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Incidence and prediction of periventricular-intraventricular hemorrhage in very preterm infants

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1 Introduction

Since the introduction of ultrasound scanning of the neonatal brain, many studies have reported incidences of periventricular-intraventricular hemorrhage (PIVH) in preterm infants. The incidences vary considerably depending on gestational age, size and selection of the study population; but, in infants born before 32 weeks or with birth weights below 1 500 grams they range between 28 and 60% [1, 6, 11, 12, 13, 19, 21].

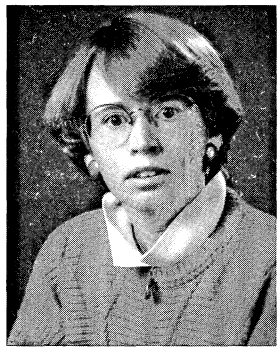
Since most studies are based on small numbers, we used the opportunity offered by a national survey of all infants born at less than 32 weeks and/or weighing less than 1500 g in the Netherlands in 1983 [26] to study the incidence of PIVH in a much larger population. The aim of our study, based on a population of 484 infants, in whom cerebral scans were available, was to establish the predictive value of perinatal factors that had, in much smaller patient populations [1, 6, 11, 12, 13, 19, 21], been associated with PIVH.

2 Patients and methods

During 1983, all infants born in the Netherlands with a gestational age of less than 32 completed weeks and/or a birth weight below 1500 g formed part of a prospective national survey (POPS-study), which had a compliance rate of 94% [26]. At that time, cranial ultrasound scanning was systematically and routinely performed in six of the eight neonatal intensive care units in the country. This offered us the opportunity to prospectively study 484 infants born before 32 completed weeks of gestation; i. e. all infants of that gestational age who were admitted to either one of the 6 units that had ultrasound scanning facilities. These 484 infants represented 48% of the 1 010 infants born at less than 32 weeks in the Netherlands, in 1983. The reliability of the gestational age classification in our entire population has been described elsewhere [26].

Ultrasound examination of the newborn brain was performed as soon as possible after admission to the neonatal intensive care unit. Further examinations were performed at least twice in the first week of life and weekly thereafter until discharge. Of all infants of less than 32 weeks admitted to the 6 units that had scanning facilities only 6 died

Curriculum vitae



MARGOT VAN DE BOR *was born in 1951 in Utrecht, the Netherlands. She received her M. D. from the Erasmus University Rotterdam in 1976. Pediatric residency and neonatal fellowship at the State University Leiden, from where she received a Ph. D. in 1986. Since 1981 on the staff of the neonatal intensive care unit, University Hospital Leiden. Her main research interest is neonatal neurology and she is involved in research into hemorrhage and ischemia in the preterm brain.*

before brain ultrasound had been performed and these were excluded from the present study population. An Advanced Technology Laboratories or Technicare mechanical sector scanner with 5 MHz transducers were used for scanning with the anterior fontanel as an acoustic window. The scans were performed in coronal and sagittal planes and, in each unit, interpreted by one neonatologist, experienced in brain ultrasound scanning. For classification of PIVH, Papile's grading system was used [17]; grade I: subependymal hemorrhage; grade II: intraventricular hemorrhage; grade III: intraventricular hemorrhage with ventricular dilatation; grade IV: intraventricular hemorrhage with parenchymal hemorrhage.

All maternal, intrapartum and neonatal factors to be studied and mentioned in the Results section were selected in advance on the basis of a literature review. Although increase in cerebral blood flow due to hypoxia, hypercapnia and acidosis [2] is considered to be an etiological factor in PIVH, we were unable to analyse this in our study, since monitoring of Po_2, Pco_2 and pH was not standardized in the various units.

Statistical analyses were based on logistic regression techniques. Forward and backward stepwise logistic regression analyses were used to determine predictive abilities of the predetermined perinatal factors (comparing log likelihoods). PIVH was the dependent variable, all perinatal factors being independent variables. Thereafter odds ratios (ORs) for all dichotomous independent variables were calculated, indicating the risk of developing PIVH when the various (independent) variables were present.

