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Hearing Loss by Week of Gestation and Birth Weight in Very Preterm Neonates

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Objective To gain insight into health and related costs associated with very preterm births, one needs accurate information about the prevalence of the disabling conditions, including neonatal hearing loss (NHL).

Study design We assessed the prevalence of NHL by week of gestation and categories of birth weight in very preterm neonates. Results of the 2-stage Automated Auditory Brainstem Response nationwide Newborn Hearing Screening Program in Dutch Neonatal Intensive Care Units and diagnostic examinations were centrally registered between October 1998 and December 2012 and included in this study. NHL was defined as impaired when the neonate conventional Auditory Brainstem Response level exceeded 35 dB near Hearing Level at diagnostic examination. Birth weight was stratified into <750 g, 750-999 g, 1000-1249 g, 1250-1499 g, and ≥1500 g, and by small for gestational age (SGA; <10th percentile) vs appropriate for gestational age. Logistic regression analyses and recursive partitioning were performed.

Results In total, 18 564 very preterm neonates were eligible. The prevalence of NHL consistently increased with decreasing week of gestation (1.2%-7.5% from 31 to 24 weeks) and decreasing birth weight (1.4%-4.8% from ≥1500 g to <750 g, all $P < .002$). Most vulnerable to NHL were girls <28 weeks, boys <30 weeks, and SGA neonates. The SGA effect started at 27 weeks.

Conclusions Gestational age and birth weight quantify the risk of NHL. This information can be used at the individual level for parent counseling and at the population level for medical decision making. *(J Pediatr 2015;166:840-3)*.

Survivors of very preterm births face a lifetime of disability.[1] The annual societal economic burden associated with preterm birth is high, especially among the smallest and most immature neonates.[2] To gain better insight into health and related costs associated with very preterm births, accurate information about the prevalence of the disabling conditions is required. Besides cerebral palsy, intellectual disabilities, and vision impairment, neonatal hearing loss (NHL) is 1 of the 4 major disabling conditions in very preterm neonates.[1,2] NHL is a serious health condition that may adversely affect speech, language development, academic achievement, and social-emotional development.[3] NHL also has an impact on societal costs, including medical, early intervention, and special education services.[2]

Although studies have shown an association between NHL and prematurity and low birth weight,[4] the prevalences of NHL by week of gestation and categories of birth weight in neonates born <32 weeks of gestation have not been reported. Our aim is to assess the prevalence by using the results of the nationwide Newborn Hearing Screening Program (NHSP) in Dutch neonatal intensive care units (NICUs).

Methods

In The Netherlands, all neonates born with a gestational age (GA) <30 weeks and most (~85%) neonates with a GA between 30 and 32 weeks are treated in 1 of the 10 level-III NICUs. From 1998 to 2002, a 2-stage automated auditory brainstem response (AABR) NHSP was implemented gradually in Dutch NICUs.[5] The 2-stage AABR screening consists of a first AABR test before discharge from the NICU and a second AABR test as an outpatient in the NICU clinic if the neonate has failed the first AABR test. Two commercially available AABR hearing screening devices were used. The ALGO Portable/ALGO3i by Natus Medical Inc (Pleasanton, California) uses a 35 dB near Hearing Level click stimulus, rate 37/sec with a broadband acoustic spectrum from 750 to 5000 Hz. The second device is the MB11 BERAphone by Maiko Diagnostics (Berlin, Germany) with the same stim-

AABR	Automated auditory brainstem response
AGA	Appropriate for gestational age
GA	Gestational age
HL	Hearing loss
NDI	Neurodevelopmental impairment
NHL	Neonatal hearing loss
NHSP	Newborn Hearing Screening Program
NICU	Neonatal intensive care unit
SGA	Small for gestational age

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ulus level (rate 93/sec), an acoustic spectrum from 135 Hz to 8000 Hz, with inbuilt CE-Chirp stimulus technology. All neonates who failed the 2-stage AABR test were referred for further audiologic diagnostic procedures.

Results of the screening and first diagnostic examination at the audiologic center in NICU graduates born between October 1998 and December 2012 with 1 or more risk factors according to the Joint Committee on Infant Hearing[3] were registered centrally in an electronic registration system and included in this study. Note that (almost) all very preterm neonates have at least 1 risk factor, because "neonatal intensive care of more than 5 days" is a risk factor according to the Joint Committee of Infant Hearing. Parents were informed about the AABR hearing screening by a brochure. Institutional review/ethical board approval was not required for this study.

