EPIDEMIOLOGY OF PERI/INTRAVENTRICULAR HAEMORRHAGE IN NEWBORNS AT TERM

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Periventricular/intraventricular hemorrhage (PIVH) has significant consequences, particularly leading to cases of adverse neurodevelopment. The aim of this study was to assess the epidemiology of peri/intraventricular haemorrhage in newborns born at term. Study was designed and performed according to epidemiological model of case-controlled studies. The study population was based on 2675 full-term neonates (the mean gestational age was 39.1 ± 1.2 weeks) admitted to Department of Neonatology of Medical University of Silesia in Katowice (Poland) between the years 2003-2005. Periventricular/intraventricular hemorrhage was diagnosed in 392 neonates (14.65%). In this group of neonates 281 (71.68%) were diagnosed as IVH I°, 108 (27.55%) as PIVH II°, 2 (0.5%) as PIVH III° and in 1 neonate (0.25%) as IVH IV°. Further research was carried out on 392 neonates who were diagnosed with PIVH (together I°-IV°) and 2283 healthy neonate. The study's inclusion criterion was term delivery (after 37th week of gestation). Mean gestational age of the group was 39.11 ±1.26 weeks and ranged from 37 to 43 weeks. The mean gestational age of neonates with PIVH was 38.91 +/- 1.26 week and -38.14 +/- 1.23 week for those neonates without this pathology. Also, the various potential risk factors of PIVH were analyzed such as: gender, newborn's condition in the 5 minutes after birth (assessed by Apgar score), type of delivery (vaginal, cesarean section, vacuum extractor), umbilical collision, intrauterine infection, hypertension, mother's inflammation of urinary tract and infection of upper airways. We postulate that the etiology of PIVH in term neonates is multifactoral. The findings suggest that male gender, lower birth weight and the mode of delivery are associated with the development of PIVH in term neonates.

Key words: peri/intraventricular hemorrhage, intracranial ultrasound, neonates at term, Apgar score, gestation
INTRODUCTION

Peri/intraventricular hemorrhage (PIVH) has significant consequences, particularly leading to cases of adverse neurodevelopment (1). PIVH is associated with increased short and long-term morbidity and mortality.

PIVH is a frequent complication in premature infants, despite the advances in neonatal intensive care. Compared to late onset PIVH, early onset of PIVH is associated with greater neonatal mortality rate and the increased risk of cerebral parenchymal injury with subsequent neurodevelopmental disability among the survivors. The early onset of PIIHV is associated with the following: a lower gestation and birth weight, steroids therapy, antenatal and postnatal complications as well as the mode of delivery (vaginal, cesarean, or instrument-assisted) (2). Several authors have suggested that instrument-assisted vaginal deliveries (vacuum or forceps) place neonates at an increased risk of PIHV (3).

Recent review studies have indicated that the rate of PIVH is approximately 25% to 30% for very low birth weight infants (4). Only a few studies have addressed PIVH newborns delivered at term (3, 5, 6).

The ability to diagnose potential neonatal brain damage was very difficult before the application of ultrasound. Computer tomography has not been the diagnostic method of choice for many physicians due to the adverse events inflicted on the neonate as a direct result of the excessive radiation emitted during the procedure. Cranial sonography is safe and it allows for the diagnosis of early brain pathological changes in neonates.

PIVH occurs mainly in premature neonates however this kind of hemorrhage is also observed in term neonates (7, 8).

MATERIAL AND METHODS

The study was designed and performed according to the epidemiological model of case-controlled studies. The study population was based on 2675 full-term neonates, with a mean gestational age of 39.1 ± 1.2 weeks, who were admitted to the Department of Neonatology at the Medical University of Silesia in Katowice (Poland) between the years 2003-2005.

Gestational age refers to the completed weeks of gestation and was determined obstetrically from the last menstrual period when it was well documented, and was confirmed or revised by an early prenatal ultrasound study. Neonatologists using a modified Dubowitz examination also determined gestational age.

Case groups were composed of 392 neonates with detected periventricular-intraventricular hemorrhage (PIVH) during cranial sonography. The control group consisted of 2283 neonates in whom this kind of pathology was not detected in ultrasound examination. The ultrasound examinations were performed using a Acuson Sequoia scanner with a 5 MHz convex transducer. The screening ultrasound examination was routinely performed at the 3rd day of age. All ultrasound findings were reviewed and finalized by a faculty pediatric radiologist.

