a flow chart to analyze the ABR results in very preterm infants. Peak III seems to be the most prominent and earliest identifiable peak in both the ipsilateral and contralateral ABR traces. From 30 weeks postconceptional age onwards an extensive ABR morphology was seen in 90% of our population. Threshold levels and identifiable peaks will improve during the following weeks, therefore neonatal hearing screening should be postponed until after 34 weeks.

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Chapter 4

An initial overestimation of sensorineural hearing loss in NICU infants after failure on neonatal hearing screening

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Abstract

Objective: Infants admitted to neonatal intensive care units have a higher incidence of significant congenital hearing loss. We classified audiologic diagnoses and follow-up in infants who had been admitted to our neonatal intensive care unit.

Methods: We included all infants admitted to the neonatal intensive care unit at Sophia Children's Hospital between 2004 and 2009 who had been referred for auditory brainstem response measurement after failing neonatal hearing screening with automated auditory brainstem response. We retrospectively analyzed the results of auditory brainstem response measurement.

Results: Between 2004 and 2009 3316 infants admitted to our neonatal intensive care unit had neonatal hearing screening. 103 infants failed neonatal hearing screening: 46 girls and 57 boys. After first auditory brainstem response measurement we found 18% had normal hearing or a minimal hearing loss. The remainder had a type of hearing loss, distributed as follows: 15% conductive, 32% symmetric sensorineural, 14% asymmetric sensorineural, and 21% absent auditory brainstem responses. Repeated auditory brainstem response measurement showed a shift in hearing outcome. The main difference was an improvement from symmetric sensorineural hearing loss to normal hearing. However, in a small percentage of children, the hearing deteriorated.

Conclusions: As many as 58% of infants in this high-risk population who failed the neonatal hearing screening were diagnosed with sensorineural hearing loss or absent auditory brainstem responses. An initial overestimation of sensorineural hearing loss of about 10% was seen at first auditory brainstem response measurement. This may be partially explained by a conductive component that has resolved. Finally, in a small percentage of children the hearing deteriorated.

Introduction

Infants admitted to neonatal intensive care units (NICUs) have a relatively high incidence of perinatal complications and risk factors associated with congenital hearing loss (1). A prevalence of 3.2% of unilateral or bilateral congenital hearing loss was found among a cohort of NICU infants (2). Another study found that 1.9% of NICU infants had a severe/profound congenital hearing loss (bilateral, >70dB HL) (3).
Universal newborn hearing screening has resulted in earlier referral, diagnosis and treatment of congenital hearing loss (4-6). While the importance of early treatment has been widely accepted, the beneficial effect of hearing screening on long-term outcome remains uncertain (7).

Several authors have studied the course of hearing impairment in infants who had been admitted to the NICU and had failed neonatal hearing screening (2-3, 8-12). While some authors only report the results of neonatal hearing screening (2, 9, 12), others report the results of complimentary audiologic testing such as auditory brainstem response (ABR) measurement (3, 8, 10-11). Nevertheless, no detailed descriptive information is available about the initial audiologic outcome and the course of hearing loss over time.

Since the degree and type of hearing loss are fundamental to the treatment and prognosis of hearing loss, the objective of our study was to classify the degree and type of hearing loss in infants who had been admitted to our NICU and failed neonatal hearing screening. As hearing loss can change over time we focused not only on primary outcome after failure on neonatal hearing screening, but also on follow-up of ABR measurement. We retrospectively analyzed the results of ABR measurement.

Material and methods

Patients

The Sophia Children's Hospital is a tertiary care centre in Rotterdam, the Netherlands. In 2008 the life birth number in the Netherlands was 184,634, of which 4003 infants required NICU care, of which 639 infants were admitted to the NICU at Sophia's Children Hospital (all deceased infants are excluded from these admittance numbers).

All infants admitted to the NICU longer than 24 hours undergo standard hearing screening by means of automated auditory brainstem responses (AABR). The first AABR screening is usually conducted upon discharge from the NICU. In case of unilateral or bilateral failure on AABR screening, AABR measurement should be repeated before 6 weeks corrected age. Upon second AABR failure children are referred for audiologic evaluation. Figure 1 presents a schematic overview of the neonatal hearing screening program in the Netherlands for NICU infants. This audiologic evaluation consists

of ABR, transient evoked otoacoustic emissions (TEOAE) and tympanometry measurement. After diagnostic evaluation all infants are seen by an experienced audiologist and otorhinolaryngologist. This ideally takes place before 3 months corrected age.

Figure 1

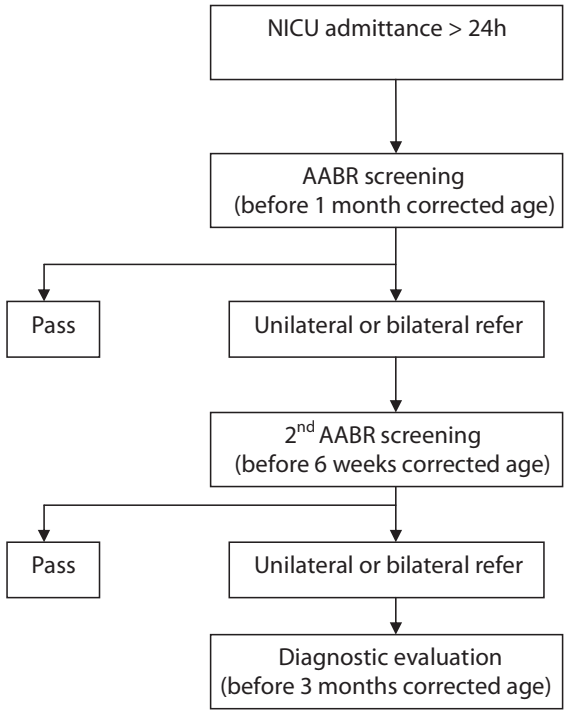


Figure 1. A schematic overview of the neonatal hearing screening in the Netherlands for infants admitted to the NICU > 24 hours.

Between 2004 and 2009 3366 infants were admitted to our NICU, of which 3316 were screened with AABR. A total of 103 infants were referred for ABR analysis after repeated failure on AABR screening. Data of these ABR recordings were used to retrospectively classify the audiologic outcome in these infants. Follow-up by means of repeated ABR measurements were available at the time of analysis in 76 infants. We studied the first and final ABR measurement in all infants to evaluate the course of hearing loss over time. When infants did not have repeated ABR measurements the result from the first ABR measurement was also considered the result of the final ABR measurement.

This research was conducted abiding the rules of the institutional ethical committee.

Apparatus and procedures

Neonatal hearing screening with AABR was measured at a stimulus intensity of 35dB. A signal-detection algorithm determined the presence of an ABR and assigned a pass or refer result.

ABR measurements were recorded at our outpatient clinic in a soundproof room. All children were in natural sleep or in calm conditions throughout the assessment. Both ears were sequentially tested. ABRs were recorded using the EUPHRA-1 system using a Toennies preamplifier. Responses were recorded using silver cup electrodes placed at both mastoids with a reference at the vertex and a ground electrode on the forehead and then band pass filtered. A band-filter was used with cut-off frequencies of 20 Hz and 3 kHz. The repetition frequency was 23 Hz. Click stimuli were used with alternating polarity. Click stimuli were presented starting at a level of 90 dB NHL. With step sizes of 10 dB the level was decreased until no response was found. The response threshold was estimated by the lowest level at which a response was found.

TEOAE measurements were performed using the Otodynamics ILO 288 USB II system with the standard settings. The stimulus level was set to 84 dB SPL, a number of 260 averages was used.

Tympanometry was performed with an Interacoustics AT 235H system using the standard settings and a 1 kHz probe-frequency. Clinical experts interpreted the results.

Analysis of response

The absolute latencies and interpeak intervals as well as the response thresholds were recorded. Experienced clinical specialists interpreted the ABR response waves. The response latencies in milliseconds were obtained by establishing the peak of the wave and reading out the digitally displayed time. The response threshold was estimated by the lowest level at which a response was found. The corresponding hearing loss is usually estimated as 10 dB below this level. The ABR thresholds that are mentioned in the results section are the ABR response thresholds.

The absolute latencies and interpeak intervals of the ABR response were compared to the reference values used in our clinic (13). These reference values are corrected for postconceptional age to account for maturational changes in ABR parameters. From the latency intensity curves the level of conductive hearing loss was estimated. This has been described in the literature as a valid method to identify a conductive hearing loss (14). TEOAE and tympanometry measurement were used to confirm the diagnosis of conductive hearing loss when available.

Results

Between 2004 and 2009 3366 infants were admitted to our NICU, of which 3316 were screened with AABR. A total of 103 infants were referred for ABR analysis after second failure on AABR screening: 46 girls and 57 boys. The median gestational age at birth was 34.7 weeks (interquartile range 27.3 to 39.3 weeks). The median birth weight was 1930 grams (interquartile range 946 to 2911 grams). The median corrected age at first diagnostic ABR measurement was 3 weeks (interquartile range -1 to 8 weeks).

In 76 (73.8%) infants ABR measurement was repeated at least once. The median corrected age at final ABR measurement was 43 weeks (interquartile range 22 to 84 weeks). In ten infants ABR measurement was not repeated because the first ABR showed normal hearing, six infants died, three infants were followed elsewhere and eight were lost to follow up. When ABR measurement was not repeated the first ABR results was also considered the final ABR result.

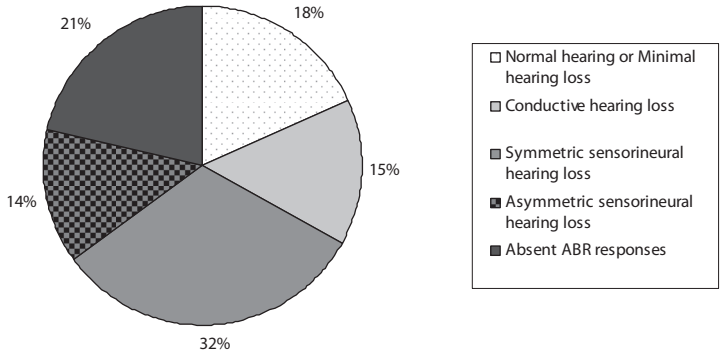
Final ABR result	First ABR result					
	Normal hearing Minimal hearing loss	Conductive	Symmetric sensorineural	Asymmetric sensorineural	Absent ABR responses	Total* (n=103)
Normal hearing Minimal hearing loss	5	4	7	1	1	28
Conductive	2	3	1	1	0	15
Symmetric sensorineural	1	0	17	2	0	23
Asymmetric sensorineural	1	0	2	8	0	13
Absent ABR responses	0	0	3	0	17	24
Not repeated	10	8 (2 †)	3 (1 †)	2 (1 †)	4 (2 †)	

Table 1. First and final ABR results (n=103)
The distribution of hearing loss at first and final ABR measurement is presented. In infants that did not have repeated ABR measurement the results of the first ABR was also considered the results of the final ABR. The numbers of infants that did not have repeated ABR measurement among different types of hearing loss are indicated in the bottom line. The median postconceptional age at first ABR measurement was 43 weeks (interquartile range 39 to 48 weeks). The median postconceptional age at final ABR measurement was 83 weeks (interquartile range 62 to 124 weeks).
* The total number of infants refers to the results found at final ABR measurement + the infants from the original diagnosis in whom ABR measurement was not repeated.
† number of infants who died

In 19 infants normal hearing or minimal hearing loss was found, with ABR response thresholds ≤40 dB HL in both ears. In 15 infants a pure conductive hearing loss was diagnosed. In 47 infants a sensorineural hearing loss was diagnosed, in 8 of these infants a small additional conductive component was present in one or both ears. In 33 infants this was a symmetric sensorineural hearing loss defined by an inter-aural threshold difference <30 dB. In 14 infants this sensorineural hearing loss was asymmetric (inter-aural threshold difference ≥30 dB). In nine of these 14 infants this was true unilateral hearing loss, with a response threshold in the best hearing ear ≤40 dB. In 22 infants no ABR response was recorded.
There were nine infants with evidence of auditory neuropathy spectrum disorder (ANSD) among the total population of 103 infants.

The table shows the course of the ABR results between the first and final diagnostic ABR measurement. The distribution among different types of hearing loss of the infants that did not have repeated ABR measurement can also be seen in the table.

