International Journal of Pediatric Otorhinolaryngology 139 (2020) 110456

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

2016 ESPO Congress

# Changes in auditory function in premature children: A prospective cohort study

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ARTICLE INFO

*Keywords:*
Hearing loss
Children
Prematurity
Long-term follow-up
Late-onset hearing loss

ABSTRACT

*Objectives:* To analyze the age-specific pattern of auditory function in preterm children as a function of their gestational age at birth.
*Study design:* longitudinal cohort study.
*Methods:* a prospective cohort study involved 271 preterm children aged from 6 months to 15 years old. Children were divided into two groups: 70 children with a gestational age at birth of 32–36 weeks (Group 1) and 201 children with a gestational age of 22–31 weeks (Group 2). Hearing was assessed by ABR, ASSR, OAE, behavioral audiometry, and pure tone audiometry. Additionally, for some children, CT, MRI, and GBJ2 evaluations were performed. Assessments of hearing impaired children were performed 3–4 times a year for children under 2 years of age; 2–3 times a year for children from 2 to 5 years of age; and 1–2 times a year for children over 5 years of age. Infants without any hearing problems were examined 2–3 times during their first year of life, followed by annual examinations as they aged.
*Results:* The initial hearing examination identified SNHL and ANSD in 18 children (25.7%) and 64 children (31.8%) in Group 1 and Group 2, respectively. No significant difference in the occurrence of auditory impairment in the two groups was found at the initial assessment ($p > 0.05$). Further long-term follow-up revealed changes in hearing in 16 children: 15 from Group 2 and only one child from Group 1. Four different kinds of hearing changes were noted: hearing recovery to normal levels in children with ANSD; late onset hearing loss; the transformation of ANSD to SNHL, and vice versa. The age, factors, and possible mechanisms of such changes are discussed in the article.
*Conclusion:* The auditory function in prematurely born children tends to be unstable, especially at a very early age. In very preterm infants, it may either deteriorate or improve. Infants born before 31 weeks' gestation require long-term follow-up at least until they are 3–4 years of age. Caution is advised regarding very early cochlear implantation for children born before 32 weeks of gestation age.

## 1. Introduction

The World Health Organization estimates premature birth rates worldwide at around 10% with a steady increase observed in the past twenty years [1]. The figure for the UK is about 7%; in the USA the rate is over 11%; in Russia 3–16% of babies are born too early [1–3]. In high-income countries, the survival rate among babies born alive before 28 weeks of pregnancy is estimated around 90% [4]. However, despite the increase in the proportion of surviving premature babies in recent decades, the occurrence of severe neuropsychiatric disorders, including the sensory impairments, has not changed and remains at 18–19% [3,5]. Premature infants are at greater risk for cerebral palsy, delays in development, hearing and vision problems, etc. The earlier a baby is born, the greater these risks. Hearing disorders are not uncommon in prematurely born children of any gestational age, and, as is the case with any other pathology resulting from preterm birth, the rate of hearing problems increases with decreasing gestational age (GA) and birth weight (BW). It should be noted that the risk for hearing loss is highest for very premature babies born before 32 weeks of pregnancy and having a birth weight of less than 1500 g [2,3,6,7]. The incidence of hearing impairment in very premature infants is 20–30 times higher than the average figure for the whole newborn population (according to

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https://doi.org/10.1016/j.ijporl.2020.110456
Received 28 July 2020; Received in revised form 13 October 2020; Accepted 13 October 2020
Available online 17 October 2020

different sources, from 10 to 50 times) [2,7–10]. Most researchers estimate the occurrence rate of sensorineural hearing impairment in premature infants at between 1.6% and 16% [2,8,10–13], while some note a rate of 32% [14]. K. Wroblewska-Seniuk et al. (2017) reported that hearing loss occurred in 11% of infants born before 25 weeks' gestational age (wga), 5% at 26–27 wga, 3.46% at 28 wga and 2–3% at 29–32 wga [15].

It is widely recognized that, apart from very preterm birth, the following factors may contribute to hearing impairment in high-risk infants: maternal chronic diseases and the pathology of the pregnancy; perinatal asphyxia or ischemia; intrauterine and postnatal infections, in particular congenital cytomegalovirus (cCMV) infection; bacterial and viral meningitis; prolonged respiratory support including mechanical ventilation exceeding 5 days; exposure to ototoxic medications such as diuretics and aminoglycoside antibiotics for more than 5 days; ambient noise exposure in intensive care units; comorbidity, i.e. co-occurring congenital heart defect, patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), neonatal sepsis; neonatal hyperbilirubinemia requiring exchange transfusion; acquired hypoxic ischemic encephalopathy accompanied by subependymal hemorrhages and intraventricular hemorrhages (IVH), periventricular leukomalacia, etc. [3,6,10,11,14,16,17]. Sensorineural hearing impairment in preterm neonates is multifactorial in nature; it may result from disruptions of transmission at different points of auditory pathway from the cochlea to the central parts of the auditory system, causing various types of hearing loss: sensorineural hearing loss (SNHL), auditory neuropathy spectrum disorder (ANSD) and auditory processing disorders (APD) [3,18,19].

