

Hearing loss in early infancy affects maturation of the auditory pathway

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The influence of early cochlear hearing loss on maturation of the auditory pathway was studied by measuring auditory brainstem responses (ABR). In a retrospective study, 85 children with normal hearing (46 males, 39 females; age range 2 months to 14 years) and 165 children with bilateral cochlear hearing impairment (89 males, 76 females; age range 1 month to 16 years) were examined. A significant positive correlation ($p < 0.001$) between the degree of hearing loss and interpeak latencies I–V (IPL_{I-V}) of the ABR was observed. No significant correlation ($p = 0.85$) was found between hearing loss and interpeak latencies I–III (IPL_{I-III}). These findings can be interpreted as indicating a marked delay in maturation of higher brainstem structures due to reduced auditory input during infancy. The correlation differs notably from results of comparable studies of adults published in recent literature. This leads to the assumption that the developing human brain is particularly sensitive to auditory deprivation. Thus, our results indicate the importance of a normal acoustic environment during sensitive periods in early childhood to ensure normal hearing and speech development.

Significant bilateral hearing loss (HL) is present in 1 to 3 per 1000 low-risk newborn infants and in 2 to 4 per 100 in a high-risk population (American Academy of Pediatrics 1999). Thus, it is one of the most common major abnormalities present at birth. In Germany, the average age at which permanent HL requiring therapy is detected is 31 months (Finckh-Krämer et al. 1998). Results from animal models and behavioural studies in humans give rise to some concern about the consequences of HL for affected children. Experimentally induced peripheral HL in animals and the resulting auditory deprivation has frequently been reported to produce specific alterations in anatomy and physiology as well as in the electrophysiology of the brainstem auditory nuclei (for review see Henry 1983, Sininger et al. 1999). There is increasing evidence in literature that deprivation of sound stimulation can negatively influence the central structures of the auditory system (Killackey and Ryugo 1977, Webster and Webster 1979, Trune 1982, Hashisaki and Rubel 1989). In some studies, these influences appeared to be greater if deprivation had taken place during an early critical period (Clopton and Silverman 1977, Trune 1982, Hashisaki and Rubel 1989).

In contrast to animal models, knowledge about the consequences of auditory deprivation in humans is still poor and mainly based on behavioural studies. These studies show significant impairment of speech, language, and cognitive development in children with hearing disabilities which correlates to the degree and time of detection of HL (Northern and Downs 1991, Yoshinaga-Itano et al. 1998, Bennett and Haggard 1999). On the other hand, early intervention has been shown to be highly effective in the prevention of these detrimental effects (Downs and Yoshinaga-Itano 1999).

Anatomical data are obviously difficult to obtain in humans. Therefore, in the early 1980s researchers frequently began to use auditory brainstem responses (ABR) to demonstrate changes of the central auditory function and maturation of the central auditory pathway during infancy and childhood. ABR now has been proved to be an effective, objective tool not only to evaluate hearing impairment in children, but also for the assessment of developmental changes of the auditory brainstem (Eggermont 1995). A number of studies provided normative data for different ABR parameters, such as wave latencies and interpeak latencies (Salamy and McKean 1976, Fawer and Dubowitz 1982, Mochizuki et al. 1982).

More recently, efforts were made to study the influence of auditory deprivation caused by conductive HL by means of ABR interpeak latencies. Although results have been somewhat conflicting, a number of electrophysiological studies have provided some evidence that the human CNS is sensitive to even minor fluctuations in hearing in early life, such as in recurrent otitis media with effusion (Folsom et al. 1983, Anteby et al. 1986, Fria and Sabo 1989, Gunnarson and Finitzo 1991). However, in contrast to cochlear HL, it remains difficult to document chronic conductive HL accurately as the disease may vary daily along a continuum.

We are not aware of any study that reports data on cochlear hearing impairment in children and its consequences for the developing brain.

The hypothesis of the present study was that cochlear HL in early infancy and childhood negatively affects maturation of the central auditory pathway. This study also attempted to find a direct correlation between the degree of HL and the extent of alterations in the central auditory pathway. Such a

correlation could provide further evidence of the importance of early diagnosis of HL in children which could prevent severe sequelae in later life.