Results first ABR measurement



Results final ABR measurement

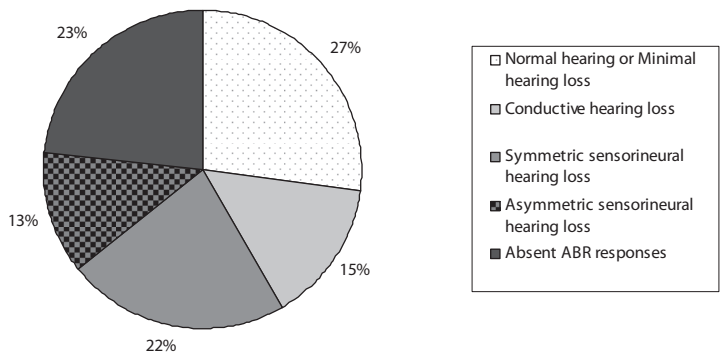


Figure 2 shows the distribution of the results of the first and final ABR measurement in infants referred for audiologic assessment after failure on AABR screening from the neonatal intensive care unit.

The majority of changes showed an improvement of hearing function. From the symmetric sensorineural hearing loss group seven infants improved towards normal hearing or minimal hearing loss and one infant to a conductive hearing loss. From the asymmetric sensorineural hearing loss group one infant improved to normal hearing and another infant to conductive hearing loss. From

the conductive hearing loss group four infants improved to normal hearing or minimal hearing loss. Remarkably, one infant from the absent ABR response group improved to normal hearing. The median gestational age at birth of the infants in whom hearing improved was 30 weeks, which is younger than the median gestational age of the total population (34.7 weeks).

In figure 2 the distribution of the first and final ABR results are shown. At first ABR measurement 67% of infants had a sensorineural hearing loss or absent ABR responses, after follow-up the number decreased to 58%.

Unfortunately, in some infants a progression of hearing impairment was found. Three infants from the symmetric sensorineural hearing loss group developed absent ABR responses. From the normal hearing or minimal hearing loss group two infants developed a conductive hearing loss, one developed a symmetric sensorineural hearing loss and another developed an asymmetric sensorineural hearing loss.

The ABR response thresholds of infants with sensorineural hearing loss or absent ABR responses were used to study the degree of hearing loss, described for the best and worst hearing ear. The degree of hearing loss of infants with an absent ABR response was defined as 110 dB. The median ABR threshold of the best hearing ear at first diagnostic ABR measurement was 70 dB (interquartile range 50-110dB). The median ABR threshold of the worst hearing ear was 90 dB (interquartile range 70-110dB).
The median ABR threshold of the best hearing ear at final ABR measurement was 60 dB (interquartile range 40-110dB). The median ABR threshold of the worst hearing ear was 80 dB (interquartile range 52.5-110dB). Considering the entire group the degree of hearing loss improved over time.

Discussion

We present the results of audiologic evaluation and follow-up of 103 infants who failed neonatal hearing screening and had been admitted to the NICU at Sophia Children's Hospital between 2004 and 2009. Repeated ABR measurement showed an improvement from symmetric sensorineural hearing loss to normal hearing or minimal hearing loss for a subset of infants. The other categories of hearing loss remained almost unchanged. Some infants showed progression of hearing impairment.

From the original diagnosis of symmetric sensorineural hearing loss 21.2% of infants improved towards normal hearing or minimal hearing loss, and one infant developed a conductive instead of sensorineural hearing loss. In addition, one of the absent ABR responses improved to normal hearing or minimal hearing loss. This apparent improvement of cochlear hearing function can probably be explained by maturation of the auditory system which is known to be delayed in preterm infants

compared to term infants (15-16). The immature auditory system of preterm infants may have been misinterpreted as cochlear hearing loss when threshold levels and latencies were increased. So it is not a true improvement in cochlear function. This is supported by the fact that in infants in whom hearing improved the gestational age at time of birth of was younger.

In addition to this, gestational age is estimated during pregnancy and can well be inaccurate with a margin of 2 weeks. In early preterm infants, a two weeks inaccuracy of gestational age can result in different ABR latency reference values and possible misinterpretation of ABR results. Since response thresholds are not as much influenced by gestational age, the misinterpretation will probably lead to false diagnoses of sensorineural hearing loss. This type of error becomes proportionally much smaller as age increases (17).

Another explanation may be an underestimation of the conductive component in these infants, which could result in improvement of hearing function when the conductive component has been resolved at final ABR measurement (3). This is unlikely since the overall number of infants with a conductive hearing loss remains stable. However, ABR measurement is not the most sensitive diagnostic tool to diagnose conductive hearing loss. Therefore, dissolving of the conductive component may partly be responsible for the improvement of hearing function.

Only a few infants showed a deterioration of hearing function from a symmetric sensorineural hearing loss to absent ABR responses. Progressive hearing loss can be explained by a genetic cause, a CMV infection or bacterial meningitis, which are known causes of delayed deterioration of hearing function (8, 18-19). It is beyond the scope of this article to study the etiologic background of hearing loss. The etiologic factors associated with sensorineural hearing loss in this population are separately described (20).

We found that 1.8% of the screened NICU population had a sensorineural hearing loss or absent ABR responses. Robertson et al. followed a large cohort of premature infants who had been admitted to the NICU up to three and five years of age (3). They found permanent hearing loss in 3.1% of NICU survivors, of which 1.9% had a severe to profound hearing loss (>70 dB NHL). The difference in prevalence of congenital hearing loss could be explained by some methodological differences. Robertson et al. studied infants longitudinally, with behavioural audiometry. Ten percent of infants in this study had delayed onset congenital hearing loss (3).
Declau et al. studied infants from the NICU and well-baby nursery after failing neonatal hearing screening (8); only 13 NICU infants were enrolled, a permanent hearing loss was found in 61.5% of these cases (median hearing loss 60 dB NHL), which is comparable to our results.

Overall, ABR response thresholds improved between the first and final ABR measurement with 10 to 20 dB. This could be explained by dissolving of middle ear effusion, but maturation of the auditory system is a more likely explanation. Although it is not clear exactly when neonatal ABR thresholds become adult-like, a 10 to 20 dB threshold difference is reported to disappear in the first 24 months of life (21).

Although we only have results of repeated ABR measurement for 73.8% of the population, only 7.8% of the population was lost to follow-up. The other children had normal hearing, were followed elsewhere or unfortunately died. Age at follow-up in our study ranged from eight months to five years and was not long enough to study the effects of hearing loss on speech and language development. The clinical assessment of the ability to hear by means of behavioural testing could also not be performed in most infants. We know that early diagnosis and treatment of hearing loss results in better receptive language at school age (7). However, since about 10% of the population were initially incorrectly diagnosed with a sensorineural hearing loss careful management and counselling strategies are warranted. Perhaps aggressive or surgical treatment decisions should not be made until after repeated ABR measurement (or other confirmatory diagnostic testing) has been conducted.

Conclusion

This study shows the diagnosis and follow-up of ABR measurement after failure on neonatal hearing screening in infants who had been admitted to the NICU. In this high-risk population we found sensorineural hearing loss or absent ABR responses in nearly two thirds of the cases. About 10% of infants were incorrectly diagnosed with a sensorineural hearing loss, which later improved to normal hearing, probably due to maturation of the auditory system. This improvement may partly be due to dissolving of a conductive component. The overall degree of hearing loss improved in infants with sensorineural hearing loss or absent ABR responses. In a small percentage of children the hearing deteriorated.

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Chapter 5

Incidence and clinical value of prolonged I-V interval in NICU infants after failing neonatal hearing screening

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Abstract

Objectives: Infants admitted to neonatal intensive care units (NICUs) have a higher incidence of perinatal complications and delayed maturational processes. Parameters of the auditory brainstem response (1) were analyzed to study the prevalence of delayed auditory maturation or neural pathology. The prevalence of prolonged I-V interval as a measure of delayed maturation and the correlation with ABR thresholds were investigated.

Methods: All infants admitted to the NICU Sophia Children's Hospital between 2004 and 2009 who had been referred for ABR measurement after failing neonatal hearing screening with automated auditory brainstem response (AABR) were included. The ABR parameters were retrospectively analyzed.

Results: Between 2004 and 2009 103 infants were included: 46 girls and 57 boys. In 58.3% (60 infants) of our population the I-V interval was recordable in at least one ear at first diagnostic ABR measurement. In 4.9% the I-V interval was severely prolonged. The median ABR threshold of infants with a normal or mildly prolonged I-V interval was 50 dB. The median ABR threshold of infants with a severely prolonged I-V interval was 30 dB.

Conclusion: In case both peak I and V were measurable, we found only a limited (4.9%) incidence of severely prolonged I-V interval (≥ 0.8 ms) in this high-risk NICU population. A mild delay in maturation is a more probable explanation than major audiologic or neural pathology, as ABR thresholds were near normal in these infants.

Introduction

Infants admitted to the neonatal intensive care unit (NICU) have a higher incidence of congenital hearing loss compared to the healthy newborn population (2-3). Several risk factors have been associated with this increased risk (4-7). Moreover, preterm infants often have a delayed maturation of the auditory system compared to term infants. This results in a vulnerable population regarding audiologic problems.

The I-V interval is often used as a measure of auditory maturation, to describe the central conduction time. It is reported to be increased in preterm infants compared to term infants (8-10). The I-V interval shows an age-dependent decline up to about two years of age (11-13). Explanations for the normalisation of the I-V interval are increased myelination or increased synaptic efficacy (9, 11, 13-16). Although it is known that infants admitted to NICUs are at higher risk of developing perinatal complications and abnormal maturational processes, the incidence of prolonged I-V interval in NICU infants who failed neonatal hearing screening is unknown.

What this study adds is the incidence of prolonged I-V interval in a large cohort of NICU infants after failing neonatal hearing screening. We also investigated whether there is a correlation between prolonged I-V interval and elevated Auditory Brainstem Response (ABR) thresholds. The development of these parameters over time was followed to study the auditory maturational changes.

Material and methods

Patients

The Sophia Children's Hospital is a tertiary care centre in Rotterdam, the Netherlands. In 2008 the life birth number in The Netherlands was 184,634, of which 4,003 infants required NICU care of which 639 were admitted to the NICU at Sophia's Children Hospital.

In the Netherlands, all infants admitted to the NICU longer than 24 hours undergo standard hearing screening by means of automated auditory brainstem responses (AABR). The first AABR screening is usually conducted upon discharge from the NICU. In case of unilateral or bilateral failure on AABR screening, AABR measurement should be repeated before 6 weeks corrected age (46 weeks postconceptional age). Upon second AABR failure children are referred for audiologic evaluation. This audiologic evaluation consists of ABR, transient evoked otoacoustic emissions (TEOAE) and tympanometry measurement. After diagnostic evaluation all infants are seen by an experienced audiologist and otorhinolaryngologist. This should ideally take place before 3 months corrected age (52 weeks postconceptional age).

Between 2004 and 2009 3,366 infants were admitted to our NICU, of which 3,316 were screened with AABR. A total of 103 infants were referred for ABR analysis after repeated failure on AABR screening. Data of these ABR recordings were used to retrospectively analyse the ABR parameters.

Apparatus and procedures

All children were discharged from the NICU by the time ABR measurement was conducted. ABR measurements were recorded at our outpatient clinic in a soundproof room.

All children were in natural sleep or in calm conditions throughout the assessment. Both ears were sequentially tested. ABRs were recorded using the EUPHRA-1 system using a Toennies preamplifier. Responses were recorded using silver cup electrodes placed at both mastoids with a reference at the vertex and a ground electrode on the forehead. A band-filter was used with cut-off frequencies of 20 Hz and 3 kHz. The repetition frequency was 23 Hz. Click stimuli were presented starting at a level of 90 dB nHL. With step sizes of 10 dB the level was decreased until no response was found.

TEOAE measurements were performed using the Otodynamics ILO 288 USB II system with the standard settings. The stimulus level was set to 84 dB SPL, a number of 260 averages was used.

Tympanometry was performed with an Interacoustics AT 235H system using the standard settings and a 1 kHz probe-frequency. Clinical experts interpreted the results.

After diagnostic evaluation all infants were seen at the outpatient clinic by an experienced audiologist and otorhinolaryngologist.

Analysis of response

The absolute latencies and interpeak intervals as well as the response thresholds were recorded. Experienced clinical specialists interpreted the ABR waves. The response latencies in milliseconds were obtained by establishing the peak of the wave and reading out the digitally displayed time. The I-V interval was obtained by subtracting the latency of peak I from peak V, measured at 90 dB nHL stimulation level. The response threshold was estimated by the lowest level at which a response was found. The corresponding hearing loss was estimated as 10 dB below this level.

The absolute latencies and interpeak intervals of ABR measurement were compared to the references values based on normal hearing infants from our clinic (17). These reference values are corrected for postconceptional age to account for maturational changes in ABR parameters.

TEOAE and tympanometry measurement were used to confirm the diagnosis of conductive hearing loss when available.