Hearing disorders in preterm children may be accompanied by unstable hearing thresholds, mainly in early childhood [20–22]. The peripheral hearing may improve over time, and may even be fully recovered. It may occur until 10–12 months of postconceptual age (PCA) [7,23,24], or 14 months of life [25], or even 15 months of PCA in case of unilateral hearing impairment [24]. J.R. Hof et al. (2013) suppose that improvement of hearing in cases of initially identified SNHL is more common for infants born before 28 wga [7]. In contrast, S. Frezza notes that such children have worse prognosis in improvement of hearing, especially in case of prolonged stays in neonatal intensive care units (NICUs) and initially identified severe or profound hearing loss [24]. At the same time, there is some evidence that hearing may improve, even to normal levels, not only in very preterm born infants but also in children born after 29 wga [26]. This is also indicated in the research of M. Koenighofer (2014), who observed full hearing recovery in an infant born 32 wga [25]. Preterm born infants with an initial ASSR threshold of less than 67.5 dB have better prognosis in hearing improvement [26]. The auditory improvement may result from: elimination of a conductive component [18,26]; maturation in the peripheral part of the auditory system (more common with initially identified ANSD) [7,18,23,25–27]; and addressing the consequences of neonatal hyperbilirubinemia (a relatively rare occurrence) [22,28,29]. Hearing changes in premature children may accompany changes in hearing loss type. J.R. Hof et al. (2013) described a transformation from initial ANSD through normal hearing to moderate SNHL at the age of 4 years old in a girl born at 34 wga [7]. On the other hand, K.S. de Graaff-Korf et al. (2019) did not report any changes in hearing loss type in children older than 3 months of life [30]. Changes in the audiological function of preterm children over time (including improvement or recovery) require long-term hearing follow-up and careful intervention programs, especially for patients referred for cochlear implantation. It is recommended that decisions concerning cochlear implantation for preterm born infants not be made earlier than 80–85 weeks of PCA [7,23,24].

In some cases the hearing loss of preterm born children may worsen as has been observed in 28% of extremely preterm children with prelingual sensorineural hearing loss [11,31]. Martinez-Kruz et al. (2017) noted, using data based on twenty years of observation, that 40% of mainly premature NICU graduates had progressive hearing loss [32]. A higher degree of SNHL was mainly associated with an exchange transfusion performed during the neonatal period. The progression of hearing loss during the first year of life in preterm infants with neonatal hyperbilirubinemia was also noted in the study of Nam et al. [22]. In addition, a delayed manifestation of hearing loss is possible. Holzinger's study (2016) demonstrated that about a half of all children with permanent moderate to profound SNHL – diagnosed on average at 10.5 years – passed newborn hearing screenings, indicating early or late-onset postnatal SNHL; the fact of late-onset SNHL in premature infants was also noted in the Weichbold's study (2006) [33,34]. C.M.T. Robertson identified late-onset bilateral permanent HL (PHL) in 4 of 40 (10%) very preterm children with PHL at the age of three years [11]. It ranged from mild loss to severe/profound high-frequency loss. All the children had required prolonged oxygen use during the neonatal period. During their prospective study, van Noort-van der Spek (2017) found three cases of mild and moderate SNHL out of 70 children who passed newborn hearing screening (4,3%) [13]. All the children were extremely preterm and had multiple risk factors for hearing loss. The authors hypothesise that there may have been a progression of initial, minimal hearing loss or late-onset SNHL. The authors recommended long-term hearing follow-up of such children until the age of 2 years.

Early detection of hearing impairments in preterm children and, consequently, early and comprehensive intervention programs are key factors for reducing the negative impact of hearing loss on a child's speech and language, emotional, social, and educational development.

The purpose of this study is to analyze the age-specific pattern of auditory function in preterm children as a function of their gestational age at birth.

## 2. Materials and methods

### 2.1. Patients

The study was carried out for 271 preterm children from 6 months to 15 years of age, which were divided into two groups. Of this total, 70 children born prematurely (GA more than 31 wks) were included in Group 1 (Gr. 1); 201 children were very premature (GA from 22 to 31 wks) composed Group 2 (Gr. 2). See Table 1:

All children with permanent conductive hearing loss were excluded from the study. The incidence of risk factors for hearing loss in each of the groups is presented in Fig. 1.

All investigations were conducted in the correspondence with the principles of biomedical ethics contained in the 1964 Helsinki Declaration and its subsequent revisions and approved by the Ethics Committee of the institution. Parents were informed of the importance of their children's participation in the long-term audiological follow-up, the purposes of the study and the benefits of the research. Parents of all participants of this study gave their voluntary informed writing consent.

### 2.2. Audiological assessment

All the children underwent: ENT examination with otomicroscopy; tympanometry and middle-ear muscle reflex measurement (MEMR); recording of two types of otoacoustic emissions (OAEs): transient

**Table 1**
Characteristics of the patients by the groups.

| | Number of patients | Range of GA at birth, weeks | Average GA, weeks | Range of birth weight, g | Average birth weight, g |
|---|---|---|---|---|---|
| Group 1 | 70 | 32–36 | 33.1 ± 1.3 | 1300–3080 | 2014 ± 358 |
| Group 2 | 201 | 22–31 | 28.1 ± 1.9 | 417–2080 | 1158 ± 325 |