Method

PARTICIPANTS

During a 5-year period, 1408 children were referred to the Department of Audiology and Paedaudiology of the ear, nose, and throat clinic of the University of Cologne Teaching Hospital to undergo measurement of ABR for advanced hearing assessment. All children who were diagnosed as having cochlear HL, as well as all children from the hospital with normal hearing, were considered for inclusion. Patients' hospital files were reviewed for detailed clinical information. Of these children, 250 met the entrance criteria (Tables I and II) and were selected for this study. Eighty-five children were classified as having normal hearing and in 165 patients a binaural cochlear HL was identified: this was defined as HL above 15 dB HL with an interaural difference in hearing level below 30 dB to rule out possible interaural interactions.

All children wearing hearing aids were excluded from the study to avoid possible influences of enhanced auditory input on maturation of the brainstem. In addition, no patient who was likely to have additional central nervous disorders (specific syndromes, foetal alcohol syndrome, intracranial injury, epilepsy) that might have affected ABR patterns was included in this study (Hecox et al. 1981). Children who were found to have additional conductive HL at the time of ABR evaluation and children with a history of recurrent middle-ear effusions were omitted as this influenced ABR development. All participants had normal tympanic membranes and no pathological findings in the middle ear.

As auditory neuropathy usually presents without an identifiable ABR pattern we did not expect any such case

Table I: Eligibility criteria and exclusionary criteria for children with normal hearing

| <i>Eligibility criteria</i> | <i>Exclusionary criteria</i> |
|-----------------------------|---|
| Hearing loss < 15 dB | Syndromes known to seriously affect CNS History of intraventricular haemorrhage/severe head trauma History of delayed speech development Conductive hearing loss Recurrent otitis media |

Table II: Eligibility criteria and exclusionary criteria for children with bilateral cochlear hearing loss

| <i>Eligibility criteria</i> | <i>Exclusionary criteria</i> |
|---------------------------------|--|
| Hearing loss > 15 dB | Conductive hearing loss |
| Bilateral cochlear hearing loss | Recurrent otitis media |
| Interaural difference < 30 dB | Hearing aids > 95 dB hearing loss Auditory neuropathy CNS disorders |

among the patients of this study. However, additional transient evoked otoacoustic emissions were performed to confirm that the losses were cochlear in origin.

According to a preliminary analysis of our data, 80% of the children with profound HL (>95 dB) did not produce a detectable ABR pattern. Therefore, we did not include these children in the study.

HEARING ASSESSMENT

Hearing assessment was carried out in a sound and electrically isolated booth by recording the ABR to monaural click-stimulation using the signal analysing system Nicolet Type Pathfinder II (Nicolet Biomedical, Madison, WI, USA). Children were sleeping, kept still by watching videos, or sedated with chloral hydrate during the investigation. Delivered stimulus was of 140 µs duration with a repetition rate of 21.3/s. Analyzing time was 15 ms. Hearing threshold was determined by visual detection of the level of wave V.

Classification of HL (normal range to profound HL) was according to the American National Standards Institute (Northern and Downs 1991; Table III).

An evaluation of interpeak latencies (IPL) between peak I and III (IPL_{I-III}) and between peak I and V (IPL_{I-V}) was performed.

STATISTICAL ANALYSIS

Data were analyzed in a retrospective design to obtain information about the maturational status of the auditory pathway. IPLs were compared with respect to the influence of peripheral hearing disorders. Descriptive statistics were provided for the determination of the correlation between IPL_{I-III} and IPL_{I-V} and severity of HL. Continuous variables were expressed as mean (SD); confidence intervals were set at 95%. The correlation between HL and IPLs was assessed with Spearman's rank correlation and partial correlation. Calculations were performed using SPSS (version 8.0). Statistical significance was set at $p < 0.05$.

Results

NORMAL HEARING

The normal hearing group consisted of 85 children (46 males, 39 females) who ranged in age from 2 months to 14 years (median 22 months).

To study the possible correlation between HL and IPL developmental changes we measured the development of the ABR parameter in our participants with normal hearing. Plotting IPL against age (Fig. 1) shows a rapid shortening of the IPL_{I-III} and IPL_{I-V} during the first 20 to 24 months of life.