Results

Between 2004 and 2009 3,366 infants were admitted to our NICU, of which 3,316 were screened with AABR. A total of 103 infants were referred for ABR analysis after second failure on AABR screening: 46 girls and 57 boys. The median gestational age at birth was 34.7 weeks (interquartile range 27.3 to 39.3 weeks). The median birth weight was 1,930 grams (interquartile range 946 to 2,911 grams). The median postconceptional age at first diagnostic ABR measurement was 43 weeks (interquartile range 39 to 48 weeks). Data of repeated ABR measurement was available for 79 of the 103 infants (76.7%). The majority (75%) of infants that had no repeated ABR measurement had a normal ABR results at primary assessment. Five infants died after primary ABR measurement. The median postconceptional age at final ABR measurement was 83 weeks (interquartile range 62 to 124 weeks).

ABR results were analysed in 103 NICU infants (206 ears). In table 1 the different types of responses at first ABR measurement are presented. In some cases all peaks were recordable, whereas in others only a single peak (mostly peak V) or no measurable ABR response was found. The peaks were not always equally measurable in both ears.

Table 1

Recordable ABR peaks	Number of infants
Peak I, V	60
Peak I	1
Peak V	19
No response	23

Table 1. The recordable ABR peaks of infants referred for ABR analysis after failing AABR neonatal hearing screening are presented. The peaks were recordable in at least one ear, but were not always symmetrically measurable. All infants with no measurable response were affected on both sides.

In 104 ears (60 infants) the I-V interval was measurable at the first diagnostic ABR after failing neonatal hearing screening. Figure 1 shows the I-V intervals of these infants and the age corrected reference values used in our clinic (17). A clear age-dependent decline of I-V interval with increasing postconceptional age is present. A prolonged I-V interval compared to our reference values is mainly seen in the younger postconceptional ages.

Figure 1

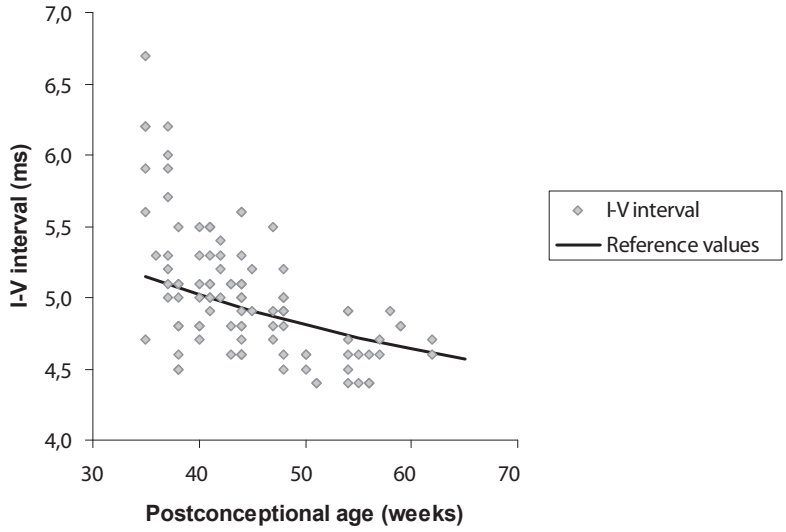

Figure 1. The I-V interval of 104 ears (60 infants) with recordable I-V interval at first diagnostic ABR measurement after failing neonatal hearing screening is presented. The black line represents the reference values used in our clinic that correct for postconceptional age.

Further on we will focus on infants instead of ears. In 44 infants the I-V interval was recordable in both ears. In eight infants the I-V interval was recordable only in the right ear and in another eight infants the I-V interval was recordable only in the left ear. Table 2 shows the number of cases in which the I-V interval was prolonged by one (mildly) or two (severely) standard deviations compared to our reference values. In 15.5% of our population (16 infants) at least a mildly prolonged I-V Interval was found, in 4.9% of our population (5 infants) the I-V interval was severely prolonged by two standard deviations. It can be concluded from table 2 that a prolonged I-V interval very often only affects one ear.

Table 2

	I-V interval mildly prolonged (≥ 0.4 ms; <0.8 ms)	I-V interval severely prolonged (≥ 0.8 ms)
Both ears	1	3*
Right ear	3	1
Left ear	7	1
Total	11	5

Table 2. The number of infants in whom the I-V interval is mildly prolonged (by one standard deviation (≥ 0.4 ms; <0.8 ms)) or severely prolonged (by two standard deviations (≥0.8 ms)) are presented.
*One infant had a mildly prolonged I-V interval (≥ 0.4 ms; <0.8 ms) in the left ear and a severely prolonged I-V interval (≥0.8 ms) in the right ear and has been classified in the severely prolonged group based on the worst ear.

Table 3 shows the follow-up of the 16 infants with a prolonged I-V interval. Nineteen percent of infants with a prolonged I-V interval, by either one or two standard deviations, developed a normal I-V interval after follow-up.

Table 3

Final ABR result	Total number of infants with a prolonged I-V interval
I-V interval becomes normal	3 (19%)
I-V interval remains prolonged (≥ 0.4 ms)	7 (50%)
I-V interval is not recordable	1 (6%)
Not repeated	5 (25%)

Table 3. Follow-up of infants with a prolonged I-V interval (by either one or two standard deviations) at primary ABR assessment

ABR response thresholds

To give a better view on the effect of a prolonged I-V interval on the ABR results, we also analysed the corresponding ABR thresholds. In infants with a normal I-V interval the median ABR threshold was 50 dB (interquartile range 32.4-70 dB). In infants with a mildly prolonged I-V interval (by one standard deviation) the median ABR threshold was 50 dB (interquartile range 37.5-70 dB). In infants with a severely prolonged I-V interval (by two standard deviations) the median ABR threshold was 30 dB (interquartile range 30-35 dB).

After follow-up the median ABR threshold of infants with a normal I-V interval was 50 dB (interquartile range 30-62.5 dB). The median ABR threshold of infants with a prolonged I-V interval after follow-up was also 50 dB (interquartile range 30-60 dB).

In 31,5% of infants with elevated ABR thresholds (≥ 50 dB) a flat tympanogram was found, it should be noted that tympanometry was not available in all infants. A conductive hearing loss will influence ABR thresholds and peak latencies, but will have no effect on the I-V interval latency.

Discussion

The prevalence of prolonged I-V interval and the correlation with ABR thresholds in a population of 103 NICU infants who failed neonatal hearing screening was analyzed. In 58.3% of infants the I-V interval was recordable at first diagnostic ABR measurement after failing neonatal hearing screening. A prolongation of the I-V interval by one or two standard deviations (≥ 0.4 ms) was found in 15.5% of our population.

Jiang et al. found an incidence of abnormal central ABR component in 17% of preterm very low birth weight infants (8). Although the populations differ with respect to birth weight and failing neonatal

hearing screening, the prevalence of prolonged I-V interval as a measure of abnormal central component concur. It is known that high-risk infants have an increased incidence of prolonged I-V interval compared to low risk infants (18).

Several studies regarding normal values and maturational changes of ABR parameters have reported no significant differences between right and left ears (9, 19-20). Therefore, it is remarkable that we found that a prolonged I-V interval often only affects one ear. However, in the three infants with a unilateral prolonged I-V interval by two standard deviations the I-V interval in the other ear was either unrecordable or prolonged by one standard deviation. Therefore no large inter aural differences in I-V interval were found.

Jiang et al. found that 14% had an elevation of ABR threshold (>30 dB) (8). In our population, the median ABR threshold was elevated at 50 dB for both infants with a normal I-V interval and infants with a mildly prolonged I-V interval. The ABR threshold of infants with a severely prolonged I-V interval was lower, median ABR threshold 30 dB. The lower ABR thresholds in infants with more severe prolongation of I-V interval suggest that a severely prolonged I-V interval has no large impact on hearing sensitivity. This also suggests that a delay in maturation is a more probable cause than major audiologic or neural pathology. This is supported by the fact that these infants are among the younger infants in our population.

The immature auditory system is characterized by increased ABR peak latencies and increased ABR thresholds. We know that auditory maturation can be delayed in preterm compared to term infants (18). The maturation effect of the response threshold is relatively small and matures sooner than the maturation of the I-V interval (21). Therefore, the combination of a normal response threshold and a prolonged I-V interval is likely to occur in case of delayed auditory maturation. Also, in the presence of a normal ABR threshold severe neural pathology is unlikely.

In 41.7% of the population the I-V could not be recorded at first diagnostic ABR measurement. In 22.3% no measurable ABR response was found. After follow-up this improved to normal or prolonged I-V interval for 8 infants (7.8% of the total population). In these infants again delayed auditory maturation or dissolving of middle ear effusion is the most likely explanation. There were only a few infants in whom a normal I-V interval deteriorated to a prolonged or absent I-V interval after repeated ABR measurement.

The aim of universal neonatal hearing screening is to diagnose hearing impairment and start treatment before the age of 6 months (2). Based on our findings that only 4.9% of infants have a prolonged I-V interval, the timing of the first diagnostic evaluation in our population seems adequate (median postconceptional age 43 weeks). When a prolonged I-V interval is found, infants

should be followed to determine if the I-V interval normalizes. Especially since we know that the maturational processes can be delayed in preterm infants.

Conclusion

I-V interval and ABR thresholds in a population of 103 NICU infants who failed neonatal hearing screening were analyzed. In 58.3% of the population I-V could be measured at primary ABR measurement. In 4.9% of the population a severely prolonged I-V interval was found. Corresponding ABR thresholds were lower compared to infants with normal I-V interval, suggesting delayed auditory maturation or at least no large impact on hearing pathology.

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Chapter 9

Risk factors for auditory neuropathy spectrum disorder in NICU infants compared to normal hearing NICU controls

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Abstract

Objectives: To evaluate independent etiologic factors associated with auditory neuropathy spectrum disorder (ANSD) in infants who have been admitted to the neonatal intensive care unit (NICU) compared to normal hearing controls.

Study design: Case control study

Methods: We included all infants (n=9) with the ANSD profile admitted to the NICU of Sophia Children's Hospital between 2004 and 2009. Each patient was matched with four normal hearing controls of the same gender and postconceptional age.

The following possible risk factors were studied: birth weight, dysmorphic features, APGAR scores (at 1, 5 and 10 minutes), respiratory distress (IRDS), CMV infection, sepsis, meningitis, cerebral bleeding, hyperbilirubinemia requiring phototherapy, peak total bilirubin level, furosemide, dexamethason, vancomycin, gentamycin and tobramycin administration.

Results: Nine infants met the ANSD criteria in one or both ears. IRDS (P=0.02), meningitis (P=0.04) and vancomycin administration (P=0.009) were significantly increased in infants with ANSD compared to controls.

Conclusions: In high-risk NICU infants IRDS, meningitis and vancomycin administration are associated with auditory neuropathy spectrum disorder.

Introduction

Auditory neuropathy spectrum disorder (ANSD) is a condition of multifactorial origin in which transmission of sound to the brain is abnormal. Children who suffer from this condition experience difficulties with speech perception, especially in noise, and the development of language skills (1-3). The ANSD profile is characterised by an abnormal Auditory Brainstem Response (ABR) and normal otoacoustic emissions (OAEs) and/or cochlear microphonics (CMs). This combination suggests normally functioning cochlear outer hair cells but an abnormal transduction from the inner hair cells to the brainstem. However, the exact pathologic and etiologic pathway remains uncertain (4-5).

Several authors studied the prevalence of ANSD and etiologic factors in a screened newborn population (6-9). Most authors compare infants with ANSD to infants with sensorineural hearing loss. A higher prevalence of ANSD among high-risk NICU infants is a common finding. They also found that low birth weight, hyperbilirubinemia, sepsis and ototoxic medication are possible etiologic factors (6-8). Because most of these risk factors are related to NICU admittance it is unclear which risk factors play an independent contributing role to ANSD. Only by comparison within the NICU population the risk factors specific to ANSD can be assessed. To our knowledge, such a comparison is not available.

What this study adds is the evaluation of the independent etiologic factors that may play a role in the development of ANSD in a high-risk NICU population. We compared NICU infants with ANSD to age and gender matched normal hearing NICU controls.

Material and methods

Study subjects

We included all patients who meet with the criteria of ANSD after failure on neonatal hearing screening who had been admitted to the NICU at Sophia's Children Hospital between 2004 and 2009. Each patient was matched with four controls of the same gender and postconceptional age. Postconceptional age was matched within a one week range. Controls had to be born in the same year to minimize changes in care practises over the study period. Controls also had to be admitted to the NICU at our hospital and all passed neonatal hearing screening.