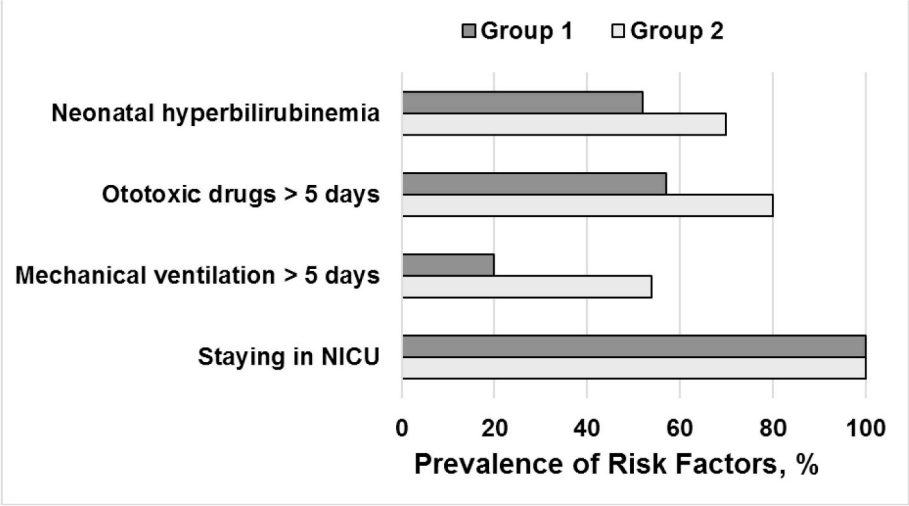


**Fig. 1.** Neonatal risk factors for hearing loss in both groups of infants born prematurely.

evoked and distortion product ones (DPOAE); registration of click-evoked auditory brainstem responses (ABR) and auditory steady state responses (ASSR); behavioral audiometry and pure tone audiometry (behavioral observation audiometry); visual reinforcement audiometry; playing audiometry; standard pure tone audiometry (depending on development age of the child); supra-threshold tests for children over 4 years of age (speech audiometry in quiet and noise; random gap detection test, duration patterns test, binaural fusion test, dichotic digit test). Temporal bone computed tomography (CT) and brain magnetic resonance imaging (MRI) were performed as necessary.

### 2.3. Equipment

OAEs were evaluated using the Otodynamics ILO 288 USB II system and Interacoustics' Eclipse system. Tympanometry and middle-ear muscle reflex measurement were performed with the Interacoustics AT 235H system using 1 kHz tympanometry for children under one year of age. ABR and ASSR were recorded by means of the Eclipse system.

### 2.4. Long-term hearing follow-up: timeframe

All children received their first hearing evaluation with the newborn hearing screening before their discharge from hospital. It included recording of OAE and automated ABR with a stimulus level of 35 dB.

The frequency of audiological examinations depended on the age and hearing status of a child. Assessments of patients diagnosed with hearing impairment were performed 3–4 times a year for children under 2 years of age; 2–3 times a year for children from 2 to 5 years of age; and 1–2 times a year for children over 5 years of age. Infants without any hearing problems were examined 2–3 times a year during their first year of life, followed by annual examinations as they got older.

The results were analyzed in terms of postconceptual age (PCA) (chronological age plus gestational age) as well as in terms of corrected age (CA) (chronological age minus the number of weeks or months a child was born early).

### 2.5. Statistical analysis

All statistical analyses were performed using Microsoft Excel 2016. The difference between two groups was analyzed by means of the independent *t*-test. All data are presented as mean values and standard deviations. A *P*-value of less than 0.05 was considered statistically significant.

## 3. Results

The results of the screening step and the first diagnostic evaluation are presented at Fig. 2. The average PCA was 37.6 ± 2.4 wks for Gr. 1 and 37.5 ± 4.1 wks for Gr. 2. No hearing impairment was detected in 47.1% of cases (33 children) in Gr. 1 and in 44.8% of cases (90 children) in Gr. 2. The first diagnostic evaluation was performed at an average corrected age (CA) of 2.8 ± 2.4 months and 3.8 ± 3.1 months for Gr. 1 and Gr. 2, respectively. The evaluation revealed no hearing pathology in 74.3% of cases (52 children) in Gr. 1 and 68.2% of cases (137 children) in Gr. 2. To these numbers we added babies featuring transitory conductive hearing loss which was caused by middle ear effusion. Otitis media with effusion (OME) in these patients subsided at different ages within the first year of life. Thus, the number of children with normal hearing increased from the screening step to the diagnostic evaluation from 47.1% to 74.3% and from 44.8% to 68.2% for Gr. 1 and Gr. 2, respectively.

The first diagnostic examination identified permanent sensorineural hearing impairment in 18 patients (25.7%) from Gr. 1, which was distributed in equal proportion between SNHL and ANSD (9 patients each). The forms of sensorineural hearing impairment detected in 64 children (31.8%) from Gr. 2 included ANSD in 46 cases, bilateral SNHL of different degrees in 14 cases, and a combination of ANSD in one ear and SNHL in the other in 4 cases. No significant difference in the occurrence of hearing impairment in the two groups of patients was found ($p > 0.05$).

Genetic evaluation of children with SNHL showed no GJB2 gene mutation. Temporal bone CTs, which were performed in cases of suspected ear malformations, and brain MRIs, carried out for children with ANSD, revealed no pathology of the auditory system.