Table III: Classification of hearing loss (according to American National Standards Institute; Northern and Downs 1991)

| <i>Hearing loss</i> | <i>Classification</i> |
|---------------------|-----------------------|
| 0–15 dB | Normal |
| 16–25 dB | Slight |
| 26–40 dB | Mild |
| 41–65 dB | Moderate |
| 66–95 dB | Severe |
| 96 + | Profound |

The biggest effects were observed during the first 6 months slowly coming to a minimum at about 25 months. Thereafter, only slight changes of the IPL with increasing age were observed. In addition, a different pattern of peripheral (IPL_{I-III}) and central development (IPL_{I-V}). These observations were confirmed by showing a significant negative correlation between age and shortening of IPL which is more marked for IPL_{I-V} (Table IV).

HEARING LOSS

The group with HL consisted of 165 children (89 males, 76 females) who ranged from 1 month to 16 years of age (mean age 41.6 months, median age 32 months). A review of the patients' files led to the following probable origins of HL: prenatal HL in four patients, perinatal in 32 patients, postnatal in four patients, and hereditary in 42 patients. In 83 children the patients' history did not provide an aetiological factor for the development of HL. Figure 2 illustrates the average age of investigation in patients with slight to severe HL.

The relation between HL and IPL was quantified by determining the partial correlation between HL and IPL controlled for age. Results are shown in Table V. A significant age-independent correlation between HL and IPL was demonstrated for IPL_{I-V} but not for IPL_{I-III} .

Figures 3a to h graphically display the correlation between age and IPL of those with hearing disability in comparison with the normal developmental range. Four groups of children with HL were created (slight to severe HL). Although IPLs were widely scattered in hearing disabled groups, a strong tendency to higher IPL values along with increasing HL was evident, particularly in patients with moderate and severe HL. Above a hearing level of 40 dB a marked delay of the IPL_{I-V} could be demonstrated. Among these patients no developmental regression of the IPL_{I-III} and IPL_{I-V} , as in the control group, could be observed. Again, a different pattern of the IPL_{I-III} and IPL_{I-V} could be shown. Additionally, it appeared that development of the ABR was hardly affected in those with only slight HL.

To emphasize the long-term consequences of early infant HL for the auditory pathway we focused finally on results of

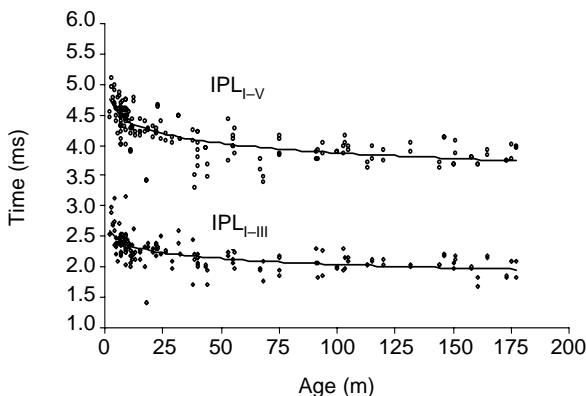


Figure 1: Developmental changes of IPL in individuals with normal hearing. IPL plotted against age, regression lines for IPL_{I-III} and IPL_{I-V} are drawn in. Each spot indicates one ear. IPL_{I-V} , $R^2=0.5721$; IPL_{I-III} , $R^2=0.4349$.

the ABR in five groups of children older than 24 months of age at the time of investigation. Under normal circumstances the ABR development would have been completed by this time (see Fig. 1). One group of children with normal hearing and four groups of children with hearing impairment, who had hereditary, perinatally, or prenatally acquired HL of four different degrees (slight to severe), were compared with respect to IPL_{I-III} and IPL_{I-V} values. In doing so we could gain information about patients whose hearing impairment must have already existed during early infancy, a time of major maturational processes of the central auditory pathway. Analyses of means and 95% confidence intervals of the IPL_{I-III} and IPL_{I-V} were performed for each group and compared as demonstrated in Figures 4a and 4b.