The following characteristics were obtained from the medical record of patients and controls: birth weight, dysmorphic features, APGAR scores (at 1, 5 and 10 minutes), respiratory distress (IRDS; on chest X-ray), CMV infection, culture proven sepsis, culture proven or clinically suspected meningitis, cerebral bleeding, hyperbilirubinemia requiring phototherapy, peak total bilirubin level, furosemide, dexamethasone, vancomycin, gentamycin and tobramycin administration.

These study characteristics were determined in advance based on literature review of risk factors associated with congenital hearing loss and ANSD.

Study setting

The Sophia Children's Hospital is regional tertiary care centre in Rotterdam, the Netherlands. In 2008 the life birth number in the Netherlands was 184.634, 4.003 infants required NICU care of which 639 were admitted to the NICU at Sophia's Children Hospital (all deceased infants are excluded from these admittance numbers).

Audiologic evaluation

All infants admitted to the NICU longer than 24 hours undergo standard hearing screening by means of automated auditory brainstem responses (AABR), measured at a stimulus intensity of 35 dB nHL. A signal-detection algorithm determined the presence of an ABR and assigned a pass or refer result. In case of second unilateral or bilateral failure on AABR screening infants are referred for audiologic evaluation at our outpatient clinic. This audiologic evaluation consists of ABR, transient evoked otoacoustic emissions (TEOAE) and tympanometry measurement. After diagnostic evaluation all infants were seen by an experienced audiologist and otorhinolaryngologist.

ABR measurements were recorded at our outpatient clinic in a soundproof room. All children were in natural sleep or in calm conditions throughout the assessment. Both ears were sequentially tested. ABRs were recorded using the EUPHRA-1 system using a Toennies preamplifier. Responses were recorded using silver cup electrodes placed at both mastoids with a reference at the vertex and a ground electrode on the forehead and then band pass filtered. A band-filter was used with cut-off frequencies of 20 Hz and 3 kHz. The repetition frequency was 23 Hz. Click stimuli were used with alternating polarity. Click stimuli were presented starting at a level of 90 dB nHL. With step sizes of 10 dB the level was decreased until no response was found. The response threshold was estimated by the lowest level at which a response was found. The corresponding hearing loss can be estimated as 10 dB below this level. Experienced clinical specialists interpreted the ABR response waves, based on our reference values that correct for postconceptional age (10). In the results section of this manuscript the ABR response threshold levels are mentioned, in stead of the estimated hearing losses.
OAE measurements were performed using the Otodynamics ILO 288 USB II system with the standard settings. The stimulus level was set to 84 dB SPL, a number of 260 averages was used.
Tympanometry was performed with an Interacoustics AT 235H system using the standard settings and a 1 kHz probe-frequency. Clinical experts interpreted the results.

ANSD profile

The ANSD profile consisted of failed neonatal hearing screening followed by abnormal diagnostic ABR in one or both ears combined with preserved OAE in the same ear. Abnormal ABR was defined as an absent response or a response threshold ≥ 70 dB without the presence of a wave I. This is in line with the current definition of ANSD as used in the literature (11). Preserved OAE required at least 3 of 4 positive frequency bands. Cochlear microphonics, which are often used to confirm

the diagnosis of ANSD, were not included in our selection criteria because they cannot by reliably analysed using standard headphones.

Statistical analysis

The SPSS 15 (SPSS Inc., Chicago, IL, USA) statistical package was used for the analysis. For continuous values the Mann-Whitney U test was used. For dichotomous values the Pearson's χ^2 was used. P-values ≤ 0.05 were considered statistically significant. No adjustments for multiple testing were made.

Results

Characteristics

Between 2004 and 2009 3,366 infants were admitted to our NICU, of which 3,316 were screened with AABR (99%). The infants that were not screened were admitted to the NICU less than 24 hours or died. A total of 103 infants were referred for ABR analysis after second failure on AABR screening. Of these 103 infants nine infants met the ANSD profile criteria in one or both ears; seven boys and six girls. Evidence of ANSD was found at the first diagnostic evaluation after failing neonatal hearing screening. Table 1 shows the main characteristics of these nine ANSD infants.

Table 1

Case	Sex	Postconceptional age at birth (weeks)	Birth weight (grams)	ANSD profile	Risk factors
1	M	26	945	Bilateral *	IRDS, sepsis, cerebral bleeding, phototherapy, furosemide, vancomycin
2	M	28	685	Bilateral *	IRDS, sepsis, phototherapy, furosemide, gentamycin, vancomycin
3	M	25	750	Unilateral	IRDS, sepsis, cerebral bleeding, phototherapy, furosemide, gentamycin, vancomycin, dexamethason
4	M	27	1280	Unilateral *	IRDS, sepsis, meningitis, cerebral bleeding, phototherapy, vancomycin, gentamycin
5	F	30	1430	Unilateral *	IRDS, meningitis, phototherapy, furosemide
6	F	29	1310	Unilateral	IRDS, sepsis, phototherapy, vancomycin, gentamycin
7	F	25	920	Unilateral	IRDS, sepsis, phototherapy, vancomycin, gentamycin, dexamethason
8	F	27	590	Unilateral	IRDS, sepsis, phototherapy, vancomycin
9	M	28	930	Unilateral	IRDS, sepsis, phototherapy, vancomycin, tobramycin, dexamethason

The characteristics of the nine infants with the ANSD profile.
M = male, F = female
* Imaging showed normal inner ear and cochlear nerve anatomy

The median postconceptional age of the ANSD infants was 27.4 weeks (interquartile range 25.6 to 28.6 weeks). These infants were matched to 36 controls with the same gender division. The median postconceptional age of the controls was 27.4 weeks (interquartile range 26 to 27.8 weeks).

Table 2 describes the characteristics of the nine infants with ANSD and the 36 controls. Comparison between infants with ANSD and controls was statistically significant for IRDS (P=0.02), meningitis (P=0.04) and vancomycin administration (P=0.009). All the other characteristics were not statistically significantly different.

Table 2

	Patients (9)	Controls (36)	Significance
Birth weight grams, *median, IQR*	930 (718-1295)	1026 (865-1180)	**P=0.55**
Dysmorphic features, *n (%)*	0 (0)	0 (0)	n.a.
APGAR 1 min, *mean SD*	5.7 (2.5)	6.1 (2.6)	**P=0.65**
APGAR 5 min, *mean SD*	7.8 (2.4)	7.9 (1.8)	**P=0.53**
APGAR 10 min, *mean SD*	8.6 (1.8)	8.8 (0.9)	**P=0.42**
IRDS, *n (%)*	9 (100)	22 (61.1)	**P=0.02**
CMV, *n (%)*	0 (0)	0 (0)	n.a.
Sepsis, *n (%)*	8 (88.9)	20 (55.6)	**P=0.07**
Meningitis, *n (%)*	2 (22.2)	0	**P=0.004**
Cerebral bleeding, *n (%)*	3 (33.3)	6 (16.7)	**P=0.26**
Phototherapy, *n (%)*	9 (100)	29 (82.9)	**P=0.18**
Peak total bilirubin, *mean SD*	203.6 (45.8)	166.2 (29.3)	**P=0.06**
Vancomycin, *n (%)*	8 (88.9)	14 (38.9)	**P=0.009**
Gentamycin, *n (%)*	5 (55.6)	25 (69.4)	**P=0.43**
Tobramycin, *n (%)*	1 (11.1)	7 (19.4)	**P=0.26**
Furosemide, *n (%)*	4 (44.4)	9 (25)	**P=0.56**
Dexamethason, *n (%)*	3 (33.3)	6 (16.7)	**P=0.25**

The characteristics of patients with the ANSD profile (absent or only peak V ≥ 70 dB nHL) and controls matched for gender and gestational age. The results of statistical testing are shown. For dichotomous values the Pearson's $\chi 2$ was used. For continuous values the Mann-Whitney U test was used.

Considering the strong correlation between vancomycin administration and ANSD we also analysed serum vancomycin levels. Peak serum levels were not available in most infants. Trough serum levels were available in 7 of the 9 ANSD infants and in 13 of the 14 controls who were treated with vancomycin. The median serum vancomycin level was 15.5 mg/l (interquartile range 7.5 to 18.3 mg/l) in ANSD infants and 16.3 mg/l (interquartile range 9.6 to 17.8 mg/l) in controls. Comparison of serum vancomycin levels between infants with ANSD and controls showed no statistically significant difference (P=0.6).

Discussion

Compared to postconceptional age and gender matched normal hearing controls IRDS, meningitis and vancomycin administration were found to be significantly more present in NICU infants with ANSD.

IRDS was significantly more common in infants with ANSD. It has been shown in animal models that the inner cochlear hair cells are sensitive to prolonged mild hypoxia, whereas the outer cells are unaffected (12). Xionis et al. found that mechanical ventilation and chronic lung disease were significantly more common in infants with ANSD compared to infants with sensorineural hearing loss (8). Our results support the evidence that hypoxia may be a risk factor in developing ANSD.

Sepsis and meningitis are known risk factors for developing congenital hearing loss (13-14). Dowley et al. found that sepsis was significantly more common among NICU infants with auditory neuropathy (7). In our study sepsis did almost reach statistical significance. Therefore it may be suggested from our results that there is a correlation between sepsis and ANSD.
We found a statistically significant correlation between meningitis and ANSD. Meningitis often results in both cochlear and retro-cochlear dysfunction. However, the number of infants with meningitis in our study is very small which may have influenced the results.

Although vancomycin has been reported not to be ototoxic in a large cohort of NICU infants (15), we found a strong correlation between vancomycin administration and auditory neuropathy. Similarly to the results by de Hoog et al. we found no relation between vancomycin through serum levels and ANSD. The correlation between vancomycin administration and ANSD has been confirmed by several other authors (6, 8). These authors did not investigate serum vancomycin levels.
To our knowledge it is not known whether vancomycin itself or the combination with associated sepsis is the causal factor leading to ANSD. However, we found that the correlation between ANSD and vancomycin administration is much stronger than the correlation between ANSD and sepsis (P=0.009 and P=0.06 respectively). In addition to this, all patients with sepsis in our ANSD group were treated with vancomycin, whereas as much as 30% of controls with sepsis were not treated with vancomycin. This suggests that vancomycin may play an independent role in developing auditory neuropathy. In order to reduce auditory complications, considering alternatives for vancomycin treatment for nosocomial infection is warranted.

The damaging effect of hyperbilirubinemia on the auditory system of infants has been known for years (9, 16-18). The ototoxic effect of unconjugated bilirubin is reported to spare the cochlea, but to selectively damage the brainstem auditory nuclei. The auditory nerve and spiral ganglion containing cell bodies of primary auditory neurons may also be affected (19). This explains the association between hyperbilirubinemia and ANSD found in other studies (1, 6, 9, 18).

In our study the number of infants that had to be treated for hyperbilirubinemia with phototherapy and the peak total bilirubin level were not statistically significantly different between the ANSD and control group. However, the peak total bilirubin level almost reached statistical significance. This might imply that the degree of hyperbilirubinemia, and probably also the duration of phototherapy play a role.

We found that 0.27% of the total NICU population and 8.7% of the infants who failed neonatal hearing screening showed the ANSD profile. This is in line with prevalence number reported in other high-risk populations (7, 20). Berg et al. found a much higher incidence (24%) of ANSD in a high-risk population, but this probably due to a methodological differences as he used referral on AABR instead of poor ABR results as selection criteria (6).

The result of stricter ANSD criteria is a relatively small sample size. This might have influenced the outcome of our statistical analysis, as there is a higher chance of a type I error. A different etiologic profile of one or two infants with ANSD may change the outcome of statistical analysis.

Another possible limitation is that we did not have imaging studies performed in all infants. Imaging studies were performed in only four infants, showing normal inner ear anatomy. In the other five infants with unilateral ANSD a case of cochlear nerve dysplasia may have been missed.

Conclusion

IRDS, meningitis and vancomycin administration are risk factors for developing ANSD independent of postconceptional age, gender and NICU admittance. This confirms the need for careful management of these risk factors to minimize the incidence of hearing loss.

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Chapter 7

Risk factors for sensorineural hearing loss in NICU infants compared to normal hearing NICU controls

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Abstract

Objectives: To evaluate independent etiologic factors associated with sensorineural hearing loss in infants who have been admitted to the neonatal intensive care unit compared to normal hearing controls.

Method: Between 2004 and 2009, 3366 infants were admitted to the neonatal intensive care unit of Sophia Children's Hospital, of which 3316 were screened with AABR. A total of 103 infants were referred for auditory brainstem response analysis after failure on neonatal hearing screening. We included all infants diagnosed with sensorineural hearing loss. Each patient was matched with two normal hearing controls from the neonatal intensive care unit of the same gender and postconceptional age.