Further long-term hearing follow-up revealed the transformation of hearing in 16 children as they grew. These results were observed mostly in Gr. 2 subjects: hearing impairments were diagnosed in 15 children (7.5%) with an average GA = 28.1 ± 1.8 wks and BW = 1098 ± 309 g. Only one case in Gr. 1 (GA = 32 wks, BW = 1800 g) was found. Table 2 presents the general characteristics of these 16 children including their risk factors for hearing loss. The children were divided into four subgroups by type of hearing loss and further modification of their hearing type with age:

- Subgroup 1 ($n = 3$): children initially diagnosed with ANSD who subsequently recovered a normal hearing
- Subgroup 2 ($n = 4$): children with initial ANSD which subsequently transformed to SNHL

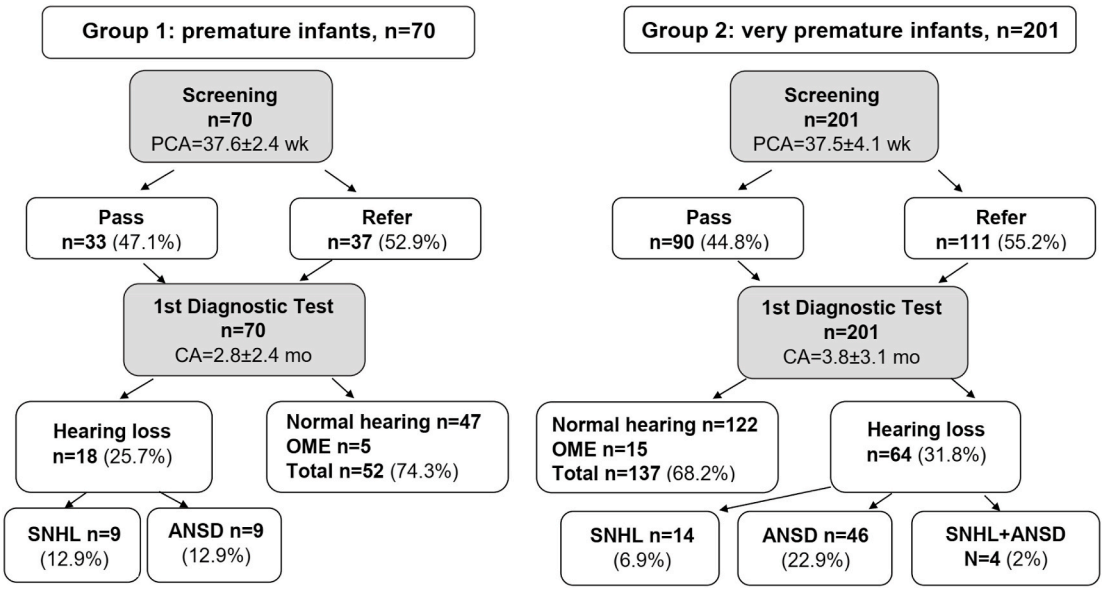


**Fig. 2.** The results of the screening step and the first diagnostic examination in both groups of patients.

- Subgroup 3 ($n = 4$): children with initial SNHL which subsequently transformed to ANSD
- Subgroup 4 ($n = 5$): children with late-onset hearing loss

The changes in hearing levels in each subgroups were:

Subgroup 1: mild degree hearing loss to normal hearing ($n = 2$), mild-to-moderate degree hearing loss to normal hearing ($n = 1$); Subgroup 2: moderate degree hearing loss to mild-to-moderate degree hearing loss ($n = 1$), mild degree hearing loss to mild degree hearing loss ($n = 1$), moderate degree hearing loss to profound degree hearing loss ($n = 1$), mild-to-moderate degree hearing loss to mild degree hearing loss ($n = 1$); Subgroup 3: moderate degree hearing loss to moderately severe degree hearing loss ($n = 1$), severe degree hearing loss to moderate degree hearing loss ($n = 2$), moderate degree hearing loss to moderately severe degree hearing loss ($n = 1$); Subgroup 4: normal hearing to severe degree hearing loss ($n = 1$), normal hearing to moderate hearing loss ($n = 4$).

Subgroup 1 comprised three children (# 1, 2, 3 in Table 2), diagnosed with ANSD of mild and mild-to-moderate degrees on initial examination who subsequently — by the age of 12 and 24 months (equivalent to 10, 9.5 and 22 months CA) — recovered normal hearing (OAEs were consistently normal; behavioral hearing and ABR thresholds came to normal over time).

Subgroup 2 consisted of four children (# 4, 5, 6, 7 in Table 2) whose initial ANSD with hearing levels from mild to moderate transformed into SNHL as they reached 12 (equivalent to 9 months CA), 24 (equivalent to 21.5 months CA), 36, and 48 months of actual age. Two cases were identified where the above noted process of transformation also featured a transitory stage in which ANSD in one ear was accompanied by SNHL in the other. During the transformation, ABR and ASSR thresholds progressively got lower and the microphonic potentials and OAEs disappeared, which resulted in SNHL of mild and moderate degrees. In Patient # 7, ABR thresholds were observed decreasing alongside unchanged OAEs and microphonic potentials; the latter disappeared completely by the age of 2.5 years with the child developing mild, high-frequency SNHL accompanied by DPOAEs registered in a frequency range of 500 Hz–1000 Hz. In another case, one child (case # 6) who had moderate ANSD diagnosed at the age of 6 months, demonstrated bilateral profound SNHL with gradually increasing behavioral thresholds along with the microphone potential and OAEs completely expired by the age of 36 months.