To correct for confounders and to exclude illogical temporal relationships, which may be mere consequences of an already considered exposure factor, the independent variables were placed in the following chronological order:

- sex of the infant,
- smoking habits of the mother,
- preeclampsia,
- tocolysis with betamimetics or indomethacin, prolonged rupture of membranes (PROM),
- fetal heart rate pattern abnormalities before labor,
- fetal heart rate pattern abnormalities during labor, gestational age, birth weight, mode of delivery,
- Apgar score after 5 minutes,
- IRDS.

Odds ratios with 95% confidence intervals were computed according to strategy no. 4 described by KLEINBAUM and KUPPER [14]; the independent variable under study being considered as an "exposure" factor and all other factors appearing in the same or in earlier time categories being listed as possible confounders or effect modifiers. Continuous variables, like gestational age and birth weight were only considered as confounders. Assessment of interaction was carried out in accordance with this strategy, using an α of 0.01. This level was chosen in order to guarantee: first, that the associations with exposure factors and confounders, which often are difficult to interpret, were strong enough; and second, to reduce an anticipated number of type I errors (declaring some interactions significant by chance) in view of the many tests of significant interaction that

Table I. Incidence and subdivision into grades of periventricular-intraventricular hemorrhage (PIVH) per gestational age group.

Gestational age (weeks)	Number of infants in study group	N (%) PIVH	%			
			gr I	gr II	gr III	gr IV
$\leq 23^{+6}$	5	1				
$24-25^{+6}$	22	10 (45)	30	30	10	30
$26-26^{+6}$	39	14 (36)	7	21	14	58
$27-27^{+6}$	61	18 (30)	17	33	22	28
$28-28^{+6}$	79	38 (48)	26	26	11	37
$29-29^{+6}$	85	27 (32)	26	22	30	22
$30-30^{+6}$	98	17 (18)	33	28	6	33
$31-31^{+6}$	95	14 (15)	43	36	14	7
Total	484	140 (28.9)				

needed to be conducted. In the results, confidence intervals are always given to indicate the power of the analyses.

3 Results

Four hundred and eighty four infants were enrolled in the study. Of those, 188 had been born at other hospitals. PIVH was detected in 140 of the 484 infants (28.9%). Occurrence and severity of PIVH decreased with increasing gestational age (table I). Fifty three babies died due to PIVH in the neonatal period (table II). The mortality rate increased with increasing severity of PIVH; but, in 24 of the 36 deaths with grade IV PIVH, treatment had been discontinued. Seven babies with grade III and IV hemorrhages developed rapid progression of lateral ventricular size. In 6, serial lumbar punctures were sufficient to restore the balance between production and resorption of cerebrospinal fluid and in 1 infant it was necessary to insert a ventriculo-peritoneal drain. Maternal and intrapartum factors studied in relation to PIVH are listed in table III and the incidence of these factors in both PIVH and non-PIVH infants are shown. The neonatal factors studied, are shown in table IV for both PIVH and non-PIVH infants.

Table II. Grading of periventricular-intraventricular hemorrhage (PIVH) and mortality in the study population.

Degree of PIVH	No. of cases	Mortality	
		N	%
Grade I	36	1	(3)
Grade II	39	3	(8)
Grade III	22	13	(59)
Grade IV	43	36	(84)
Total	140	53	(37)

Table III. Maternal and intrapartum factors studied in relation to periventricular-intraventricular hemorrhage (PIVH).

Factor	Incidence (%) in groups	
	non-PIVH N = 344	PIVH N = 140
Smoking	23.5	27.8
Preeclampsia	18.6	10.0
Tocolysis with betamimetics (> 24 hours)	52.3	53.6
Indomethacin treatment (> 24 hours)	6.1	6.4
Prolonged rupture of membranes (> 24 hours)	26.8	17.8
Fetal heart rate pattern abnormalities		
before delivery	12.2	7.1
during delivery	7.6	9.2
Mode of delivery		
vertex	46.5	47.1
breech	11.6	20.0
cesarean section	41.9	32.9

Table IV. Neonatal factors in relation to periventricular-intraventricular hemorrhage (PIVH).