NHL was defined as impaired when the conventional auditory brainstem response level exceeded 35 dB near Hearing Level in 1 (unilateral) or 2 (bilateral) ears at diagnostic examination at the audiologic center. Birth weight, GA, and sex also were registered in the registration system. Birth weights were measured by trained health professionals by the use of calibrated digital baby scales. GA was determined from early ultrasound examination during pregnancy. We included all neonates with a GA <32 weeks who survived the admission period. We excluded neonates with missing values on birth weight and those with birth weights exceeding 5 SD above the median at the GA and sex-specific growth charts ("outliers").[6]

Birth weight was stratified into 2 categories of extremely low birth weight (<750 g, 750-999 g), 2 categories of very low birth weight (1000-1249 g, 1250-1499 g), and in the category ≥1500 g. Birth weight also was categorized in 2 groups: small for gestational age (SGA; <−1.3 SD [ie, below the 10th percentile] on GA and sex-specific growth charts[6]) vs appropriate for gestational age (AGA). GA was truncated to complete weeks (eg, from 26 weeks and 0-6 days to 26 weeks). Descriptive statistics and exact binomial CIs were calculated for subgroups with a sufficient (>100) sample size. Logistic regression analyses were performed with unilateral or bilateral NHL as dependent variable and GA in weeks and/or birth weight in kilograms as independent variables. Note that the OR of the logistic regression analyses present the odds of NHL given a certain GA (or category of birth weight) divided by the odds of NHL when GA is 1 week less (or one category of birth weight lower). The variance inflation factor was calculated to analyze the magnitude of multicollinearity in the analysis because GA and birth weight are correlated.

Recursive partitioning (classification tree) was performed to explore subgroups with high risks of NHL according to (interactions of) GA, SGA, and sex. These subgroups were defined as most vulnerable to NHL. Recursively partitioning splits the data into homogeneous subgroups (ie, subgroups with relatively high or low risks of NHL). We first allowed a very complex model: (1) the complexity parameter was set at 0.001 and served as a penalty term to control the tree size; (2) we allowed a minimum size subgroup of 5; and (3) a minimum size of 10 to make a split. Then we used cross-validation to prune back the tree ("1 − SE" rule).[7] We calculated the relative error (ie, average deviance of the current tree divided by the average deviance of the null tree), and the cross-validation error (ie, a 10-fold cross-validation measured relative to the deviance of the null model). We set the prior probability at 0.5. The statistical analyses were performed in SPSS version 20.0 (SPSS Inc, Chicago, Illinois) for Windows (descriptive analyses and logistic regression analyses) and R version 3.0.2 (rpart). *P* values < .05 (2-sided) were considered statistically significant.

Results

Of the 18 636 surviving neonates born <32 weeks of gestation, 30 neonates were excluded because of missing values on birth weight, and 42 neonates were excluded as their birth weights exceeded 5 SD on the growth charts. Of the 18 564 eligible neonates, 318 (1.7%) had bilateral NHL, 85 (0.5%) had unilateral NHL, 2096 (11.3%) were SGA, and 9992 (53.8%) were male.

The prevalence of NHL in these neonates consistently increased with decreasing week of GA and birth weight (**Table I**). Logistic regression analyses revealed significant associations between GA and unilateral and bilateral NHL (OR 0.84, 95% CI 0.75-0.94 and OR 0.76, 95% CI 0.72-0.81, respectively), as well as between birth weight and unilateral and bilateral NHL (OR 0.22, 95% CI 0.11-0.44 and OR 0.31, 95% CI 0.22-0.43, respectively). GA and birth weight were independent risk indicators of NHL (aOR 0.83, 95% CI 0.77-0.88 and aOR 0.58, 95% CI 0.39-0.87, respectively; variance inflation factor 1.7).

Figure 1 compares the distribution of GA within very preterm neonates with NHL and within the total group of very preterm neonates. The number of neonates increased with increasing weeks of GA, and the number of neonates with NHL remained almost stable between 26 and 31 weeks of gestation. A small (11%) group of neonates born at 24-26 weeks' GA contributed more than a one-quarter of the total number of very preterm neonates with NHL.