Subgroup 3 featured four children (# 8, 9, 10, 11 in Table 2). Three of them were initially diagnosed with SNHL and the fourth child (# 11) was diagnosed with combined hearing loss (SNHL on one side and ANSD on the other). The diagnosis in all cases was confirmed by behavioral audiometry as well as objective measurements: ABR, ASSR, tympanometry, acoustic reflex, and OAEs. SNHL later transformed to ANSD which occurred at the ages of 12, 14, 16, and 18 months of actual life (equivalent to 9.5, 11, 13.5, 15 months CA). Two patients (cases # 9 and 10, with extremely low birth weight and identified severe SNHL) demonstrated a decrease in behavioral hearing thresholds (an improvement from severe to moderate degree hearing loss) which allowed for the effective use of hearing aids without the need for cochlear implantations. While the ABR thresholds of these three children remained unchanged, high-amplitude microphonic potentials were detected combined with absent OAEs. Child #11 (extremely low birth weight and intrauterine growth restriction) was initially identified with moderate SNHL on one side and moderate ANSD on the other. His hearing impairments transformed to bilateral ANSD of moderate-to-severe degree with a ski slope audiogram by the age of 18 months of actual life. On the side initially diagnosed as SNHL, along with a moderate growth of behavioral thresholds, an increase in ABR thresholds up to 90 dB HL was noted, and well-identified microphonic potential began to be visualized on ABR curves. Child # 8 demonstrated an elevation of ABR thresholds from 30-60 dB to 95–100 dB nHL, coupled with detection of low-amplitude microphonic potential. At the same time, his behavioral hearing thresholds diverging from the ABR data increased by 25–30 dB from moderate to moderately severe degree hearing loss. Hearing aids use did not have any effect; cochlear implantation did, however, yield benefits.

Five children from Subgroup 4 (#12–16 in Table 2) developed late-onset hearing loss at 10, 15, 36, 24 and 28 months of actual age. Three children had cCMV: one case was symptomatic infection, and two were asymptomatic (subclinical) ones. The symptomatic child demonstrated a rapid deterioration of the hearing function from normal at 3 months to severe degree at 10 months of age which demanded CI. In the other two children with suspicion to cCMV, moderate SNHL formed at 15 and 36 months of age. In Patients # 15 and 16, moderate SNHL was identified during long-term hearing follow-ups. The impairments were detected at 24 (in the child with extremely low birth weight) and 28 months of actual age. All children had hearing and speech delays.

Case # 5 is an example of hearing changing over time. Child # 5 was a boy with severe perinatal complications: he was born at 29 weeks of gestational age; birth weight was 1270 g; Apgar score was 4/6. He

**Table 2**
Medical characteristics of 16 children with hearing function transformation over time.

| Child | Gestationalage, week | Birth weight, g | Apgar score at 1/5 min | Perinatal infections | Max. Levels of total serum bilirubin, mcmol/L | Respiratory support, days | | Administration of ototoxic drugs | Retinopathy of prematurity | Hemody-namically significant PDA | BPD | Cerebral complications | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | MV | Total | | | | | SEH | IVH | PVL |
| **1. P.** | 30 | 1630 | 7/7 | ++ | 52 | 14 | 20 | – | – | – | – | ++ | ++ | ++ cystic form |
| **2. A.** | 31 | 980, IUGR | 6/7 | – | 172 | 6 | 8 | ++ | + | + | – | ++ | ++ | ++ |
| **3. M.** | 30 | 1130, IUGR | 6/8 | ++ | 283 | 3 | 36 | ++ | – | – | – | ++ | ++ | ++ |
| **4. P.** | 27 | 900 | 4/6 | ++ | 235 | 10 | 40 | ++ | + | + | – | – | – | – |
| **5. Zh.** | 29 | 1270 | 4/6 | – | 252 | 3 | 30 | + | – | – | – | + | + | ++ cystic form |
| **6. F.** | 32 | 1800 | 6/7 | – | 127 | 0 | 4 | – | – | +, PFO | – | + | – | – |
| **7. Ya.** | 28 | 1070 | 5/6 | – | 87 | 41 | 48 | + | + | + | + | ++ | ++ | ++ |
| **8. A.** | 28 | 1180 | 5/7 | – | 260 | 30 | 90 | ++ | + | + | + | ++ | ++, PHH | ++ |
| **9. B.** | 26 | 970 | 5/6 | – | 240 | 34 | 90 | + | + | + | + | ++ | ++ | – |
| **10. T.** | 26 | 980 | 3/4 | – | 291 | 7 | 40 | ++ | + | – | – | ++ | ++ | – |
| **11. V.** | 28 | 417, IUGR | 7/7 | + | 251 | 13 | 43 | ++ | + | – | – | + | + | – |
| **12. V.** | 29 | 1410 | 5/6 | cCMV | 22 | – | 150 | ++ | – | – | + | – | – | – |
| **13. D.** | 28 | 1050 | 5/7 | cCMV? | 263 | 6 | 21 | – | + | – | – | + | + | – |
| **14. I.** | 28 | 1300 | 4/5 | cCMV? | 52 | 7 | 45 | + | + | – | – | – | – | – |
| **15. M.** | 24 | 690 | 5/6 | – | 68 | 60 | 81 | ++ | + | + | – | + | ++ | + |
| **16. K** | 29 | 1500 | 5/6 | – | 127 | 10 | 45 | + | + | – | – | + | + | – |

"–" absence of factors; "+" presence of a factor; "++" using more than one ototoxic drug; presence of severe perinatal infection, SEH, IVH, PVL.