Neonatal factor	Non PIVH infants (N = 344)	PIVH infants (N = 140)
Gestational age (weeks; mean ± SD)	29.3 ± 1.8	28.5 ± 1.7
Birth weight (g; mean ± SD)	1239 ± 350	1192 ± 276
Sex (% male)	49.0	57.1
Apgar score at 5 min < 7 (%)	20.8	23.1
Idiopathic respiratory distress syndrome	56.2	75.8

3.1 Predictive ability of factors studied

Stepwise forward and backward logistic regression analyses modelling the probability of a higher or lower risk of developing PIVH as a function of the predetermined maternal, intrapartum and neonatal factors, showed that gestational age is the most predictive of all factors. It was followed in order of importance by IRDS, prolonged rupture of membranes and birth weight; together these constituted a set of predictors for PIVH, that could not significantly be improved by adding either one of the other factors studied. The relative importance of these four factors was further quantitated by comparing the full model to each of the 4 models that arise by in turn deleting one of the factors from the full model. The differences in log

likelihood between the full model and each of the other models provides a measure for the importance of each of the factors in the full model for predicting PIVH. The associated log likelihoods, degrees of freedom and p values are shown in table V.

3.2 Odds ratios (ORs) of factors studied

Infants born after prolonged rupture of membranes had a significantly lower overall risk of developing PIVH (OR: 0.5; confidence interval: 0.3–0.8) after adjustment was made for all other factors (table VI). Infants of mothers with preeclampsia also had a significantly lower risk of developing PIVH (OR: 0.5; confidence interval: 0.3–0.9). On the other hand, infants who developed IRDS after birth, had a significantly higher risk of developing PIVH (OR: 2.2; confidence interval: 1.4–3.5). None of the other factors studied caused an overall increase or decrease in the probability of developing PIVH (table VI). Furthermore, there was no evidence that the other factors altered the impact of those factors that were found to significantly influence the risk of developing PIVH.

4 Discussion

There are no studies in which the incidence of and the risk factors for PIVH were examined in so large a population as that reported on here. We studied 48% of all infants of less than 32 weeks gestation born in the Netherlands in 1983. These infants were not different from the remaining 52% for gestational age, birth weight, 5 minutes Apgar score and sex, although they had a significantly higher incidence of IRDS (62.3% vs 52.3%, $p < .001$) for which they had to be transported more frequently to neonatal intensive care units (42.9% vs 23.5%, $p < .001$). The overall incidence of PIVH in our study was 28.9%, which is at the lower end of the range reported by others in smaller and probably more selected patient popu-

Table V. Prediction of periventricular-intraventricular hemorrhage: log likelihood (χ^2), degrees of freedom (df) and p value when comparing the full model to each of the 4 submodels.

		χ^2	df	p
Model without gestational age	compared with full model	22.3	3	0.0001
Model without IRDS	compared with full model	11.4	1	0.001
Model without PROM	compared with full model	6.0	1	0.025
Model without birth weight	compared with full model	9.1	3	0.05

Table VI. Odds ratios (OR), confidence intervals and p values of the perinatal factors.

Perinatal factor	OR	confidence interval	p
Sex	1.4	0.9–2.1	0.08
Smoking	1.2	0.8–1.9	0.36
Preeclampsia	0.5	0.3–0.9	0.027
Tocolysis			
Betamimetics	1.1	0.7–1.7	0.72
Indomethacin	0.9	0.4–2.1	0.81
Prolonged rupture of membranes	0.5	0.3–0.8	0.008
Fetal heart rate pattern abnormalities			
before delivery	0.6	0.4–1.1	0.13
during delivery	1.1	0.6–2.0	0.75
Cesarean section	1.7	0.7–2.0	0.62
Breech position	1.5	0.8–2.7	0.17
Apgar score < 7 at 5 min	1.0	0.6–1.6	0.88
Idiopathic respiratory distress syndrome	2.2	1.4–3.5	0.0013

lations [1, 6, 11, 12, 13, 19, 21]. Our obstetrical estimates of gestational age, as reported elsewhere [26], were found to be in agreement with pediatric maturity scores [3, 8] to such an extent that only 2% of the cases might possibly have been misclassified. We believe that our results provide reasonably accurate estimates of the associations between various risk factors and the incidence of PIVH in infants of less than 32 weeks gestation.