Table IV: Spearman's correlation between age and IPL_{I-III} , IPL_{I-V} , for individuals with normal hearing

| | IPL_{I-III} | IPL_{I-V} |
|-----|----------------|----------------|
| r | 0.73 | 0.79 |
| n | 170 | 170 |
| p | $\leq 0.001\%$ | $\leq 0.001\%$ |

Table V: Relation of intensity of hearing loss and ABR—partial correlations for hearing level (dB) and IPL_{I-III} and IPL_{I-V} (ms) controlling for age

| | IPL_{I-III} | IPL_{I-V} |
|-----|---------------|----------------|
| r | 0.01 | 0.36 |
| n | 438 | 443 |
| p | 0.854 | $\leq 0.001\%$ |

n represents detectable IPL of control and experimental group pooled for statistical analyses.

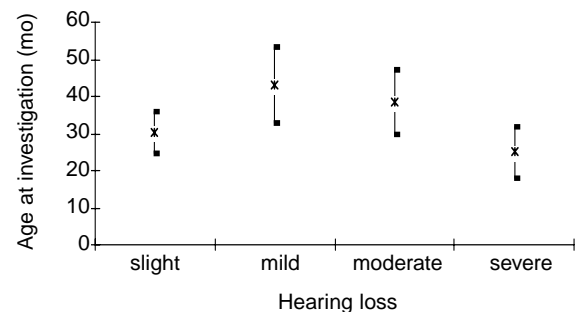


Figure 2: Age at investigation. Comparison of children with slight to severe hearing loss. Means and 95% confidence intervals (lower and upper bars).

With regard to IPL_{I-V} , no significant group differences could be seen between participants with normal to mild HL. The remaining groups differed significantly, reflecting prolonged IPLs in children with HL >40 dB. The most dramatic impairment of IPL_{I-V} affects children with HL above 65 dB HL (see Fig. 4b).

No significant changes were observed for IPL_{I-III} even in cases of severe HL although values are more scattered among these individuals (see Fig. 4a).

Discussion

Onset of synchronized auditory conduction in humans at around the 28th week of gestation is signalled by simultaneous appearance of acousticomotor reflexes, myelin in the auditory nerve, brainstem pathways, and auditory cortex and recordable ABRs (Moore et al. 1995). During further development, ABR patterns show marked changes reflecting the rapidly increasing speed of conduction due to increased myelin density, arborization, and synaptogenesis. Various