received mechanical ventilation in the NICU for 3 days and further oxygen support for 30 days. The maximum level of total bilirubin in the newborn was 252 μmol/L. Hypoxic-ischemic brain injury and a cystic form of periventricular leukomalacia were diagnosed at the age of 2 months. He is now 8 years old and has mild SNHL and cerebral palsy. A recent brain MRI revealed a thinning of the corpus callosum in its posterior regions. The boy attends a mainstream school and has slight academic difficulties. The child failed the audiological screening at the age of 38 weeks of PCA. At first follow-up at the age of 7 months, ANSD was revealed (click-ABR threshold were 80 dB nHL with bilateral clear cochlear microphonic and normal OAEs; MEMR absence). At his 22 month follow-up, he demonstrated mild SNHL (click-ABR threshold 60 dB nHL with low-amplitude cochlear microphonic and normal OAEs in both ears; MEMR registered). At 8 years he had mild SNHL (click-ABR threshold 50 dB nHL, no cochlear microphonic; low amplitude OAE at a frequency region 500–1000 Hz; MEMR registered; PTA revealed mild degree of high frequency hearing loss). Data of his audiological evaluations are represented at Fig. 3. Recent hearing examinations showed: speech intelligibility of monosyllabic words was 90% and 70% in quiet and in noise, respectively; signal-to-noise ratio providing 50% speech intelligibility in the Simplified RuMatrix Test was low normal range (−6.6 dB SNR). Supra-threshold tests revealed the signs of APD: Dichotic Digit test 50%; Random Gap Detection Test failed; and Rapidly Speech Altering test 85%.

## 4. Discussion

The present study was not aimed at evaluating the epidemiologic parameters of hearing disorders in premature infants, as the sampling was neither representative nor randomly chosen. The children were referred for hearing monitoring at our institution at irregular times and from different NICUs. We have, however, been able to analyze the main trends pertaining to the development and incidence of various forms of hearing impairment in children born at different gestational ages.

Apparently, improvement in hearing in the first few weeks and months after preterm birth is due to the development of the auditory system. At the end of the second trimester of pregnancy (by the 26-27th weeks), the cochlea already has an adultlike structure, and all of the main components of the cochlear nerve and brainstem can be identified. After the start of myelination (from the beginning of the third trimester of pregnancy), which proceeds from the cochlear through the brainstem and up to the thalamus, the first responses to sound can be detected. Final maturation of the cochlea and auditory nerve occurs during the perinatal period through the 6th month of life. The delayed maturation can result in improvement of hearing thresholds in preterm infants. There is also a difference between preterm and full-term infants in the maturation of the auditory system, as revealed by an assessment of ABR parameters: premature infants showed a lower maturation rate compared to full-term ones. In most cases, premature babies' auditory receptors reach the same level of development as their full-term counterparts' by the time their PCA rises to the at-time age level of a full-term pregnancy. A similar trend is observed in the maturation of retrocochlear auditory pathways, although the process may, in some cases, take another several months [7,35,36]. In addition, the activating the processes of maturation of the peripheral part of the auditory system, which are known to be more pronounced with extreme prematurity, is possible [7,18,23,25,27,37]. Another factor contributing to improved hearing is the successful treatment of minor neurological disorders [7] or the elimination of an additional conductive component [7,18].

It is worth noting that the incidence of various types of hearing loss in relation to the degree of prematurity. It was found that, while preterm children were equally frequently diagnosed with SNHL and ANSD, severely preterm infants were more susceptible to ANSD. These findings accord with the results obtained by Wang et al. (2017), ANSD is mostly associated with fetal pathology, i. e. extremely preterm birth, which often implies lower birth weight. The mentioned fact can be seen as part of a broader trend of a high risk of neurological complications in such children [38]. The prevalence of ANSD cases among all hearing impairments in preterm NICU graduates was recorded in a long-term study conducted by K.S. de Graaff-Korf et al. [30].

Hearing disorders which transformed over time were most likely associated with perinatal risk factors in those children. As shown in the table, only three out of 16 patients featured a BW higher than 1500 g. It is known that the risk of permanent hearing loss is higher with decreased GA and BW. In particular, the risk of hearing loss increases from 1.4% with BW higher than 1500 g to 4.8% with BW lower than 750 g [6,17]. Moreover, all children in this study had two or more risk factors for hearing loss, including congenital infection (e.g. cCMV), prolonged respiratory support, neonatal hyperbilirubinemia, comorbid pathology represented by persistent hemodynamically significant PDA, BPD, ROP, and hypoxic-ischemic brain injury. These observations reflect the results of other recent studies which show that the risk of hearing loss in very premature infants is higher when there is a combination of different risk factors involved [3,8,11,17,39]. It is also known that this risk increases from 1.3% in cases featuring no comorbid pathology to 25% in cases where three comorbid conditions are co-present [17,40]. Since genetic tests revealed no obvious pathology, we attributed the hearing impairments in all the children in question to premature birth and related risk factors.

Children in Subgroup 1, initially diagnosed with ANSD, demonstrated improvement in their hearing up to complete recovery. Although such positive outcomes have been described by many researchers, they are a rare occurrence [41]. It should be noted that, despite children # 2 and 3 featuring gestational ages of 31 and 30 weeks, respectively, they had very low and extremely low birth weights caused by intrauterine growth restrictions. Additionally, both children, as newborns, were