Gestational age appeared to be the most important factor determining the risk of developing PIVH. Both occurrence and severity of PIVH were gestational age dependent; after 29 weeks both showed a rapid decline. These findings are in agreement with anatomical studies of PAPE and WIGGLESWORTH [16], who demonstrated that the germinal matrix, which is the most frequent site at which PIVH originates, is most prominent in very preterm infants and dissipates gradually with increasing gestational age. Although birth weight was also found to be a predictive factor with regard to PIVH, its importance was much less pronounced than that of gestational age. This is in accordance with the overall study in the Netherlands which showed gestational age to be more important than birth weight also for determining survival in infants of less than 32 weeks gestation [26].

Of all other factors analyzed, there was only one that showed a positive correlation with an increased risk of developing PIVH, namely the presence of IRDS. We found the incidence of PIVH to be on average twice as high in infants with than in those without IRDS. Our odds ratio of 2.2, with a confidence interval of 1.4 to 3.5, further specifies and substantiates the known association between IRDS and PIVH [5, 10, 23, 24]. The mechanism of the association is believed to be related to hypoxia and hypercapnia, consequences of IRDS, which cause an increase in cerebral blood flow that may lead to rupture of the immature capillary bed in the germinal matrix, thus resulting in PIVH [18, 24].

Of several maternal and prenatal factors (tables III and VI) only two, preeclampsia and prolonged rupture of the membranes, were found to significantly influence the incidence of PIVH. Both appeared to reduce the incidence of PIVH to about half with a relative odds ratio of 0.5 and confidence intervals from 0.3 to 0.8 and 0.9. The mechanism(s) by which either of these conditions may lower the risk of PIVH are entirely unknown. Although one may speculate that prolonged rupture of the membranes exerts maturational effects that are not limited merely to pulmonary function but extend to other organ systems as well, further experimental evidence will be required to substantiate such hypotheses. Fetal distress has been variably associated with PIVH in the neonate. Some found a higher incidence of ominous fetal heart rate patterns in the history of infants with PIVH [20], whereas others failed to demonstrate such relationship [22]. In our study, abnormalities of the fetal heart rate either before or during labor bore no significant relationship to neonatal PIVH. Neither was a low Apgar score at 5 min related to the likelihood of developing PIVH.

In view of current interest in mode of delivery of very preterm infants, it is of interest to note that cesarean section afforded no protective effect against the subsequent development of PIVH. This is contrary to some [9, 15] but in agreement with other [4, 5, 7, 19, 20, 22] studies, all of which were based on much smaller infant populations. Even after correcting for all preceding factors, including gestational age, there was no evidence for a protective effect of cesarean section in our study population. Neither was there a significant association between fetal position at birth and the subsequent development of PIVH in the neonate (table VI). Other factors frequently associated with the occurrence of PIVH, such as pneumothorax and coagulopathy were not included in this study, since we reported previously [24, 25] that these factors usually were not antecedents of PIVH, though they occurred more often in infants who had already developed PIVH than in infants without PIVH. At present, it appears that gestational age is the single most important predictive factor for the development and the severity of PIVH in preterm infants. It is followed in importance by IRDS, prolonged rupture of membranes and birth weight. After adjustment for these factors is made, only preeclampsia shows a further relationship with the occurrence of PIVH. With regard to clinical practice, prevention or at least postponement of preterm delivery would seem to be the most effective way of preventing PIVH in preterm infants.

Summary

During a prospective national survey of mortality and morbidity in infants born before 32 weeks gestation in the Netherlands in 1983, the incidence of periventricular-intraventricular hemorrhage (PIVH) was studied with ultrasound, in 484 of those infants. Stepwise logistic regression analyses were used to examine the predictive value of several maternal, prenatal and postnatal factors for the development of neonatal PIVH.