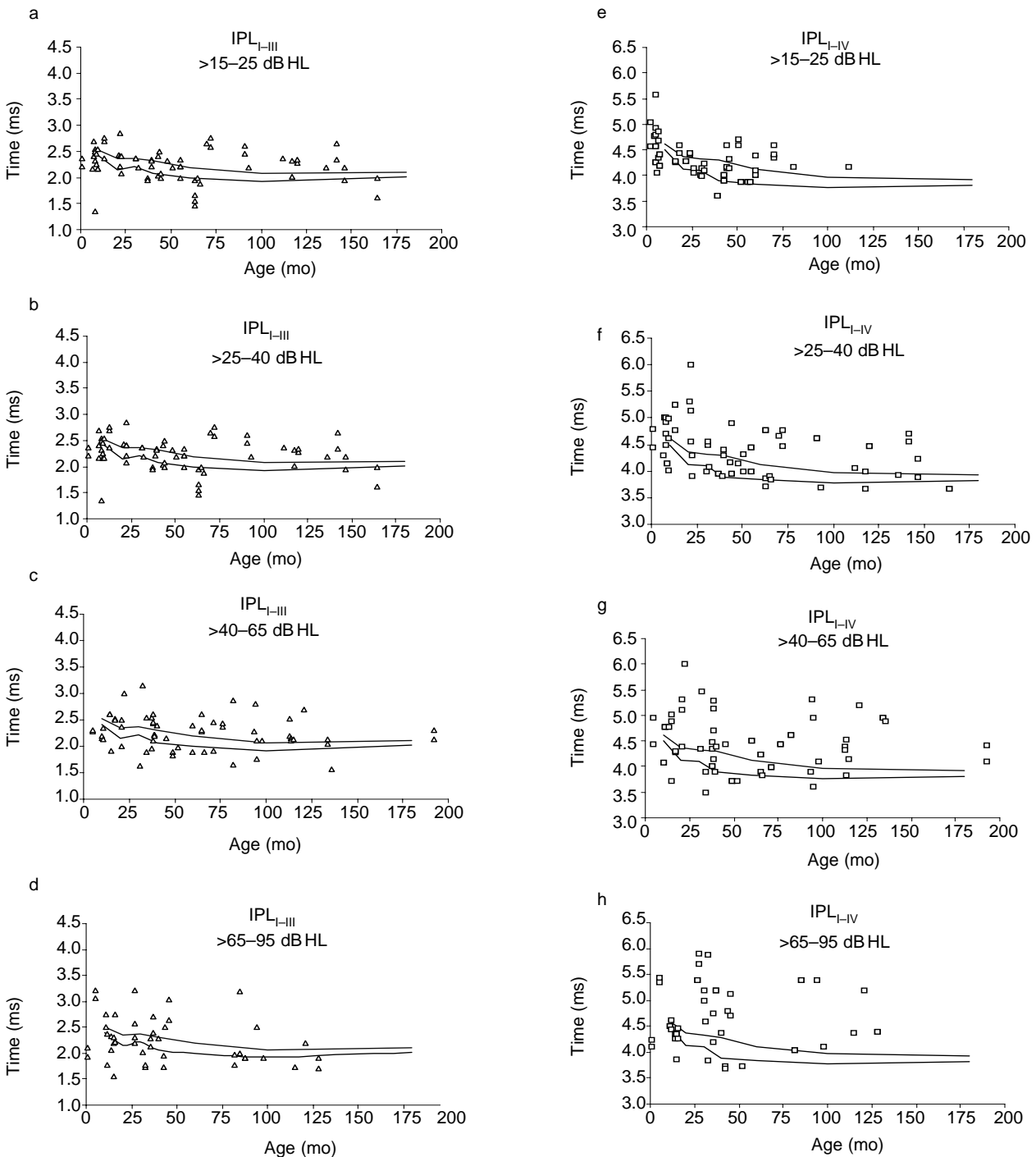


Figure 3a–h: Developmental changes of IPL_{I-III} (left) and IPL_{I-V} (right) in children with hearing disabilities compared with normal development. IPL plotted against age for children with slight to severe hearing loss in relation to 95% confidence intervals drawn from infants with normal hearing (upper and lower line). Each symbol represents one ear.

researchers have described developmental changes of the ABR patterns (Salamy and McKean 1976, Fawer and Dubowitz 1982, Mochizuki et al. 1982). Normative data are now available for different ABR parameters leading to a rising clinical application, not only for early objective hearing assessment but also to demonstrate changes of central auditory function and maturation of the central auditory pathway in infancy and childhood (Salamy and McKean 1976, Fawer and Dubowitz 1982, Eggermont 1995).

In our patients with normal hearing, shortening of the IPL_{I-III} and IPL_{I-V} was most rapid during the first 24 months of life. Thereafter, only slight changes were detectable. Thus, our results obtained in the control group are in agreement with most published reports on developmental changes of ABR in animals and humans.