The following risk factors were studied: birth weight, dysmorphic features, APGAR scores (at 1, 5 and 10 minutes), respiratory distress (IRDS), CMV infection, sepsis, meningitis, cerebral bleeding, cerebral infarction, hyperbilirubinemia requiring phototherapy, peak total bilirubin level, furosemide, dexamethason, vancomycin, gentamycin and tobramycin administration.

Results: Fifty-eight infants were diagnosed with sensorineural hearing loss: 26 girls and 32 boys. The incidence of dysmorphic features (P=0.000), low APGAR score (1 minute) (P=0.01), sepsis (P=0.003), meningitis (P=0.013), cerebral bleeding (P=0.016) and cerebral infarction (P=0.000) were significantly increased in infants with sensorineural hearing loss compared to normal hearing controls (n=116).

Conclusion: Dysmorphic features, low APGAR scores at 1 minute, sepsis, meningitis, cerebral bleeding and cerebral infarction are associated with sensorineural hearing loss independent of neonatal intensive care unit admittance.

Introduction

Infants admitted to the neonatal intensive care unit (NICU) have an increased risk of developing congenital hearing loss (1-2). Multiple risk factors have been associated with congenital hearing loss. This has resulted in a universal newborn hearing screening program aimed at early diagnosis and treatment of congenital hearing loss (3). In high-risk NICU infants the screening program focuses at diagnosing sensorineural hearing loss (SNHL) and auditory neuropathy spectrum disorder (ANSD) since these conditions are known to cause long-term problems on language and speech development (4-5).

Several authors have studied the presence of risk factors identified by the Joint Committee on Infants Hearing (JCIH) among NICU infants (1-2, 6-9). Most studies concerned a relative small number of NICU infants, or did not have a control group of normal hearing infants. Robertson et al. studied the long-term hearing outcome and risk factors of a large cohort of NICU infants (2). Risk factors that are commonly found among NICU infants are prolonged mechanical ventilation, asphyxia, low birth weight and ototoxic medication.
Because most of these risk factors are related to NICU admittance it is unclear which risk factors play an independent contributing role to SNHL. Only by comparison within the NICU population the risk factors specific to SNHL can be assessed.

This study adds the evaluation of the independent etiologic factors that may play a role in the development of SNHL in a high-risk NICU population. We compared NICU infants with SNHL to age and gender matched normal hearing NICU controls.

Material and methods

Study subjects

We included all patients diagnosed with SNHL after failure on neonatal hearing screening who had been admitted to the NICU at Sophia's Children Hospital between 2004 and 2009. Each patient was matched with two controls of the same gender and postconceptional age. Postconceptional age was matched within a one week range. Controls had to be born in the same year to minimize changes in care practises over the study period. Controls also had to be admitted to the NICU at our hospital and they all passed neonatal hearing screening.
The following characteristics were obtained from the medical record of patients and controls: birth weight, dysmorphic features, APGAR scores (at 1, 5 and 10 minutes), respiratory distress (IRDS), CMV infection, culture proven sepsis, culture proven or clinically suspected meningitis, cerebral bleeding, cerebral infarction, hyperbilirubinemia requiring phototherapy, peak total bilirubin level, furosemide, dexamethason, vancomycin, gentamycin and tobramycin administration.
These study characteristics were determined in advance based on risk factors identified by the JCIH and the literature review.

Study setting

The Sophia Children's Hospital is tertiary care centre in Rotterdam, the Netherlands. In 2008 the life birth number in the Netherlands was 184,634, of which 4,003 infants required NICU care of which 639 were admitted to the NICU at Sophia's Children Hospital (all deceased infants are excluded from these admittance numbers).

Audiologic evaluation

All infants admitted to the NICU longer than 24 hours undergo standard hearing screening by means of automated auditory brainstem responses (AABRs), measured at a stimulus intensity of 35 dB nHL. A signal-detection algorithm determined the presence of an ABR and assigned a pass or refers result. In case of second failure on AABR screening infants are referred for audiologic evaluation at our outpatient clinic. This audiologic evaluation consists of ABR, transient evoked otoacoustic emissions (TEOAE) and tympanometry measurement. After diagnostic evaluation all infants were seen by an experienced audiologist and otorhinolaryngologist.

ABR measurements were recorded at our outpatient clinic in a soundproof room. All children were in natural sleep or in calm conditions throughout the assessment. Both ears were sequentially tested. ABRs were recorded using the EUPHRA-1 system using a Toennies preamplifier. Responses were recorded using silver cup electrodes placed at both mastoids with a reference at the vertex and a ground electrode on the forehead and then band pass filtered. A band-filter was used with cut-off frequencies of 20 Hz and 3 kHz. The repetition frequency was 23 Hz. Click stimuli were used with alternating polarity. Click stimuli were presented starting at a level of 90 dB nHL. With step sizes of 10 dB the level was decreased until no response was found. The response threshold was estimated by the lowest level at which a response was found. The corresponding hearing loss can be estimated as 10 dB below this level. Experienced clinical specialists interpreted the ABR response waves, based on our reference values that correct for postconceptional age. In the results section of this manuscript the ABR threshold levels are mentioned, in stead of the estimated hearing losses.
TEOAE measurements were performed using the Otodynamics ILO 288 USB II system with the standard settings. The stimulus level was set to 84 dB SPL, a number of 260 averages was used.
Tympanometry was performed with an Interacoustics AT 235H system using the standard settings and a 1 kHz probe-frequency. Clinical experts interpreted the results.

Sensorineural hearing loss

Sensorineural hearing loss was defined as elevated ABR response thresholds (≥ 40 dB) in the best hearing ear. Infants with evidence of ANSD were excluded from the analysis. Evidence of ANSD was defined as an abnormal diagnostic ABR: absent response or a response threshold ≥ 60 dB. Preserved TEOAE required at least 3 of 4 positive frequency bands. Cochlear microphonics which are often used to confirm the diagnosis of ANSD were not measured. If tympanomtry and TEOAE were not performed successfully, SNHL was diagnosed based on the ABR results.

Statistical analysis

The SPSS 15 (SPSS Inc., Chicago, IL, USA) statistical package was used for the analysis. For continuous values the Mann-Whitney U test was used. For dichotomous values the Pearson's χ^2 was used. P-values ≤ 0.05 were considered statistically significant.

Results

Between 2004 and 2009, 3366 infants were admitted to our NICU, of which 3316 were screened with AABR (99%). A total of 103 infants were referred for ABR analysis after second failure on AABR screening. Of these 103 infants, 58 infants were diagnosed with SNHL; 26 girls and 32 boys. The diagnosis of SNHL was made at the first diagnostic evaluation after failing neonatal hearing screening. Thirteen infants with suspected ANSD were excluded from the analysis. The median postconceptional age at birth of the infants with SNHL was 37.1 weeks (interquartile range 29.1-39.6 weeks). These infants were matched to 116 controls with the same gender and age division. The median postconceptional age of the controls was 37.3 weeks (interquartile range 29.8-39.1 weeks).

In table 1 the different types of SNHL that were found at the first diagnostic ABR measurement are described. The median postconceptional age at first diagnostic ABR measurement was 44 weeks (interquartile range 40-48 weeks). A symmetric SNHL was defined as an inter-aural threshold difference <30 dB. An asymmetric SNHL was defined as an inter-aural threshold difference ≥30 dB. In all infants with no recordable ABR responses both ears were affected. The ABR response thresholds were used to study the degree of hearing loss, described for the best and worst hearing ear (Table 1). The majority of hearing losses can be regarded as profound to severe.

Table 1

Type of SNHL	Number of infants	ABR response threshold dB Best hearing ear *Median (IQR)*	ABR response threshold dB Worst hearing ear *Median (IQR)*
Symmetric SNHL	29	60 (50-80)	70 (70-80)
Asymmetric SNHL	11	40 (40-55)	110 (85-110)
No measurable ABR response	18	110 (110-110)	110 (110-110)

Table 1 presents the types of SNHL loss found at first diagnostic ABR measurement after failing neonatal hearing screening. Symmetric SNHL is defined as an inter-aural threshold difference <30dB. An asymmetric SNHL is defined as an inter-aural threshold difference ≥30dB. In all infants with no measurable ABR response both ears were affected. The corresponding ABR response thresholds are mentioned for the best and worst hearing ear. The degree of hearing loss of infants with an absent ABR response was defined as 110 dB.

Table 2 describes the characteristics of the 58 infants with the SNHL and the 116 controls. Comparison between infants with SNHL and controls was statistically significantly different for dysmorphic features (P=0.000), APGAR scores (1 minute) (P=0.01), sepsis (P=0.003), meningitis (P=0.013), cerebral bleeding (P=0.016) and cerebral infarction (P=0.000). All the other characteristics were not statistically significantly different.

Table 2

	Patients (58)	Controls (116)	Significance
Birth weight grams, *median (IQR)*	2253 (1029-3189)	2444 (1205-3383)	ns
Dysmorphic features, *n (%)*	22‡ (37.9)	2‡ (1.7)	**P=0.000***
APGAR 1 min, *mean (SD)*	5.8 (2.7)	7.0 (2.5)	**P=0.01***
APGAR 5 min, *mean (SD)*	7.8 (1.9)	8.4 (1.8)	ns
APGAR 10 min, *mean (SD)*	8.6 (1.1)	8.9 (1.4)	ns
IRDS, *n (%)*	21 (36.2)	35 (30.2)	ns
CMV, *n (%)*	1 (1.7)	0 (0)	ns
Sepsis, *n (%)*	23 (39.7)	22 (19.0)	**P=0.003***
Meningitis, *n (%)*	3 (5.2)	0 (0)	**P=0.013***
Cerebral bleeding, *n (%)*	11 (19.0)	8 (6.9)	**P=0.016***
Cerebral infarction, *n (%)*	12 (20.7)	1 (0.9)	**P=0.000***
Phototherapy, *n (%)*	25 (43.1)	43 (37.1)	ns
Peak total bilirubin, *mean (SD)*	186.8 (119.3)	175.7 (131.2)	ns
Vancomycin, *n (%)*	11 (22)	19 (16.7)	ns
Gentamycin, *n (%)*	25 (51)	59 (51.8)	ns
Tobramycin, *n (%)*	7 (14)	21 (18.4)	ns
Furosemide, *n (%)*	9 (15.8)	13 (11.2)	ns

Table 2 shows the characteristics of patients with sensorineural hearing loss and controls matched for gender and gestational age. The results of statistical testing are shown when statistically significant.
ns: not significant
‡ Different associated syndromes
* Pearson's $\chi 2$

Discussion

We found that 1.7% of the total NICU population and 56.3% of the infants who failed neonatal hearing screening were diagnosed with SNHL. Hille et al. and Robertson et al. found a slightly higher prevalence of congenital hearing loss (3.1% and 3.2% respectively) (1-2). The exclusion of 13 cases of suspected ANSD from our analysis partly explains this difference. We chose to exclude cases of ANSD because this seems to be a different entity of hearing loss with a partially different aetiology (10). Since TEOAE could not be successfully measured in all infants, a few cases of ANSD may have been missed.

In addition to the exclusion of infants with suspected ANSD, the difference in prevalence of congenital hearing loss compared to Hille et al. and Robertson et al. could also be explained by some methodological differences. Robertson et al. studied infants longitudinally, with behavioural audiometry. Ten percent of infants in this study had delayed onset congenital hearing loss (2). Both studies only included extremely premature infants of younger postconceptional age and lower birth weight compared to our study population which could also contribute to the higher incidence of congenital hearing loss (1-2). Hille et al. only studied the results of AABR screening instead of diagnostic ABR measurement which could also have lead to a higher incidence of congenital hearing loss (1).

Compared to postconceptional age and gender matched normal hearing NICU controls dysmorphic features, low APGAR scores (1 minute), sepsis, meningitis, cerebral bleeding and cerebral infarction are significantly more present in NICU infants with SNHL.

The dysmorphic features that were found among these infants are related to a variety of syndromes associated with congenital hearing loss. For example Down syndrome, CHARGE and Jervell Lange-Nielsen were diagnosed. Readers are referred to Morton et al for an extensive overview of the prevalence of different types of syndromic and non-syndromic genetic causes of hearing loss (11). Dysmorphic features and syndromes were found among all subtypes of congenital sensorineural hearing loss (asymmetric SNHL, symmetric SNHL, no recordable ABR response).

The APGAR score is a method to asses the health of a newborn immediately after childbirth. APGAR scores at one minute were significantly lower in infants with SNHL compared to controls. Overall the APGAR scores at 5 and 10 min were also lower in the infants with SNHL. At 10 min the difference in APGAR scores between the controls and infants with SNHL were smallest, probably as a result of adequate treatment of the newborn infant. Low APGAR scores are an indicator of perinatal hypoxia. It has been shown in animal models that the cochlear hair cells are sensitive to prolonged mild hypoxia (12). Hille et al. and Vohr et al. also found a relation between low APGAR scores and hearing loss in NICU infants (1, 8). Several other authors found a relation between other parameters of hypoxia, such as prolonged mechanical ventilation, and hearing loss (2, 6, 9).

