Chapter 5

Small cerebellar hemorrhage in preterm infants: perinatal and postnatal factors and outcome

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Abstract

Purpose: To determine perinatal and postnatal factors that may affect the occurrence of small cerebellar hemorrhage (CBH) and to evaluate the effect of small CBH on neurodevelopmental outcome in very preterm infants.

Patients and Methods: This prospective study in an unselected cohort of very preterm infants was approved by the medical ethics committee and informed parental consent was obtained. Presence of small CBH (< 4mm) was assessed with magnetic resonance imaging around term equivalent age in 108 preterm infants (<32 weeks gestation). We compared infants with and without small CBH for perinatal and postnatal factors, supratentorial brain injury, and for neurodevelopmental outcome at 2 years corrected age. Follow-up consisted of a neurological examination, mental and developmental assessment (Bayley Scales of Infant Development), and behavior checklist. Univariate and multivariate logistic regression analyses were performed to examine the relationships between variables.

Results: Small CBH was diagnosed in 16/108 very preterm infants. Univariate analyses identified gestational age, high-frequency oscillation (HFO) ventilation and grade 3-4 intraventricular hemorrhage (IVH) as factors associated with small CBH. HFO ventilation and severe IVH were independent predictors of small CBH. We found no association between small CBH and neurodevelopmental outcome at 2 years of age.

Conclusion: Small CBH is a frequent finding in preterm infants. These hemorrhages are independently associated with HFO ventilation and severe supratentorial hemorrhage and seem to have a favorable short-term prognosis.

Introduction

Thanks to improvements in cranial ultrasound (CUS) techniques and the more widespread use of magnetic resonance imaging (MRI), cerebellar hemorrhage (CBH) is increasingly recognized as an important complication of preterm birth. The reported incidence ranges from 2.3-19% (1-6) depending on the studied population and the imaging techniques applied. In a previous study we diagnosed CBH in 11 (19%) of 59 infants examined with both CUS and MRI. Larger lesions were depicted by CUS using the mastoid fontanelle (MF) as an additional acoustic window, but small punctate CBH were only detected by MRI (4).

Previous studies have shown that large CBH affects the sickest and most immature infants. The etiology is multifactorial in accordance with the etiology of supratentorial germinal matrix/intraventricular hemorrhage (1,7,8). Large CBH may have a disastrous effect on cerebellar development, which is rapid and critical in the late fetal and preterm period (8,9). It is associated with higher neonatal mortality and significant risk for adverse neurodevelopmental outcome. This includes neuromotor disabilities and cognitive disorders (1,10-13).

The more frequent use of MRI in preterm infants has led to increased detection of small hemorrhagic cerebellar lesions that are usually not detected by CUS (4,6). Perinatal or postnatal factors that may be associated with small CBH are unknown and information on neurodevelopmental outcome is limited. Only one study assessed the outcome of infants with smaller CBH, diagnosed on MRI (6). Although outcome was more favorable than in infants with larger CBH, infants with small CBH were at increased risk of neurological abnormalities at preschool age. However, the number of cases in this study was small.

The objectives of the present study were to determine perinatal and postnatal factors that may affect the occurrence of small CBH and to evaluate the effect of small CBH on short-term neurodevelopmental outcome in an unselected, prospective cohort of very preterm infants. In addition, we wanted to assess the association between supratentorial brain injury and CBH.

Patients and methods

Patients

This study was part of a larger prospective neuroimaging study performed in very preterm infants (gestational age [GA] <32 weeks), admitted to the tertiary neonatal unit of the Leiden University Medical Center between May 2006 and November 2007 and comprised serial CUS throughout the neonatal period and MRI around term equivalent age (TEA) (14). Exclusion criteria were congenital anomalies of the central nervous system, severe other congenital anomalies, chromosomal disorders, metabolic disorders, and neonatal meningitis. The institutional review board approved this prospective study, and parental consent was obtained. Data on brain imaging findings, white matter injury (WMI), and cerebellar injury in this cohort have been published previously (4,14-16).