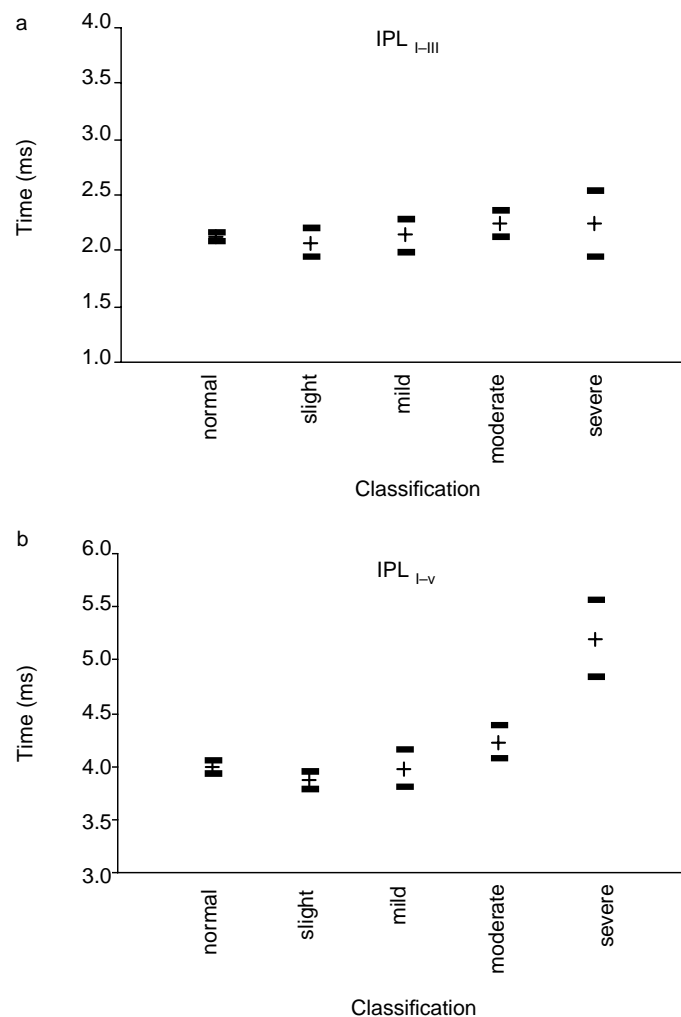
Studying preterm newborn infants, Fawer and Dubowitz (1982) found a close correlation in the latencies of wave I and V and in the I-V interval with a gestational age of 29 to 36 weeks. Salamy and McKean (1976) showed a rapid shortening of the IPL_{I-III} and IPL_{I-V} from birth to the age of 6 weeks followed by a smaller regression until the end of the first year of life which is consistent with anatomical and electrophysiological studies of Matschke (1993). Differences between the development of IPL_{I-III} and IPL_{I-V} were first described by

Salamy and McKean (1976) who measured adult values of the periphery of the auditory pathway (wave I) already at the age of 6 weeks, whereas IPL_{I-V} reaches an adult level after 12 months. However, the exact age at which maturation of the ABR is completed remains uncertain although there is general agreement that the most important changes take place during the first 2 years of life.

In Germany, hearing assessment in children is still mainly based on high-risk hearing screening programs which are insufficient. High-risk screening will only identify 50% of newborn infants with significant congenital HL (Watkin et al. 1991, Davis and Woods 1992). As a consequence, the average age at detection of HL in Germany is as late as 31 months and can reach 45 months in mild HL (Finckh-Kramer et al. 1998). This trend is again reflected by our data. Those who had severe HL were investigated at an earlier age. Surprisingly, children with slight HL were investigated earlier than those with mild and moderate HL.

However, to rule out the influence of only age-related differences in the groups of children with hearing impairment and normal hearing, we used partial correlation controlling for age when assessing the relation between HL and IPL. Therefore, group differences are independent of the age of investigation.

Figure 4: Comparison of means and 95% CI (lower and upper bars) of IPL_{I-III} and IPL_{I-V} of children with different hearing levels (classified as normal to severe HL). All children > 24 months of age. +, mean; -, 95% CI.



We demonstrated a significant delay of the developmental changes of IPL_{L-V} but not IPL_{L-III} along with increasing cochlear HL in patients with hearing disability. Compared with children with normal hearing, IPL_{L-V} were prolonged in children with moderate and severe HL. The detection of IPL_{L-V} abnormalities in the presence of only slightly altered IPL_{L-III} characteristics suggest that the origin of the abnormalities is located in the auditory brainstem rather than in the periphery. Additionally, it was indicated that the typical age-dependent shortening of the IPL shown in those with normal hearing was less predictable, especially in cases of moderate and severe HL.

Beyond this it seems noteworthy that in about 80% of the patients with profound HL (>95 dB) no ABR patterns were detectable, leading to the assumption that the severely deprived auditory system did not experience sufficient synchronization of the auditory response.

Although it appeared that those with slight and mild HL were generally less affected, it needs to be emphasized that marked interindividual differences were demonstrable. A number of these children still presented with serious ABR alterations. Considering the data available in this study, this phenomenon, as well as the fact that persons can have normal ABR patterns despite severe HL, remains, as yet, unexplained.

From the findings mentioned above it can be concluded that auditory deprivation in early infancy and childhood leads to marked alterations in the development of the ABR, suggesting a significant delay of the corresponding anatomical and physiological maturation of the auditory brainstem. According to dipole studies by Scherg and von Cramon (1985) regarding the tonotopy of the ABR, waves III to V represent the brainstem auditory pathway from the ventral cochlear nuclei to the contralateral lateral lemniscus. Therefore, fundamental deficits in central auditory processing may be presumed in affected children.