Meningitis is a known cause of SNHL and is recorded in the list of risk factors for congenital hearing loss defined by the Joint Committee on Infant Hearing (3). Since meningitis is a rather rare condition it is not found in many studies evaluating risk factors. Sepsis is a common condition in NICU infants with a poor effect on general outcome and health (13-14). Although sepsis is not listed as a risk factor for congenital hearing loss, we found a strong correlation between sepsis and SNHL.

We found a correlation between both cerebral bleeding and cerebral infarction and hearing loss. Eleven infants in our study had an intracranial haemorrhage. In three infants this was a grade I haemorrhage or subependymal haemorrhage. The other eight infants had a grade II or larger intracranial haemorrhage. Cerebral infarction was sometimes found in combination with cerebral bleeding. Meyer et al. studied the role of cerebral bleeding and periventricular leukomalacia in infants at risk of congenital hearing loss, but found no correlation (13). However, it is known that brain injury greatly influences the risk of late death or neurosensory impairment in extremely low birth weight infants (14). Depending on the localisation it is likely that extensive cerebral bleeding and infarction can cause hearing loss. We found cases of cerebral bleeding or cerebral infraction among all types of SNHL.

The majority of infants with SNHL in our population have a severe to profound hearing loss. Robertson et al. found a similar incidence of 1.9% severe to profound hearing loss (>70 dB NHL) (2).. The effects of hearing loss on speech and language development and functioning in daily life are determined by the degree of hearing loss of both ears. Unilateral hearing impairment does usually not cause as many problems in daily life as bilateral hearing impairment does. The majority of infants in our population with a symmetric or asymmetric sensorineural loss will be candidates for hearing aid revalidation based on the degree of hearing loss of their best hearing ear. For the infants with absent ABR responses cochlear implantation can also be considered. Early and adequate intervention is required to minimize future problems with speech and language development (15)

Conclusion

Dysmorphic features, low APGAR scores (at 1 minute), sepsis, meningitis, cerebral bleeding and cerebral infarction are risk factors for SNHL independent of postconceptional age, gender and NICU admittance.

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Chapter 8

General discussion

The goal of this thesis was to gain more insight on the normal physiological maturation and pathology of the auditory system in our NICU population. Therefore we investigated several aspects that play an important role in these developments:

1. An important aspect is the auditory brainstem response (ABR) measurement in relation to normal physiological maturation. To correct ABR response latencies for postconceptional age, a fitting model based on a theoretical background is developed such that normal values can be determined. Next, the underlying mechanism of auditory maturation and specific differences in preterm compared to term infants are discussed. Because of the poor detectability of various components of the ABR response in very preterm infants, analysis can be very difficult. As a first step to overcome this difficulty, a flowchart to analyze the ABR of preterm infants in an unambiguous stepwise fashion is designed.

2. Another aspect is the audiologic outcome of NICU infants who failed neonatal hearing screening. Because an exact audiologic diagnosis is important for adequate treatment and counseling strategies, we investigated the incidence, type and follow-up of congenital hearing loss in infants who failed neonatal hearing screening. Also some possible explanations for the improvement of hearing function during follow-up are discussed.

3. A third aspect that plays an important role in the development of the auditory system of preterm infants who fail neonatal hearing screening, is a delayed auditory maturation or neural pathology. A common finding in ABR measurement of NICU infants is a prolonged I-V interval, which can be a measure of delayed auditory maturation or neural pathology. Because the significance of this finding is not clear, we determined the incidence of a prolonged I-V interval and the correlation with neural pathology.

4. Finally, we investigated the etiologic factors associated with congenital hearing loss. Several etiologic factors for hearing loss have been identified over the past years. Many of these etiologic factors are also indicators of a poor clinical condition and are common in daily NICU care. Independent of postconceptional age and NICU admittance, we evaluated which etiologic factors are associated with sensorineural hearing loss (SNHL) and auditory neuropathy spectrum disorder (ANSD).

ABR and auditory maturation

We developed a fitting model to correct ABR latencies for postconceptional age based on a theoretical background and based on the ABR results of a clinical population of 175 normal hearing infants.

$$L_{III,V}(S,P) = L_I(S) + I_{I\_III,I\_V}\frac{1-e^{-\frac{P}{\tau_1}}}{1-e^{-\frac{P}{\tau_2}}}$$

Our fitting model describes the age-dependent decrease of peak III and V latencies, I-III interval and I-V interval with increasing postconceptional age (1). Note that this age-dependent decrease was not observed for peak I from term age onwards. In our fitting model the age-dependent effect found for ABR latencies is explained by two fitting parameters with an opposite effect. The time constant in the denominator (τ_2) results in decreased ABR latency intervals with increasing age, while the time constant in the numerator (τ_1) results in increased ABR latency intervals with increasing age.

There are several explanations for the decrease of ABR latencies with increasing age. A first plausible explanation for the decrease of ABR latencies (τ_2) with increasing age is nerve maturation, thereby reducing axonal conduction time (2-7). This rapid decrease of conduction time before term age can be explained by development of a myelin sheet (6, 8). Myelin formation begins during the third trimester of pregnancy and continues until six to twelve months of age. Simultaneously with the myelin formation, the diameter of the auditory axons increases. Just like the development of a myelin sheet, an increase of the axon diameter also results in decreased conduction time. As a third explanation of the maturation effect, increased synaptic efficacy is mentioned (2, 7, 9). Synaptic transmission time continues to shorten until three years of age (6). The interpeak latencies as a function of age show a nonlinear decrease. This can be explained by the fact that myelin formation, maturation of the axonal conduction time and synaptic efficacy reaches asymptotic values at different ages (7).

In contrast, the increase of latencies with increasing age (τ_1) can be explained by growth of the nerves, because a longer pathway results in increased conduction time. Although brainstem length is adult-like at the age of one, portions of the auditory pathway in the brainstem lengthen until three years of age primarily due to growth in brainstem circumference (6). The effect of the nerve growth (τ_1) fitting parameter is relatively small and was mainly added to improve the accuracy of our fitting model in the youngest infants.

Combining these opposite effects leads to a decrease of ABR latencies with increasing age, i.e. the effect of nerve maturation is stronger than the effect of nerve growth (6). This is in line with the two fitting parameters in our fitting model.

Although our fitting model is able to accurately correct ABR latencies for postconceptional age, it is no longer suitable when it concerns very preterm infants, due to the poor detectability of various components of the ABR response. By analyzing the morphology of the ABR response of preterm low birth weight infants who were admitted to our NICU, we tried to determine normal values in another way. Based on the outcome of this analysis a flow-chart was designed to analyze the ABR results in an unambiguous stepwise fashion. The presence of a typical negative peak III pattern in the ipsilateral (stimulated side) and contralateral (not stimulated side) traces seems to be a clear characteristic of the early ABR response in preterm infants. This typical "bow tie" pattern was found

in the majority (82 %) of infants (Figure 1). The early identification of peak III compared to peak V is in line with the peripheral to central maturation of the auditory system (10). An advanced peripheral development of the brainstem as a result of early sound stimulation ex utero as suggested by Jiang et al. could also be a contributing factor (11-12).
From 30 weeks postconceptional age onwards not only a clear ipsilateral but also a contralateral response is present in 90% of infants. This suggests that the maturation of the contralateral ABR response starts around 30 weeks and not after 34 weeks, as was previously suggested (13).

Figure 1

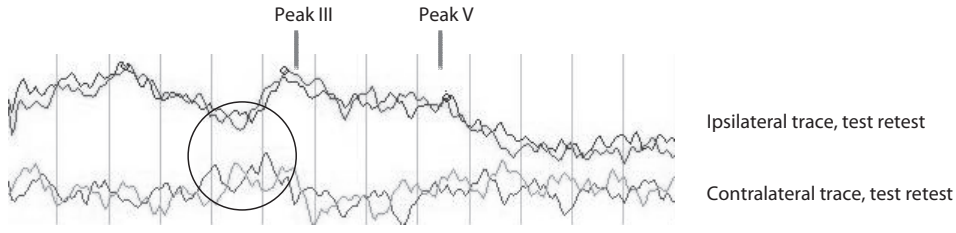

Figure 1. Typical "bow tie" pattern recorded at 90 dB, at 30 weeks postconceptional age. The first trace is the ipsilateral trace, showing test retest recordings. The second trace is the contralateral trace, showing test retest recordings. Peak III and V are indicated. The "bow tie" pattern is encircled. It appears just before peak III and is predominantly characterized by a negative wave III. It can be amplified by a positive peak III in the contralateral trace.

Audiologic outcome

During the preterm and perinatal period the auditory system is in full development and therefore highly vulnerable. Especially preterm birth during the period of fast myelination (between 30 and 34 weeks postconceptional age) can result in delayed auditory maturation (8). Perinatal complications may impair the auditory part of the brainstem or delay its maturation (11). These facts, together with the complications and poor clinical condition accompanying preterm birth, make NICU infants a vulnerable population regarding congenital hearing loss.

The degree and type of hearing loss are fundamental to the treatment and prognosis. Therefore, we classified audiologic diagnoses and follow-up in infants from the NICU who failed neonatal hearing screening.
In figure 2 the hearing outcome of NICU infants after failing neonatal hearing screening is presented. Repeated ABR measurement showed a shift in hearing outcome. The main shift in diagnoses consisted of an improvement from symmetric sensorineural hearing loss to normal hearing or minimal hearing loss. In other words an initial overestimation of infants diagnosed with SNHL of about 10% was seen at first ABR measurement. The other categories of hearing loss remained almost unchanged. Only a few infants (4.9%) showed progression of hearing impairment.

Figure 2

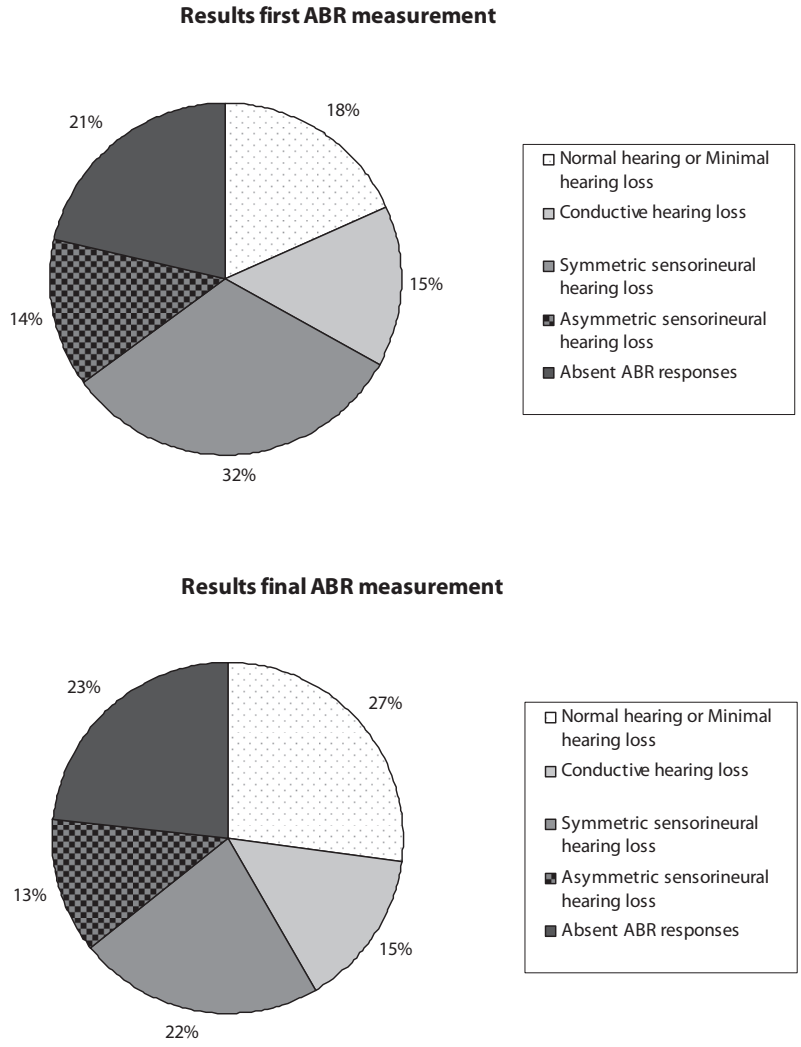

Figure 2 shows the distribution of the results of the first and final ABR measurement in infants referred for audiologic assessment after failure on AABR screening from the neonatal intensive care unit.