Table II shows the prevalence of NHL in very preterm neonates stratified by weeks of gestation, SGA, and sex. The

Table I. Prevalence of NHL in very preterm neonates (n = 18 564)

	n	NHL,* % (95% CI)	Unilateral NHL, % (95% CI)	Bilateral NHL, % (95% CI)
GA, wk				
24.0-24.9	133	7.5 (3.7-13.4)	0.8 (0.02-4.1)	6.8 (3.1-12.5)
25.0-25.9	631	5.2 (3.6-7.3)	0.8 (0.3-1.8)	4.4 (3.0-6.4)
26.0-26.9	1336	4.6 (3.5-5.8)	1.0 (0.5-1.7)	3.6 (2.7-4.7)
27.0-27.9	1942	2.8 (2.1-3.7)	0.6 (0.3-1.0)	2.3 (1.7-3.0)
28.0-28.9	2521	2.2 (1.7-2.9)	0.4 (0.2-0.7)	1.8 (1.3-2.4)
29.0-29.9	3256	2.0 (1.5-2.5)	0.4 (0.2-0.7)	1.6 (1.2-2.1)
30.0-30.9	4188	1.6 (1.2-2.0)	0.4 (0.3-0.7)	1.2 (0.9-1.5)
31.0-31.9	4557	1.2 (0.9-1.6)	0.3 (0.2-0.5)	0.9 (0.7-1.2)
Birth weight, g				
<750	1193	4.8 (3.6-6.2)	1.0 (0.5-1.8)	3.8 (2.8-5.0)
750-999	3611	3.3 (2.7-3.9)	0.7 (0.5-1.1)	2.5 (2.0-3.1)
1000-1249	4722	2.1 (1.7-2.5)	0.4 (0.3-0.7)	1.6 (1.3-2.0)
1250-1499	4449	1.5 (1.1-1.9)	0.3 (0.2-0.6)	1.1 (0.8-1.5)
≥1500	4589	1.4 (1.1-1.8)	0.2 (0.1-0.4)	1.2 (0.9-1.6)

*Unilateral and bilateral.

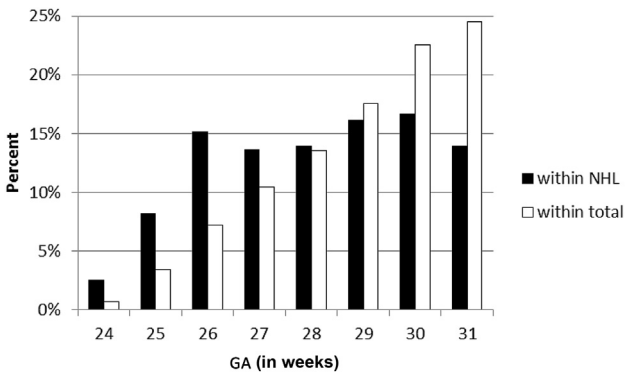

Figure 1. The distribution of GA within very preterm neonates with NHL loss (in *black*), and within the total group of very preterm neonates (in *white*).

sex effect is most pronounced at less than 30 weeks of gestation, with boys having a greater prevalence of NHL than girls (OR 1.42, 95% CI 1.11-1.82). The SGA effect is only present from 27 weeks onwards, with SGA neonates having a greater prevalence of NHL than AGA neonates (OR 2.15, 95% CI 1.62-2.86). Recursive partitioning resulted in 4 splits (complexity parameter = 0.006, relative error = 0.76, cross-validation error = 0.79 [SD = 0.03]): (1) split at <28 weeks of gestation; (2) split at SGA (within 28-31 weeks group); (3) split at <30 weeks of gestation (within AGA group); and (4) a split at boys (within <30 weeks' group) (**Figure 2**; available at www.jpeds.com). This analysis implies that high risks of NHL were found in neonates <28 weeks (prevalence of 3.9%), SGA neonates 28-31 weeks (prevalence of 3.4%), and AGA boys 28-29 weeks (prevalence of 2.4%). Most vulnerable to NHL were, therefore, girls <28 weeks, boys <30 weeks, and SGA neonates.