Our results are most consistent with results from animal research on acoustic deprivation. Histological studies frequently found morphological changes of the brainstem nuclei leading to the assumption that auditory deprivation causes developmental disturbances at brainstem level (Powell and Erulkar 1962, Trune 1982, Hashisaki and Rubel 1989). In young rats and mice these alterations mainly affected the number and length of cell bodies and the size of neurons (Killackey and Ryugo 1977, Webster and Webster 1979) as well as the symmetry of dendrite cells of the cochlear nuclei, superior olivary complex, and inferior colliculus (Feng and Rogowski 1980). These effects were described to be much smaller in adult animals. A study performed by Moore and colleagues (1994) examining seven adults with profound deafness, focused on cell size within the ventral cochlear nucleus. Compared with normally developing individuals, cell size was reduced most in those who had been deaf for the longest period of time.

More recent animal studies concentrated on the electrophysiological consequences of auditory deprivation revealed by ABR and middle latency response, (MLR). Laska and coworkers (1992) found clear alterations in the maturation of binaural interaction components in the auditory brainstem response of guinea pigs. A study by Walger and colleagues (1996) analyzed the effects of reversible binaural conductive hearing on IPL and MLR latencies in which they

identified a delayed development of the ABR, IPL, and the MLR latencies. One week after deprivation ended the IPL reached control values while the delay in MLR needed more time to recover. Keilman (1995) found a significant temporary prolongation of the IPL_{L-IV} in rats deprived immediately after birth until the age of 21 days.

Several attempts have been made to provide evidence that a critical period for auditory development exists. Results of animal studies provide some support by describing age-dependent consequences of auditory deprivation in gerbils (Nordeen et al. 1983, Hashisaki and Rubel 1989). However, the hypothesis of a critical period is not generally accepted (Ferguson et al. 1998).

Although our study does not provide comparative data for early and late-onset HL, the differences between those with normal hearing and those with early onset HL suggests that young age at onset might be an important prognostic factor. This is further supported by well-designed electrophysiological studies investigating the effects of adult onset cochlear HL on the IPL_{L-V}. Kirsh and colleagues (1992) studied the effects of audiometric configuration on the ABR in adults with cochlear HL. Compared with a hearing control group, no significant differences of the IPL_{L-V} were observed in those with hearing impairment who had cochlear HL regardless of the kind of audiometric configuration was found. In a similar study by Keith and Greville (1987), results were predominantly in accordance with those of Kirsh and colleagues (1992) although in notched audiometric configuration a significant delay in the IPL_{L-V} was found. However, this configuration has rarely been seen in infants.

In summary, these findings give some evidence that ABR changes in childhood and infancy differ markedly from those in adults, suggesting that there is a certain critical period during which the maturation of the auditory brainstem is particularly vulnerable to deprivation.

Although it has been indicated that effects of auditory deprivation may be too subtle to be measured by current tools, ABR is still considered to be a useful instrument for providing information about brainstem auditory development and processing. Therefore, results of our human study can be interpreted as indicating that acoustic stimulation is necessary during early infancy to ensure normal neural development. If auditory input is missing, brainstem auditory processing may be disturbed in relation to the severity of HL.

As shown by the American Academy of Pediatrics (1999), high-risk screening can only identify about 50% of newborn infants with significant congenital HL (Watkin et al. 1991, Davis and Woods 1992). Thus, our results give some support to the demand for general hearing screening as has been published primarily by the National Institute of Health and Human Services (1993) followed by the American Speech, Language, and Hearing Association (1994), and the European Consensus Statement (1999). In the meantime, several governments have agreed to introduce universal neonatal screening (UNS), most recently in the UK (Kennedy 2000).

Following early detection, adequate rehabilitation measures like tympanostomy tubes, hearing aids, cochlear implants, along with auditory training, could be instituted in early infancy and chances of a poor outcome reduced.

The limitations of our study are those inherent in a retrospective analysis. Further studies are required to confirm our results in a prospective design.

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