The observed improvement of the auditory function is most likely explained by maturation of the auditory system, which is known to be delayed in preterm infants compared to term infants (8, 14). An immature auditory system is characterised by increased ABR peak latencies and increased ABR thresholds and consequently the ABR results of preterm infants may have been misinterpreted as sensorineural hearing loss. As discussed in more detail in the previous section of the discussion already, increased myelination, axonal growth and increased synaptic efficacy are thought to be responsible for the maturation of the auditory system.

Another explanation for the improvement of the hearing function is an inaccurate estimation of gestational age during pregnancy. The estimation of gestational age can be inaccurate with a margin of two weeks. In early preterm infants, a two weeks inaccuracy of gestational age can result in different ABR latency reference values and possible misinterpretation of ABR results. This misinterpretation can lead to false diagnoses of sensorineural hearing loss. As preterm infants get older, the inaccurate estimation of gestational age becomes less important, such that this type of error becomes proportionally much smaller as age increases (15).

A third possible explanation is an underestimation of the conductive component (otitis media with effusion). When the conductive component has resolved, this could result in improvement of hearing function (16). Otitis media with effusion is a very common finding in infants who failed an OAE neonatal hearing screening programme (17). However, in our population this explanation is not very likely since the overall number of infants with a conductive hearing loss remains stable between the first and second ABR measurement.

In line with the observed shifts to an improved category of hearing loss we also found that ABR thresholds improved. Although it is not exactly clear when neonatal ABR thresholds become adult-like in case of normal auditory maturation, the threshold level is reported to decrease with 10 to 20 dB in the first 24 months of life (18). The theoretical background regarding maturation of the auditory system and ABR response thresholds is described in the previous section of the discussion.

Unfortunately, in a small group of infants hearing deteriorated after repeated ABR measurements. Progressive hearing loss can be explained by either a genetic cause or an infection such as CMV infection or bacterial meningitis, which are known causes of delayed deterioration of hearing function.

In conclusion, a delayed auditory maturation is the most likely explanation for the improvement of hearing function found in this group of NICU infants who failed neonatal hearing screening. This knowledge of the developing auditory system may have consequences for future counselling and treatment guidelines. The JCIH guidelines require diagnosis of congenital hearing loss before the age of three months. It can be argued that this may be too young for preterm NICU infants, since we now know that as many as 10% of infants with a sensorineural hearing loss will demonstrate an improvement of hearing function over time. Parents should be carefully counselled that the auditory system has not fully developed at first diagnostic evaluation and that changes in hearing function may still occur. Therefore aggressive or surgical decisions, such as cochlear implantation, should not be made until repeated ABR measurement (or other confirmatory diagnostic testing) has confirmed the diagnosis.

Delayed auditory maturation and neural pathology

It is known that high-risk (the youngest and smallest) NICU infants have an increased incidence of prolonged I-V interval as a measure of delayed auditory maturation compared to low-risk NICU infants (11). We applied our fitting model to investigate the prevalence of prolonged I-V interval as a measure of delayed auditory maturation or neural pathology in our population of NICU infants who failed neonatal hearing screening. We found a severely prolonged I-V interval (by two standard deviations or more) in 4.9% of our population, however ABR thresholds were near normal. In the majority of these infants the I-V interval normalized after follow-up. This and the fact that these infants were among the younger infants in our population and that corresponding ABR thresholds were near normal, supports the concept of delayed auditory maturation instead of neural pathology. In daily clinical practice this implies that delayed auditory maturation is a likely explanation of prolonged I-V interval in NICU infants after failing neonatal hearing screening. Infants should be carefully followed to determine if the I-V interval normalizes.

Auditory maturation can also affect the ABR threshold levels. We found that just like the I-V interval, ABR thresholds improve in the majority of our NICU population. Therefore, as a diagnostic tool to evaluate auditory maturation, we suggest that the I-V interval should be used in combination with ABR thresholds. The challenge is to be able to determine in which infants hearing function will improve as a result of auditory maturation and in which infants hearing function is truly impaired. A combination of postconceptional age, I-V interval and ABR threshold will provide a reasonable approach. Frequent repetition of ABR measurements is essential to monitor possible maturation effects.

Etiologic factors of congenital hearing loss

The etiologic factors for congenital hearing loss as formulated by the JCIH consist of a variety of conditions (Table 1 introduction) (19). In our opinion this list comprises an amorphous group of conditions in which the causal relation with congenital hearing loss is not clear. For example, a direct relation between the length of NICU stay and congenital hearing loss is unlikely. Many etiologic factors reflect a poor general clinical condition and accompanying treatments and are often related to NICU admittance. It is difficult to determine which etiologic factors play an independent contributing role within a NICU population.

Table 1

Risk indicators associated with permanent congenital, delayed-onset, or progressive hearing loss in childhood	
1	Caregiver concern regarding hearing, speech, language, or developmental delay
2	Family history of permanent childhood hearing loss
3	Neonatal intensive care of more than 5 days or any of the following regardless of length of stay: ECMO, assisted ventilation, exposure to ototoxic medications (gentamycin and tobramycin) or loop diuretics (furosemide/Lasix), and hyperbilirubinemia that requires exchange transfusion
4	In utero infections, such as CMV, herpes, rubella, syphilis, and toxoplasmosis
5	Craniofacial anomalies, including those that involve the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies
6	Physical findings, such as white forelock, that are associated with a syndrome known to include a sensorineural or permanent conductive hearing loss
7	Syndromes associated with hearing loss or progressive or late-onset hearing loss, such as neurofibromatosis, osteopetrosis, and Usher syndrome; other frequently identified syndromes include Waardenburg, Alport, Pendred, and Jervell and Lange-Nielson
8	Neurodegenerative disorders, such as Hunter syndrome, or sensory motor neuropathies, such as Friedreich ataxia and Charcot-Marie-Tooth syndrome
9	Culture-positive postnatal infections associated with sensorineural hearing loss, including confirmed bacterial and viral (especially herpes viruses and varicella) meningitis
10	Head trauma, especially basal skull/temporal bone fracture that requires hospitalization
11	Chemotherapy

Table 1. The risk indicators of permanent congenital, delayed-onset, or progressive hearing loss in childhood, as defined by the 2007 JCIH position statement are listed.

We studied independent etiologic factors that may play a role in the development of ANSD and SNHL. The direct causal relation of these etiologic factors has not been proven, but seems more reasonable than the list comprised by the JCIH.
Although ANSD and SNHL seem to have some etiologic factors in common, a different etiologic background is suggested (20). Therefore, we studied the etiologic background of both disease entities separately.

Table 2 shows the etiologic factors that are significantly more present in infants with ANSD and SNHL compared to postconceptional age and gender matched normal hearing NICU controls. It is clear from this table that ANSD and SNHL have some etiologic factors in common and some specific etiologic factors. The significant risk factors are discussed in the next paragraphs.

Table 2

ANSD	SNHL
IRDS	Dysmorphic features
Meningitis	Low APGAR scores (1 minute)
Vancomycin administration	Sepsis
	Meningitis
	Cerebral bleeding
	Cerebral infarction

Table 2 shows which etiologic factors were significantly more common in NICU infants with the ANSD or SNHL, compared to gender and postconceptional age matched normal hearing controls.

Sepsis and meningitis are the possible etiologic factors that both groups seem to have in common. Sepsis is a common condition in NICU infants with a poor effect on general outcome and health (21-22). The endotoxins and cytokines that are released in the septic state may be ototoxic to the immature auditory system. Although sepsis is not listed as a specific risk factor for congenital hearing loss by the JCIH, we found a strong correlation between sepsis and SNHL and a possible correlation with ANSD. Dowley et al. also suggested that sepsis was significantly more common among NICU infants with ANSD (23).
Meningitis often causes both cochlear and retro-cochlear dysfunction and was found to be a significant etiologic factor for both ANSD and SNHL. However, the number of infants with meningitis was very small, which influences the reliability of the results due to possible statistical errors. Because meningitis is such a rare condition it is not found in many studies evaluating risk factors. Nevertheless, it is a well known cause of hearing impairment and / or deafness.

Different signs of respiratory diseases are found as possible etiologic factors among both groups. Infant respiratory distress syndrome (IRDS) is more present in ANSD and low APGAR scores at one minute is more present in SNHL compared to normal hearing controls.
It has been shown in animal models that the inner cochlear hair cells are sensitive to prolonged mild hypoxia (24), in contrast with acute anoxia in which all the aspects of cochlear function are simultaneously lost (24). This might explain the specific relation between ANSD and (mild) hypoxia. The relation between low APGAR scores and hearing loss in NICU infants has been described by Vohr et al. and Hille et al. (25-26). Other parameters of respiratory disease and hypoxia, such as prolonged mechanical ventilation, have also been related to congenital hearing loss (16, 27-28).

The damaging effect of hyperbilirubinemia, more specifically kernicterus, on the auditory system of infants has been known for years (29-30). The pathogenesis of bilirubin encephalopathy is complex, but both bilirubin-albumin binding and the integrity of the blood-brain barrier are thought to play significant roles in bilirubin toxicity (31). The ototoxic effect of unconjugated bilirubin is reported to

spare the cochlea, but to selectively damage the brainstem auditory nuclei. The auditory nerve and spiral ganglion cell bodies may also be affected (32).
Laboratory measurement of unconjugated or "free" bilirubin is historically controversial and not widely implemented (33). Therefore, the peak total bilirubin level or the bilirubin / albumin ratio are often used. Although, free bilirubin has been reported to have a stronger correlation with ABR changes than total bilirubin, it cannot be measured in our clinic (31).
Since we found a near significant relation between peak total bilirubin level and ANSD, but no relation with the number of infants that had to be treated for hyperbilirubinemia, maybe the degree of hyperbilirubinemia, and consequently the duration of phototherapy play a role. Furthermore, the fact that the correlation was only found for ANSD and not for SNHL confirms the hypothesis of selective neural damage. Although serum bilirubin levels are already kept within a very strict range in NICU infants, these results may give rise to even more aggressive treatment strategies of hyperbilirubinemia.

Even though vancomycin has been reported not to be ototoxic in a large cohort of NICU infants (34), we found a strong correlation between vancomycin administration and ANSD in our case control study. The correlation between vancomycin administration and ANSD has been confirmed by several other authors (20, 35). The fact that de Hoog et al. did not find this relation may be explained by the fact that the incidence of ANSD is very low and because ANSD can also be caused by other factors such as OTOF syndrome. We found that only 0.27% of the total NICU population showed the ANSD profile. A case control study may therefore be more sensitive to identify etiologic factors of ANSD, such as ototoxic medication. To our knowledge it is not known whether vancomycin itself or the combination with associated sepsis is the causal factor leading to ANSD.

In line with the JCIH, we found a higher incidence of dysmorphic features associated with a variety of syndromes among infants with SNHL. For example Down syndrome, CHARGE and Jervell Lange-Nielsen were diagnosed. Morton et al. gave an extensive overview of the prevalence of different types of syndromic and non-syndromic genetic causes of hearing loss (36). Genetic counselling and mutation analysis are not standard care for infants who fail neonatal hearing screening in our clinic. It is mainly conducted in infants with a family history of congenital hearing loss or in infants with clinical features of a syndromic cause of hearing loss. Therefore, the genetic profile and most common mutations among our population are not always known.

We found a correlation between both cerebral bleeding and cerebral infarction and SNHL. Although it is known that brain injury greatly influences the risk of late death or neurosensory impairment in extremely low birth weight infants (22), the correlation with congenital hearing loss cannot always be confirmed (21). In addition to direct damage of the auditory pathway maybe hypoxia induced by cerebral bleeding or infarction contributes to the development of SNHL.

It is remarkable that infants with ANSD or SNHL differ not only with respect to the discussed possible etiologic factors but also with respect to postconceptional age and birth weight. In our population infants with the ANSD profile have a median postconceptional age of 27 weeks, whereas infants with SNHL have a median postconceptional age of 37 weeks. Consequently, birth weight of infants with ANSD was also lower compared to infants with SNHL. This is in line with the results of Xionis et al. who suggested that infants with ANSD are significantly younger and smaller compared to infants with SNHL (20). Apparently the younger preterm infants seem to be more vulnerable to neural damage.

It can be concluded from these results that ANSD and SNHL are different disease entities with a different etiologic background.