PIVH was detected in 140 infants (28.9%); of these, 36 were grade I, 39 grade II, 22 grade III and 43 grade IV. The mortality rate increased from 3 to 84% with increasing severity of PIVH. Gestational age appeared to be the strongest predictive factor for both incidence and severity of PIVH, followed by idiopathic respiratory distress syndrome (IRDS), prolonged rupture of membranes and birth weight. Of the maternal and prenatal factors studied, only prolonged rupture of membranes (> 24 hours) and preeclampsia appeared to influence the risk of developing PIVH. Both were associated with a 50% reduction in the incidence of PIVH. None of the intrapartum factors studied showed a significant association with subsequent development of PIVH. Development of IRDS appeared to result in a twofold increase in the incidence of PIVH.

Keywords: Brain, hemorrhage, preterm, ultrasound.

Zusammenfassung

Inzidenz und Vorhersage peri- bzw. intraventrikulärer Blutungen bei sehr kleinen Frühgeborenen

In den Niederlanden wurde 1983 eine nationale, prospektive Studie zur Mortalität und Morbidität bei Frühgeborenen unterhalb der 32. Woche durchgeführt. Im Rahmen dieser Studie wurde bei 484 Kindern mit Ultraschall nach peri- bzw. intraventrikulären Blutungen (PIVH) gefahndet. Mit Hilfe von multiplen Regressionsanalysen wurde die Aussagekraft verschiedener Parameter wie maternale, pränatale und postnatale Faktoren, die die Entwicklung einer PIVH beeinflussen, untersucht.

Bei 140 Kindern (28.9%) wurden PIVH diagnostiziert; davon hatten 36 Kinder eine PIVH Grad I, 39 Grad II, 22 Grad III und 43 Grad IV. Die Mortalität betrug 3% bei leichten Blutungen und stieg auf 84% bei schweren Blutungen an. Das Gestationsalter scheint sowohl im Hinblick auf die Inzidenz wie auch das Ausmaß einer PIVH der wichtigste prädiktive Faktor zu sein, danach ein RDS, danach der länger zurückliegende vorzeitige Blasensprung und schließlich das Geburtsgewicht. Von den mütterlichen und pränatalen Parametern, die untersucht wurden, schienen lediglich der vorzeitige Blasensprung (> 24 Stunden) und die Präeklampsie das Auftreten einer PIVH zu beeinflussen. Hier war die Inzidenz von PIVH um 50% reduziert. Zwischen den untersuchten intrapartalen Faktoren und der Entwicklung einer PIVH gab es keine Assoziation. Bei Vorliegen eines RDS stieg jedoch die Inzidenz von PIVH auf das Doppelte an.

Schlüsselwörter: Blutung, Frühgeburt, Gehirn, Ultraschall.

Résumé

Incidence et prédiction des hémorragies péri- et intraventriculaires chez les grands prématurés

L'incidence des hémorragies péri- et intraventriculaires (P. I. V. H.) a été étudié par échographie chez 484 enfants au cours d'une étude prospective nationale sur la mortalité et la morbidité des enfants nés avant 32 semaines de gestation aux Pays Bas en 1983. On a utilisé des analyses de regression logistique par étapes pour étudier la valeur prédictive de plusieurs facteurs maternels prénataux et post-nataux sur le développement d'une P. I. V. H. néonatale.

On a mis en évidence une P. I. V. H. chez 140 enfants (28,9%); 36 étaient de grade I, 39 de grade II, 22 de grade III, et 43 de grade IV. Le taux de mortalité s'est élevé de 3 à 84% en fonction de l'augmentation de la sévérité des P. I. V. H. Il apparaît que l'age gestationnel est le facteur prédictif le plus puissant en ce qui concerne l'incidence et la sévérité des P. I. V. H. suivi par le syndrome de détresse respiratoire idiopathique (S. D. R. I.), la rupture prolongée des membranes et le poids de naissance. Parmi les facteurs maternels et les facteurs prénataux étudiés, seules la rupture prématurée des membranes (> 24 heures) et la préeclampsie apparaissent influencer le risque que se développe une P. I. V. H. Les deux facteurs s'accompagnent d'une diminution de 50% de l'incidence de P. I. V. H. Aucun des facteurs intrapartum étudiés ne montre une liaison significative avec la survenue d'une P. I. V. H. toutefois l'apparition d'un S. D. R. I. semble entraîner un doublement de l'incidence de P. I. V. H.

Mots-clés: Cerveau, hémorragie, prématurité, ultra-sons.

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