Findings of PIVH were graded according to the criteria of Papile et al. (9). Grade 1 refers to a hemorrhage which is confined to the germinal layer. Grade 2 is an intraventricular haemorrhage,
grade 3 is an intraventricular haemorrhage with ventricular dilatation, and grade 4 includes associated parenchymal haemorrhage or extension.

The exclusion criteria were: congenital anomalies, intrauterine growth retardation, and in utero diagnoses of cerebral abnormalities or premature infants. The study's inclusion criterion was term delivery (after 37th week of gestation).

During examinations, the following was analyzed: the stage of hemorrhage, assessment of the general condition at birth according to Apgar score at the 5th minute, respiratory distress syndrome (RDS), intrauterine infection, the mode of delivery (vaginal, cesarean section) presence of high-risk pregnancy and labour.

The statistical analysis was performed using standard procedures available in Statistica 7.1 for Windows package. The statistical significance of differences between continuous variables were analyzed by t-Student or U Mann-Whitney test. The normality of distributions was tested using the Shapiro - Wilk test. Differences between categorical variables were examined using the chi-square test.

Logistic regression analysis was used to examine associations between PIVH and its potential risk factors. For each risk factor variable, the logistic odds ratio (logOR) and 95% confidence interval were calculated. The statistical inferences were based on the level of significance p<0.05.

RESULTS

From the years 2003 to 2005, 2675 term neonates were hospitalized at Department of Neonatology. The group comprised of 1362 (50.9%) boys and 1312 (49.1%) girls.

PIVH was diagnosed in 392 neonates (14.65%). In this group of neonates 281 (71.68%) were diagnosed as PIVH I°, 108 (27.55%) as PIVH II°, 2 (0.5%) as PIVH III° and in 1 neonate (0.25%) as PIVH IV°. Further research was carried out on the basis of 392 neonates with diagnosed PIVH (together I°-IV°) and 2283 healthy neonate. Mean gestational age of the group was 39.11 ±1.26 weeks and ranged from 37 to 43 weeks. The mean gestational age of neonates with PIVH was 38.91 +/- 1.26 week and in neonates without this pathology - 38.14 +/- 1.23 week (p=0.5). The mean birth weight of neonates with PIVH was 3283.47 ± 521.26 g, in neonates without PIVH it was 3362.79 ± 443.38g with these differences being statistically significant (p=0.003) (Table 1). The mothers' mean age was 28.5 ± 4.7 years, with no statistically significant differences observed (p=0.5) between mothers of infants with PIVH (28.38± 4.62) and those without PIVH (28.56±4.67).

The analyzed gender differences between the two groups were found to be statistically significant (p=0.01). The group of neonates with PIVH consisted of 56.4% boys while the group without PIVH was 50% male (Table 1).

In the examined group 72.2% of the neonates were in good condition (Apgar score 8-10 points), 25.9% in mean condition (Apgar score 6-7 points), and 1.8% in severe condition (Apgar score 1-5 points). These examinations took place 5 minutes after the birth. Analysis of differences in the state of newborn condition assessed by Apgar score between groups with PIVH and without this pathology revealed statistically significant differences (p=0.0001) (Table 2).
In order to study the potential risk factors of PIVH, the following were analyzed: gender, newborn's condition in the 5th minute after birth (assessed by Apgar score), the type of delivery (vaginal, cesarean section, vacuum extractor), umbilical collision, intrauterine infection, hypertension, mother's inflammation of urinary tract and infections of upper airways.

An analysis of the differences revealed that vaginal labor was observed in 42.0% of newborns with PIVH compared to 55.2% of newborns without PIVH and this was noted to be statistically significant (p=0.00009). Cesarean section was performed in 58.0% of cases with PIVH and in 44.8% of the cases within the control group (p=0.000001). In relation to the frequency of the remaining potential risk factors (umbilical collision, intrauterine infection, hypertension, mother's inflammation of urinary tract and infections of upper airways) no statistically significant differences were observed. 

Basic risk assessment revealed that male sex is a potential risk factor of PIVH in full-term neonates: OR = 1.29 (95% CI: 1.04 - 1.6). Taking this aspect into account and the above mentioned differences in the gender structure the further analysis of potential risk factors of PIVH was based on the results of logistic regression analysis. Results show significant impact for increased risk of developing PIVH in the newborn condition in the 5th minutes after birth, cesarean section and male gender.