Discussion

With a large sample of very preterm neonates from the NHSP in Dutch NICUs, we were able to present the prevalence of NHL by week of gestation and categories of birth weight. The prevalence of NHL consistently increases with decreasing weeks of GA (1.2%-7.5% from 31 to 24 weeks) and decreasing birth weight (1.4%-4.8% from ≥1500 g to <750 g). These rates are much greater than the prevalence of NHL in the well baby clinics (0.1%).[8] Both GA and birth weight are independent risk indicators of NHL and negatively associated with NHL in a dose-response relationship. Both the recursive partitioning and the descriptive statistics showed that girls born <28 weeks of gestation, boys born <30 weeks of gestation, and SGA neonates are most vulnerable to NHL. The sex effect is most pronounced <30 weeks, and the SGA effect started at 27 weeks.

Table II. Prevalence of NHL stratified by SGA and sex in very preterm neonates (n = 18 564)

GA, wk	n	SGA, % NHL (95% CI)	AGA, % NHL (95% CI)	Boys, % NHL (95% CI)	Girls, % NHL (95% CI)
24.0-26.9	2100	5.0 (2.8-8.3)	4.9 (4.0-6.1)	5.5 (4.2-7.0)	4.4 (3.2-5.8)
27.0-27.9	1942	3.7 (1.8-6.7)	2.7 (2.0-3.6)	3.3 (2.4-4.6)	2.2 (1.3-3.4)
28.0-28.9	2521	4.2 (2.2-7.3)	2.0 (1.4-2.6)	2.7 (1.9-3.7)	1.6 (1.0-2.6)
29.0-29.9	3256	3.4 (1.7-6.1)	1.8 (1.4-2.4)	2.4 (1.7-3.2)	1.5 (1.0-2.3)
30.0-30.9	4188	3.7 (2.2-5.9)	1.3 (1.0-1.8)	1.5 (1.1-2.1)	1.7 (1.2-2.4)
31.0-31.9	4557	2.5 (1.3-4.3)	1.1 (0.8-1.5)	1.1 (0.8-1.7)	1.3 (0.9-1.9)

SGA is defined as a GA-specific z-score <−1.3 (ie, P10).

Our results are in agreement with a meta-analysis of the neurodevelopmental impairment (NDI) including hearing loss (HL) at ages 4-8 years of children born at 22-25 weeks' GA.[9] This meta-analysis demonstrates that there is a statistically significant increase in moderate–to-severe NDI between each decreasing week of gestation in extremely preterm infants. In addition, a review among preterm infants showed that all grades of NDI increase as GA and birth weight decrease.[10] Also, a greater risk of NHL is reported in neonates born with a very low birth weight compared with low or average birth weights.[4] Our study with hearing impairment figures evaluated within approximately 3 months of corrected GA gives further support that NDI in this group of very preterm neonates is most probably related to congenital or neonatal pathology than based on acquired pathology later in life.

Our study defined subgroups that are particularly vulnerable to NHL; girls born <28 weeks of gestation, boys born <30 weeks of gestation, and all very preterm neonates born SGA. An Australian study among toddlers born <29 weeks of gestation reported that boys have lower hospital survival rates, greater incidences of neonatal morbidities, and poorer long-term neurologic outcomes than girls.[11] This finding is in agreement with our sex differences. A large European study showed that the neonatal mortality rate in 24-27 weeks of gestation is approximately 4-fold greater compared with the 28- to 31-week group.[12] This supports our first split at <28 weeks of gestation. From these results, we assume that our definition of vulnerability may also hold to other disabling conditions. Further research is needed to confirm this.

A strength of our study is that we only included very preterm neonates (<32 weeks of gestation) in our study. Because almost all of these neonates are treated in a level-III NICU in The Netherlands, our study group can be considered as an unselected nationwide cohort of very preterm neonates. Another strength is the large sample size, which enables us to provide detailed information on the associations. Furthermore, the NHSP in Dutch NICUs is highly effective with a low loss to follow-up, due, among other reasons, to the electronic registration system that facilitates screening, tracking, and follow-up after abnormal screening results.[13] Coverage rates for this program are 98.7% at the first, 92.1% at the second stage, 92.3% for diagnostic examination, and 97.9% for the complete program.[13] Therefore, the prevalence rates are assumed to be unbiased.