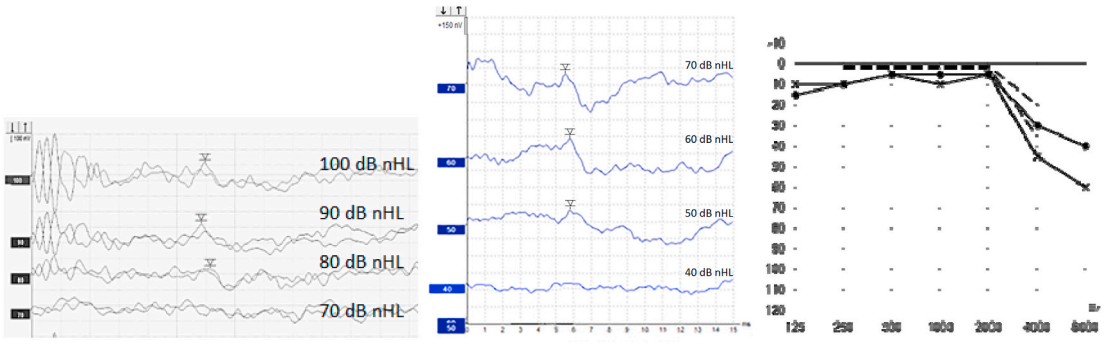


**Fig. 3.** Data of long-term follow-up for Child # 5. A – click ABR at the age of 7 months; B –click ABR at the age of 8 years; C – pure tone audiogram at the age of 8 years.

given prolonged courses of antibiotics (aminoglycosides and glycopeptides) and loop diuretics, and their previous medical history suggested they had suffered from neonatal hyperbilirubinemia. For child # 1, the risk factors contributive to hearing loss were prolonged respiratory support and hypoxic-ischemic brain injury. It is widely recognized that ANSD in very premature infants can be associated with low birth weight, cerebral ischemia, ototoxic medication, and bilirubin toxicity with damage to spiral ganglion neurons and the cochlear nerve [28,29]. However, hearing improvement in children initially diagnosed with ANSD can be achieved through dealing with consequences of hyperbilirubinemia [42] and may also result from progressive axonal growth, synaptogenesis, and cochlear nerve myelination - events which may be delayed in very preterm children. These processes may, in some cases, lead to higher synchronicity of impulse conduction in nerve fibers and, consequently, improved or fully restored ABR and peripheral hearing function even after the children's PCA reaches the level of a full-term pregnancy [7,23,28,29,37,43,44]. This is exactly what was observed with children in the current study. However, it should be remembered that recovery of normal ABR parameters in such children may take up to 24 months of actual life, which means that caution is advised regarding very early cochlear implantation [7,19,23,45,46].

The key risk factors for children in Subgroup 2, whose ANSD later transformed into SNHL, were hyperbilirubinemia, hypoxic-ischemic brain injury, ototoxic medication, and prolonged respiratory support. We therefore interpreted the changes in hearing of these children in the same way we did with Subgroup 1 but with one difference: maturation and reparation processes in the auditory system (children 4, 5 and 6) did not result in its complete functional recovery, and subsequent lesions in the Corti organ and reduction in OAEs (children 4 and 5) were observed. In recent years, similar results were obtained from both experimental and clinical studies [7,23,42]. However, we explain the appearance of impairment and significant deterioration in hearing over time (both in behavior and objective tests results) in child # 6 as follows. On the one hand, the child did not have multiple risk factors for hearing loss, except prematurity, postnatal respiratory distress syndrome and neonatal pneumonia. However, the child failed newborn hearing screening, which was indicative of impaired auditory function at that time. It should be noted that in this case we cannot confidently state that the child had no asymptotic cCMV, although no signs of the disease were revealed. On the other hand, there had been history of moderate persistent PFO and persistent PDA postnatally. Besides, the child had a neurodevelopmental delay both in neonatal and early childhood. PDA was hemodynamically significant at the first week of life and tended to spontaneous closure. Taking into account the relatively small size of PDA, the high probability of its spontaneous closure [47,48], as well as a high risk of early and long-term complications of medical and surgical treatments [49], PDA treatment was not performed. However, a long-term altered flow pattern caused by relatively low volume left to right shunt might have contributed to systemic hypoperfusion, affecting the brain, causing its ischemia [50]. Such ischemia, in turn, may have caused delayed complications, in particular, impairment of the central nervous system, including the auditory system, with the developmental delay and exacerbation of hearing loss [51–53]. Persistent PFO is a structural anomaly and, as a rule, does not have any pathological complications. However, the coexistence of constant PDA and PFO in this case might have aggravated the situation leading to the increase of left-right shunt and an even greater depletion of systemic blood flow, contributing to functional insufficiency of systemic blood circulation.