Newborns with critically low (1-4 points) and fairly low (5-7) Apgar score are significantly more likely to develop PIVH, risk assessed by Odds Ratio is 2.55 (95% CI: 1.23-5.29) and 1.64 (95% CI: 1.29-2.09) respectively. Babies born by cesarean section have almost two times higher risk of developing PIVH than those born vaginally: OR 1.69 (95% CI: 1.33-2.15). The risk of PIVH was not

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**Table 1.** The demographic characteristics of examined groups

| Condition (Apgar Score) | Examined group N=2675 (100%) | PIVH present N=2283 (100%) | PIVH not present N=392 (100%) | p =*
|-------------------------|-----------------------------|---------------------------|-----------------------------|------
| 8-10 points             | 1932 (72.2%)                | 244 (62.2%)               | 1688 (73.9%)               | 0.0001
| 5-7 points              | 694 (25.9%)                 | 136 (34.7%)               | 558 (24.4%)                |     
| 1-4 points              | 49 (1.8%)                   | 12 (3.1%)                 | 37 (1.6%)                  |     

* results of Chi² test

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**Table 2.** The condition of neonates examined in the 5th minute after birth according to Apgar score.
affected by the type of cesarean section (urgent or elective), or the use of a vacuum extractor during vaginal delivery as well as umbilical collision. Analysis show that intrauterine infection increases (OR 1.52) the probability of developing PIVH, but the result is not statistically significant (95% CI: 0.95-2.54). It seems that male sex increases risk of PIVH by 1.24 times (95% CI: 1.00-1.55). The biggest relation was observed in case of hypertension: OR 1.42 (95% CI: 0.95-2.16) (Table 4).

In addition it was observed that neonates with PIVH suffer from respiratory distress syndrome RDS (9.9% vs. 2.3%; p=0.0001) and hyperbilirubinemia (14.8% vs. 9.1%; p=0.0005) more frequently than those without. It seems that the presence of PIVH increases the risk of RDS by 4.21 folds (95% CI: 2.71 - 6.53) and almost doubles the occurrence of hyperbilirubinemia: OR = 1.73 (95% PU: 1.27 - 2.37).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Occurrence of PIVH</th>
<th>Whole group log OR</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.24</td>
<td>1.00-1.55</td>
<td></td>
</tr>
<tr>
<td>Apgar score 5-7points*</td>
<td>1.64</td>
<td>1.29-2.09</td>
<td></td>
</tr>
<tr>
<td>Apgar score 1-4 points*</td>
<td>2.55</td>
<td>1.23-5.29</td>
<td></td>
</tr>
<tr>
<td>Elective cesarean section **</td>
<td>1.69</td>
<td>1.33-2.15</td>
<td></td>
</tr>
<tr>
<td>Urgent cesarean section***</td>
<td>0.79</td>
<td>0.55-1.15</td>
<td></td>
</tr>
<tr>
<td>Vacuum extractor</td>
<td>1.18</td>
<td>0.47-2.99</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.42</td>
<td>0.95-2.16</td>
<td></td>
</tr>
<tr>
<td>Mothers’ urinary tract infections</td>
<td>1.18</td>
<td>0.94-1.49</td>
<td></td>
</tr>
<tr>
<td>Mothers’infection of upper airways</td>
<td>1.00</td>
<td>0.73-1.38</td>
<td></td>
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<tr>
<td>Intrauterine infection</td>
<td>1.52</td>
<td>0.92-2.54</td>
<td></td>
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<tr>
<td>Umbilical collision</td>
<td>1.18</td>
<td>0.94-1.49</td>
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</tr>
</tbody>
</table>

With reference to: *good condition (Apgar 8-10); **vaginal labour; ***elective cesarean section.
Intracranial ultrasound is an easy and simple tool employed to assist physicians in making accurate diagnoses. In the field of neonatal medicine it is performed mainly in preterm newborns (10). Some researchers have suggested, that only infants with a gestational age of less than 30 weeks should be included in ultrasonographic screening (11). According to the research we have undertaken, intracranial ultrasonography should be performed on every newborn due to our findings of PIVH in 14.65 % of babies born at term. In the PIVH group of newborn 62.2 % babies were born in good condition (12.6 % of all babies born with Apgar score 8-10 points within analyzing period of 3 years). Our data demonstrates that asphyxied newborns twice the risk of PIVH in comparison to babies born in good condition.