In conclusion

As we know, the auditory system of preterm infants is still in full maturational process. This makes adequately diagnosing hearing loss in these infants a challenge. The ABR morphology is immature and sometimes poorly detectable. When an ABR response is present, age-adjusted normal values are required that correct for these maturational changes. Careful counselling strategies are required when hearing loss is presumed, since we found that the audiologic diagnosis may well change over time. Therefore aggressive treatment decisions should not be made until repeated ABR measurement (or other confirmatory diagnostic testing) has confirmed the diagnosis.
We have found several etiologic factors associated with ANSD or SNHL independent of postconceptional age, gender and NICU admittance. The knowledge of these etiologic factors, in which the causal relation with hearing loss is likely, provides a tool for the clinical assessment of NICU infants with congenital hearing loss. It may not always be possible to eliminate these etiologic factors, but careful management may minimize the incidence of hearing loss. ANSD and SNHL have some etiologic factors in common and some specific etiologic factors. A different disease entity is confirmed by the fact that infant with ANSD are younger and smaller than infants with SNHL.

Recommendations for further research

The aim of this thesis was to investigate the incidence and course of congenital hearing loss in NICU infants. Methods to assess hearing function using ABR measurement and etiologic factors associated with congenital hearing loss were studied. This has provided us with new insights in the normal development and the risks that can compromise the immature auditory system of NICU infants.

Future research should extend the knowledge of the ABR morphology in preterm infants. Long-term follow-up is needed to study the correlation between early ABR morphology and the effects on hearing function, speech and language development later in life. ABR measurement may provide us with a tool to assess general neurodevelopmental outcome in NICU infants. Prospective analysis of etiologic factors associated with congenital hearing loss is also recommended, especially the ototoxicity of bilirubin needs to be further addressed. The effect on hearing outcome of serum bilirubin levels and the treatment regimens such as duration of phototherapy needs to be carefully studied, including factors that may influence the bilirubin metabolism such as feeding regimen.

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Chapter 6

Summary

Samenvatting

Summary

In this thesis the presence and course of hearing loss in our population of NICU infants is described. NICU infants are at greater risk of congenital and acquired hearing loss compared to infants admitted to the well-baby nursery. The specific characteristics of the auditory system in these infants have not been thoroughly studied. The purpose of the research described in this thesis was to investigate the diagnostic process, the course and the etiologic factors associated with hearing loss in these at-risk NICU infants.

ABR measurement is the most important tool to diagnose hearing loss in infants. To adequately diagnose hearing loss in infants age-adjusted normal values are required that correct ABR parameters for maturational changes. In chapter 2 a simple and powerful fitting model is described that corrects ABR response parameters for postconceptional age, based on a theoretical background. Auditory maturation is most likely the result of increased myelination and synaptic efficacy. The age-dependent decline of the latencies of ABR parameters continues for 2 to 2.5 years based on our fitting model.

In very preterm infants ABR parameters are often poorly detectable, resulting in a different ABR morphology. This often makes the interpretation of the ABR results based on normal values or a fitting model inadequate. The ABR morphology was evaluated and a flowchart was developed to extend the current assessment system in chapter 3.

In chapter 4 the audiologic outcome in NICU infants after failing neonatal hearing screening is described. We classified the audiologic diagnoses after primary ABR measurement and after follow-up. In 58% of infants in this high-risk population a sensorineural hearing loss or absent auditory brainstem responses was diagnosed. An initial overestimation of about 10% was seen at first auditory brainstem response measurement. Again this improvement of the auditory function may well be the result of maturational processes.

In chapter 5 we analyzed ABR parameters to study the prevalence of delayed auditory maturation in our population of NICU infants who failed neonatal hearing screening. The I-V interval is often used as a measure to describe the central conduction time. A prolonged I-V interval can be a sign of delayed auditory maturation. In 4.9% of our NICU population a prolonged I-V interval (by two standard deviations) was found. These infants were among the youngest infants and very often a near normal ABR response threshold was found. This implies that a mild delay in auditory maturation is a more probable explanation than major audiologic or neural pathology.

The etiologic factors that are currently associated with congenital hearing loss comprises of an amorphic group of conditions in which the causal relation with hearing loss is not always clear.

Many of these etiologic factors are associated with NICU admittance. In chapter 6 and 7 we studied the etiologic factors associated with ANSD and SNHL respectively independent of gender, postconceptional age and NICU admittance. IRDS, meningitis and vancomycin administration were found to be risk factors for ANSD. Dysmorphic features, low APGAR scores at 1 minute, sepsis, meningitis, cerebral bleeding and cerebral infarction are associated with SNHL. Although ANSD and SNHL have some etiologic factors in common a different etiologic background is suggested.

In conclusion, the immature auditory system and multiple conditions that may cause hearing loss make the prevention, diagnosis and management of hearing loss in NICU infants a challenging task.

Samenvatting

In dit proefschrift wordt de prevalentie en het beloop van gehoorverlies bij kinderen die opgenomen zijn geweest op de NICU beschreven. NICU kinderen hebben een grotere kans op aangeboren of verworven gehoorverlies. De specifieke kenmerken van het auditieve systeem van deze kinderen die hieraan ten grondslag liggen zijn nog niet grondig bestudeerd. Het doel van het onderzoek, zoals beschreven in dit proefschrift, was om het diagnostisch traject, het beloop en de etiologische factoren geassocieerd met gehoorverlies bij NICU kinderen te bestuderen.

ABR is de belangrijkste methode om gehoorverlies bij kleine kinderen te diagnosticeren. Om een correcte diagnose te kunnen stellen zijn leeftijdsgecorrigeerde normaalwaarden nodig die rekening houden met het rijpingseffect van het auditieve systeem. In hoofdstuk 2 wordt een eenvoudig en krachtig fitting model gepresenteerd, gebaseerd op een theoretisch achtergrond, die de ABR respons parameters corrigeert voor de postconceptionele leeftijd. Rijping van het auditieve systeem wordt hoogst waarschijnlijk veroorzaakt door toegenomen myelinisatie en een verhoogde synaptische efficiëntie. De leeftijdsafhankelijke afname van de latentietijden van de ABR parameters houdt 2 tot 2,5 jaar aan, uitgaande van de gegevens van het fitting model.

Bij extreem premature kinderen zijn de ABR parameters vaak moeilijk te identificeren, wat resulteert in een afwijkende ABR morfologie. Dit maakt de interpretatie van de ABR resultaten met behulp van de huidige normaalwaarden ontoereikend. In hoofdstuk 3 wordt de morfologie van de ABR bij deze extreem premature kinderen beschreven en er wordt een alternatief systeem geïntroduceerd om de morfologie van de ABR te analyseren.

De uitkomst na uitval op de neonatale gehoorscreening bij NICU kinderen wordt in hoofdstuk 4 beschreven. We hebben de verschillende audiologische diagnosen in kaart gebracht en het verloop na vervolgonderzoek bestudeerd. Bij 58% van de kinderen in deze hoogrisico populatie werd een perceptief of maximaal gehoorverlies vastgesteld. Een initiële overschatting van 10% werd gezien na de eerste diagnostische ABR meting. Deze verbetering van het gehoor kan opnieuw meest waarschijnlijk worden verklaard door rijping van het auditieve systeem.

In hoofdstuk 5 wordt aan de hand van de ABR parameters de prevalentie van een vertraagde auditieve rijping bij NICU kinderen die zijn uitgevallen op de neonatale gehoorscreening bestudeerd. Het I-V interval wordt vaak gebruikt als maat om de centrale verwerking van geluid weer te geven. Een verlengd I-V interval kan een teken zijn van vertraagde auditieve rijping. Bij 4.9% van de kinderen in onze NICU populatie werd een verlengd I-V interval vastgesteld. Deze kinderen waren relatief jonger en daarnaast werd er vaak een normale of bijna normale ABR drempel gevonden. Deze gegevens ondersteunen een milde vertraging van de rijping als meest waarschijnlijke verklaring in plaats van ernstige auditieve afwijkingen of neuronale pathologie.

De etiologische factoren die op dit moment worden geassocieerd met aangeboren gehoorverlies bestaan uit een uiteenlopende groep aandoeningen waarbij de causale relatie met gehoorverlies niet altijd duidelijk is. Veel van deze etiologische factoren hangen samen met een opname op de NICU. In hoofdstuk 6 en 7 onderzoeken we respectievelijk de etiologische factoren die samen hangen met auditieve neuropathie en een perceptief gehoorverlies onafhankelijk van geslacht, leeftijd en opname op de NICU. IRDS, meningitis en het gebruik van vancomycine zijn risicofactoren voor het ontwikkelen van auditieve neuropathie. Dysmorfe kenmerken, lage APGAR score na 1 minuut, sepsis, meningitis en cerebrale bloedingen en infarcten zijn risicofactoren voor een perceptief gehoorverlies. Hoewel de etiologische factoren voor auditieve neuropathie en een perceptief gehoorverlies deels overeenkomen lijkt er sprake te zijn van een verschillende etiologische achtergrond.

Samenvattend, het onrijpe auditieve systeem en de verschillende aandoeningen die gehoorverlies kunnen veroorzaken maken de preventie, diagnose en behandeling van gehoorverlies bij NICU kinderen een uitdagende taak.

List of abbreviations

AABR	automated auditory brainstem response
ABR	auditory brainstem response
ANSD	auditory neuropathy spectrum disorder
CAPAS	compact Amsterdam pedo-audiometric screener
CM	cochlear microphonics
CMV	cytomegalovirus
dB	decibel
ECMO	extracorporeal membrane oxygenation
IRDS	infant respiratory distress syndrome
JCIH	Joint Committee on Infant Hearing
nHL	normal hearing level
NICU	neonatal intensive care unit
OAE	otoacoustic emissions
PCA	postconceptional age
SNHL	sensorineural hearing loss
TEOAE	transient evoked otoacoustic emissions
UNHS	universal newborn hearing screening

PhD Portfolio Summary

Summary of PhD training and teaching activities

Name PhD student: S Coenraad Erasmus MC Department: KNO-heelkunde	PhD period: 2008-2011 Promotor(s): Prof. Dr. R.J. Baatenburg de Jong, Prof. Dr. J.B. van Goudoever Supervisor: Dr. L.J. Hoeve, Dr. Ir. A. Goedegebure

1. PhD training		
	Year	**Workload (Hours/ECTS)**
General academic skills		
- Biomedical English Writing and Communication	2009	4 ECTS
- Research Integrity (BROK cursus)	2009	1 ECTS
Research skills		
- Biostatistics for Clinicians	2009	1 ECTS
- Introduction to Clinical Research	2009	0,9 ECTS
In-depth courses (e.g. Research school, Medical Training)		
- Head and neck anatomy (dissection)	2008	2 ECTS
Presentations		
- KNO vergadering (april)	2010	1 ECTS
- ESPO, Pamplona	2010	2 ECTS
- KNO vergadering (november)	2010	1 ECTS
- Poster ASPO, Chigaco	2011	1 ECTS
International conferences		
- KNO vergadering (2 / year)		1 ECTS
- ESPO, Pamplona	2010	1 ECTS
- COSM, Chicago	2011	1 ECTS
Seminars and workshops		
- Training: "Implementatie Portfolio"	2009	0.5 ECTS
- Workshop: "Geavanceerde beeldvormende technieken voor dokters"	2009	0.5 ECTS
Other		
- Refereeravond KNO (4 / year)		1 ECTS

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Curiculum vitae

Saskia Coenraad, dochter van Wim Coenraad en Conny Coenraad-van Daatselaar, werd op 7 februari 1983 geboren in het Oude Rijn ziekenhuis te Utrecht. Hierna groeide zij op in Ede, waar zij de basisschool "Edese Schoolvereniging" doorliep. Haar middelbare school onderwijs volgde ze aan het Marnix College te Ede, waar ze in 2001 cum laude het VWO eindexamen heeft behaald. Vervolgens keerde zij terug naar haar geboorteplaats om aan de Universiteit Utrecht geneeskunde te studeren. Na keuzecoschappen bij de afdeling KNO van het ziekenhuis de Gelderse Vallei te Ede en de afdeling chirurgie van het Universitair Medisch Centrum Utrecht, werd in december 2007 de studie afgesloten met het artsexamen. Na acht maanden als arts-assistent werkzaam te zijn geweest op de afdeling chirurgie van het ziekenhuis de Gelderse Vallei te Ede, is zij sinds 1 oktober 2008 werkzaam als arts-assistent op de afdeling KNO van het Erasmus Medisch Centrum te Rotterdam, onder leiding van Prof. Dr. R.J. Baatenburg de Jong. In samenwerking met de afdeling neonatologie van het Sophia Kinderziekenhuis onder leiding van Prof. Dr. J.B. van Goudoever, werd promotieonderzoek verricht dat na drie jaar resulteerde in dit proefschrift. Hierna zal zij de opleiding tot kno-arts vervolgen, waaraan ze per 1 oktober 2010 is begonnen.