Children of Subgroup 3 had the following risk factors which could have contributed to hearing loss: severe perinatal hypoxia-ischemia and hypoxic-ischemic brain injury, including IVH; neonatal hyperbilirubinemia with high level of total bilirubin (e.g. posthemorrhagic, hemolytic jaundice); the use of ototoxic medication; prolonged respiratory support; and comorbid conditions (PDA, ROP, BPD). As a result of IVH, child #8 developed posthemorrhagic occlusive hydrocephalus with the formation of the isolated fourth ventricle which required ventriculosubgaleal shunting. We interpreted the changes in hearing of children in Subgroup 3 in two ways. Inner hair cells are more vulnerable to hypoxia-ischemia than outer hair cells, both during and after exposure to harmful factors [54,55]. In addition, damage to the cochlea's neuroepithelial cells may result from hydrocephaly due to IVH (the process may be reversible), or from inner ear hemorrhage [56]. Bilirubin toxicity affects the synapses between inner hair cells and the spiral ganglia the most, with lesser damage caused to the spiral ganglia neurons and the afferent fibers of the auditory nerve [42]. The profound SNHL in this subgroup may therefore result from simultaneous damage to the sensory hair cells and cochlear afferent system. The observed improvement in behavioral hearing thresholds with the appearance of microphonic potential can be seen as evidence of the maturation and/or recovery (possibly, regeneration) in the cochlea, such as partially restored function of the outer hair cells as they are more damage-resistant and play the dominant role in generation of microphonic potential [46]. Other researchers' observations support such an explanation, prompting them to recommend that long-term follow-up be performed until preterm infants reach at least 80 weeks PCA before making decisions concerning cochlear implantation [18,23,25]. Deterioration in the hearing function with a sharp increase in ABR threshold and relatively unchanged function of outer hair cells, which caused SNHL transformation into ANSD in child #8, may be associated with a delayed onset of auditory toxicity [57] and/or the so-called "mass effect" [56] — the gradually increasing compression of the brainstem and, apparently, the proximal part of the auditory nerve, caused by the enlarged fourth ventricle due to a dysfunctional ventriculo-subgaleal shunt. The child was diagnosed with this condition (the diagnosis based on an MRI performed on him at the age of 25 months of actual life) and underwent a ventriculostomy between the fourth ventricle and the left lateral ventricle. However, the surgical intervention failed to restore the auditory nerve function, probably because of irreversible fiber degeneration. Further neural discharge desynchrony, possibly coupled with concomitant disruption of afferent innervation, which may have resulted from extensive injury to the CNS [38], may have led, apart from reduced speech comprehension, to an impaired medial olivocochlear system thus causing cochlear dysfunction and, consequently, progressive hearing loss. In our practice we have repeatedly observed similar changes in hearing function in prematurely born infants diagnosed with ANSD [58]. Child # 11, whose hearing loss was initially the combination of SNHL and ANSD of moderate degrees in different ears, the transformation from SNHL to ANSD (confirmed with electrophysiological data and accompanying the increment in hearing thresholds to moderate-severe degree in both ears), mainly exhibited an exacerbation of impairment of the auditory pathway on the side of the transformation. To a lesser extent, it appears outer hair cells were affected. These changes could be the result of a delayed or impaired development of the auditory system, including those due to IUGR, as well as the result of a wide range of risk factors for hearing loss and the possibility of their prolonged neglect. These factors included bilirubin neurotoxicity (the child had high levels of total bilirubin with extremely low body weight), prolonged oxygen support, the use of ototoxic drugs, as well as ischemic-hypoxic damage to CNS [18,22,57,59,60].

It is widely recognized that children diagnosed with cCMV are at risk of developing late-onset SNHL up until their teenage years, with the risk being higher in symptomatic infection, rather than in asymptomatic cases [61–64]. This is the most plausible explanation for children # 12–14 from Subgroup 4 developing hearing loss as they grew older. Children # 15 and 16, diagnosed with SNHL in the long-term follow-up, had the following risk factors: extremely low birth weight (child # 15); severe perinatal hypoxia-ischemia (Apgar score was 5/6), and breathing disorders in the first year of life, which necessitated prolonged oxygen support for 45 and 81 days, respectively; comorbid conditions (ROP, PDA, severe hypoxic-ischemic brain injury); and ototoxic medication. Recent research has shown that around 50% of children diagnosed with hearing loss at the age of 10 years passed newborn hearing screening

[33], and even full-term children having been treated in NICUs and not having other risk factors for hearing loss are at high risk of late-onset SNHL [65]. It is also known that 40% of children with SNHL, who needed prolonged intensive therapy upon birth, feature progressive hearing loss [32]. In preterm infants, the risk of subsequent hearing impairments (besides other risk factors such as PDA, ototoxic medication, metabolic disorders, etc.) is also highly dependent on the intensity and duration of treatment in a NICU (e.g. prolonged respiratory support) [10,66]. Moreover, it is assumed that there may be a connection between prolonged respiratory support and late-onset and progressive hearing loss, which, according to longitudinal cohort studies, are diagnosed in 4.3–10% and 28% of cases, respectively [11,13]. It is known that prolonged respiratory support of extremely preterm neonates, as well as hypoxia during birth and a PDA, can cause severe hypoxic-ischemic brain injury that may, in some cases, be progressive [67]. The latter may well lead to late-onset and progressive hearing loss in such patients.

The variability in hearing observed in preterm children which includes hearing improvement, worsening or even late-onset hearing loss, suggests the necessity of long-term hearing monitoring at least up to the age of 3–4 years. The effectiveness of intervention programs depends very directly on timely hearing diagnostics. The importance of long-term hearing monitoring for preterm children proposed in this study is supported by the recommendations of the Joint Committee on Infant Hearing of the American Pediatric Academy [68], even for children that passed newborn hearing screening. We share the opinion of E.E. Rogers and S.R. Hintz [3,69], who assume that the age limits of hearing monitoring of children belonging to risk groups should be extended. A possible solution to this issue may be hearing screenings of children of preschool and primary school age [70,71].

## 5. Conclusion

- The auditory function in prematurely born children tends to be unstable, especially at a very early age. In very preterm infants, it may either deteriorate or improve.
- ANSD is a common type of hearing impairment in premature infants, which, in particular, is associated with their high susceptibility to neurological disorders in general.
- Late-onset hearing loss is most typically found in very preterm babies, and can be caused by (un)diagnosed cCMV or progressive hypoxic-ischemic brain injury.
- Infants born before 32 weeks' gestation require long-term hearing follow-up at least until they are 3–4 years of age.
- Special caution should be paid with respect to very early cochlear implantation (before age of 24 months) for children born before the 32 nd week of gestation because of possible delayed maturation of their auditory pathway.

## Declaration of competing interest

None.

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