An interesting finding was that hypertension or preeclampsia does not increase the frequency of PIVH, however it was diagnosed more frequently in mothers of asphyxied newborns and baby girls. This finding is similar to those presented by previous research (12, 13). According to Shankaran et al. (14) hypertension or preeclampsia was found to have protective qualities against neonatal grade IIIo and IV o PIVH. Perlman et al. (15) had reported that PIVH has a lower incidence even among premature infants born to mothers with pregnancy induced hypertension (PIH). The mechanism responsible for this reduction remains unclear but may be related to PIH itself or the consequences of medications used to treat mothers with the condition (e.g. magnesium sulfate).

In our study it was noted that cesarean sections doubled the risk of PIVH in babies born term (ratio, 1.69; 95 % CI: 1.33 - 2.15). Anderson et al. (16) proved that cesarean section before the active phase of labor does not change the overall occurrence of hemorrhages. The observation is similar to other investigators (17, 18). Shankaran et al. (14) do not share these opinions. They noted a relationship between the type of labor and delivery (vaginal delivery, cesarean section with labor or without labor) and grade IIIo and IVo PIVH. Thus studying the relationship between the type of delivery and occurrence of neonatal PIVH is still controversial.

Previous studies examining perinatal risk factors for PIVH have found associations with asphyxia (19, 20). In perinatal asphyxia, there is a hemodynamic disturbance and the adequate perfusion of brain vessels are compromised. Experimental animal models proved that PIVH is related to an aberration of cerebral blood flow and a hyperperfusion-reperfusion cycle (21).

The pathophysiology of PIVH in human preterm infants may also relate to hyperperfusion-reperfusion cycle, due to the fact that 80% of upper body blood flow travels to the brain, so that when the superior vena cava flow is very low, it is probable that cerebral blood flow is also low. Data on humans have pointed to early low cerebral flow being a risk factor for PIVH, and the germinal matrix is uniquely vulnerable to ischemic injury (22).

Autoregulation, which is related to a newborns’ developmental maturity, is responsible for endurance of cerebral vessels to disturbances of blood pressure.
Furthermore, asphyxia and the following reoxygenation of brain cells induces a production of proinflammtive cytokines, such as IL-6, IL-1 β, TNF-α which may damage the endothelium of germinal matrix vessels (24 - 26).

An increase of inflammatory proteins is accompanied by an accumulation of neutrophils within the damaged area, activation of microglia, macrophages, lymphocytes and astrocytes which may persist for days after the insult implicates a chronic state of inflammation. It is similar to production of pro-inflammatory cytokines during intrauterine infection. Those cytokines are able to mediate blood-brain barrier alterations, intravascular cells adhesion, coagulation and thrombosis, which can lead to endothelial damage of the fragile germinal matrix capillaries and PIVH (27).

Some pro-inflammatory cytokines are produced by cells within fetal circulation, presumably in response to amniotic/placental cytokines. Those cytokines might then gain access to the fetal brain and might cause damage to the white matter directly (28 -32).

In presented study both intrauterine inflammation and perinatal hypoxia increase the risk of intraventricular hemorrhage in term infants.

In our study, we observed that the birth weight in the group with PIVH was lower than in the group without PIVH (p=0,003) in spite of the fact that only term babies were examined. The same relation is shown by Patra et al. (4) in a group of preterm babies. Respiratory distress syndrome (RDS) is found to be another risk factor for PIVH and also highly associated with a premature birth (2, 7, 33). The relationship between PIVH and RDS was reported. Furthermore, infants who acquired PIVH had significantly worse indices of respiratory function estimated by oxygen requirement, oxygenation index or mean airway pressure (34). Our study suggests that RDS can be also risk factor for PIVH in full term neonates. Severe respiratory distress may be induced by antenatal and perinatal infection, possibly giving rise to proinflammatory cytokines produced before and during the birth process (35).

In summary we postulate that etiology of PIVH in term neonates is multifactoral. Male gender, lower birth weight and mode of delivery are associated with the development of PIVH in term neonates.

Conflict of interest statement: None declared.

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