Another strength of our study is the use of GA-specific reference charts to define SGA, which enables us to adjust the association between birth weight and NHL for GA. The prevalence of NHL consistently increased with decreasing

week of gestation (1.2%-7.5% from 31 to 24 weeks) and decreasing birth weight (1.4%-4.8% from ≥1500 g to <750 g), and in the sample from 2003 onwards these numbers were respectively 1.1%-7.3% and 1.5%-4.5%, respectively. A limitation is that the vulnerable group was identified by explorative analysis. Although our definition of vulnerability seems to generally agree with results from other studies, we recommend further validation in other neurologic domains.

Another limitation is that the associations do not provide insight into the underlying mechanisms of NHL. In other words, our study does not imply causal associations between NHL and GA and birth weight. It is already known that a low age of gestation and a low birth weight usually are associated with other risk factors and medical interventions that may cause NHL.[14] For example, a congenital infection[15] or a chromosome anomaly[16,17] may cause both SGA and NHL, which results in an association (that is not causal) between SGA and NHL. However, this does not change the fact that it is important to know the association between NHL and GA and birth weight, because GA and birth weight information are available, both at the individual and population level, and provide immediate insight into the risk of NHL.

For the investigated group the consistency (or stability) of the HL is unknown because the program has follow-up information embedded until the first diagnostic auditory brainstem response (~2-4 months after term age). In some cases, hearing levels improve to normal levels after diagnostic examination.[18] Still, health professionals, parents, and the newborns have to deal with the fact that at the identification of NHL, therapeutic intervention should be started based on international standards to provide the developing brain with adequate input to assure speech and language development. Also, in some cases HL may become more impaired during early life. Both mechanisms may influence the established population-based figures in this study. Moreover, changes in perinatal management on NDI may also have an impact on our figures.[19] We, therefore, recommend future studies to apply our methodology on data concerning HL and other disabling conditions in very preterm neonates to investigate trends.

GA and birth weight are highly negatively associated with NHL in a dose-response relationship. Although the associations are significant for both unilateral and bilateral NHL, the prevalence as well as the impact on health and development differs largely between them. Because our study provides the prevalence of NHL by week of gestation and categories of birth weight, tailored early parental information about their neonates' risk of NHL can be provided. Also, health professionals can better assess the risk of NHL. Because GA and birth weight are available at the population level, our study may contribute to a better insight into health and related costs associated with very preterm births. ■

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Appendix

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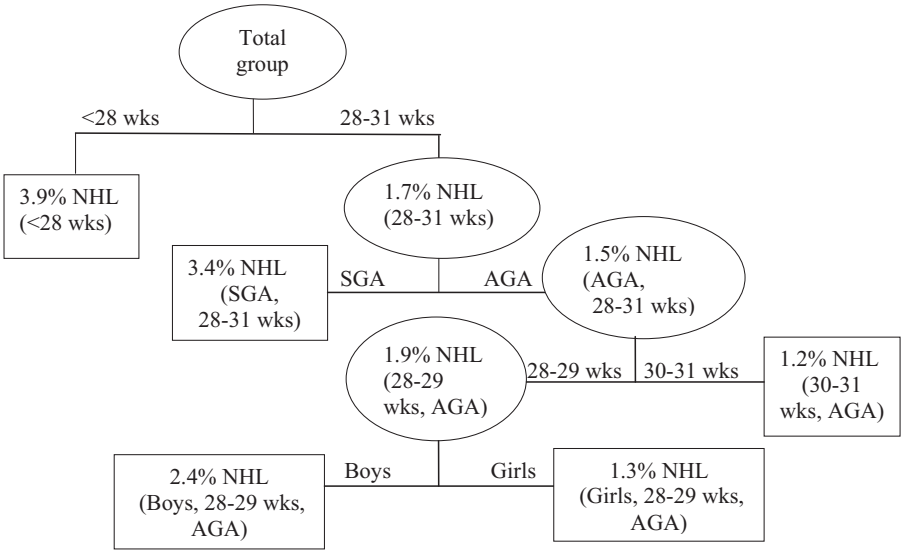

Figure 2. Subgroups with relatively high and low risks of NHL. Results of the recursive partitioning. Internal nodes are represented as circles and terminal nodes as rectangles.