Cranial ultrasound

All serial CUS scans performed in this cohort were reviewed by at least two experienced investigators (G.v.W.M., S.J.S. and L.L.) for presence of intraventricular hemorrhage (IVH). IVH was classified according to Volpe (17) and divided into mild (grade I and II) and severe (grade III and/or periventricular hemorrhagic infarction (PVHI)). For details about the CUS procedure we refer to previous papers (4,14).

MRI

MRI of the brain was performed around TEA (preferably 40-44 weeks post-menstrual age) by using a 3.0 Tesla MR system (Achieva 3T; Philips Medical Systems, Best, The Netherlands). Details on the MRI procedure were described previously (18). All MRI examinations included T1-weighted three dimensional turbo field-echo sequence (repetition time ([TR] 9.7ms, echo time [TE] 4.6ms, field of view [FOV] 180mm, slice thickness 1mm, no gap), T2-weighted turbo spin-echo sequence (TR 6269ms, TE 120ms, FOV 180mm, slice thickness 2mm) and T2* fast field-echo sequence (TR 735ms, TE 16ms, FOV 230mm, slice thickness 4mm). All scans were reviewed by an experienced pediatric neuroradiologist (F.T.d.B.) and at least two other experienced investigators (G.v.W.M., S.J.S., and L.L.). The investigators reviewed the scans together, and any discrepancies in interpretation were solved by consensus. Scans were reviewed for presence of subacute/chronic hemorrhagic lesions in the cerebellar hemispheres and/or vermis, using a combination of T2- and/or T2*-weighted images. CBH was identified as a hypo-intense lesion on the T2- and/or T2*-weighted

images, or blooming artifacts on T2*-weighted images. We distinguished posterior fossa subarachnoid hemorrhage (hemorrhagic lesions outside and surrounding the cerebellum) and hemorrhage within the fourth ventricle from CBH. The size, number and location of CBH were noted. Small CBH was defined as hemorrhage within the confines of the cerebellum, with a diameter less than 4 mm on T2-weighted MRI or only depicted on T2* images (6). The white matter was classified as normal/ mildly abnormal, moderately abnormal or severely abnormal, adapted from Leijser et al (16).

Perinatal and postnatal factors

We reviewed the medical records and collected relevant demographic, maternal, intrapartum, and postnatal data, based on previous studies describing perinatal and postnatal factors associated with cerebellar injury in preterm infants (1,7,19) (Table 1).

Perinatal factors included GA, birth weight (BW), gender, use of antenatal steroids, mode of delivery and Apgar score at 5 minutes. Postnatal data included respiratory distress syndrome (RDS) defined as the need for mechanical ventilation and surfactant treatment, high-frequency oscillation (HFO) ventilation as a rescue treatment for severe respiratory failure, hypotension needing inotropic support, postnatal sepsis with positive blood culture, 5-day minimum platelet count, patent ductus arteriosus (PDA) requiring pharmacological or surgical treatment, necrotizing enterocolitis ≥ stage 2 (20) and moderate-severe bronchopulmonary dysplasia (BPD) at 36 weeks GA (21).We additionally recorded duration of mechanical ventilation and supplemental oxygen requirement, and use of postnatal steroids.

Outcome assessment

At a corrected age of 2 years, the infants were seen by an experienced neonatologist (M.R.) who was unaware of the imaging findings. To assess minor neurologic dysfunction (MND), each child underwent a standardized neurological examination according to Hempel, assessing five domains of function: fine motor function, gross motor function, posture and muscle tone, reflexes and visuomotor function (22,23). The children were grouped into three categories: (a) neurologically normal, (b) simple MND, denoting presence of dysfunction in one functional cluster, (c) complex MND, denoting presence of dysfunction in more than one cluster. To assess presence of cerebral palsy (CP) a Gross Motor Function Classification System (GMFCS) score was assigned (24). A GMFCS score of 2 or more was considered moderate to severe CP.

Mental and psychomotor development was assessed by a psychological assistant, unaware of the MRI findings, using the Dutch version of the Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III) (25). Because of the limited time a child can concentrate on different tasks during one session, we tested only the cognitive and fine and gross motor skills. Cognitive and motor composite scores were calculated for the corrected age of the child. A score between one and two standard deviation (SD) below the normative mean was defined as mild, and a score of two or more SD below the normative mean as severe developmental delay. Infants with severe CP, in whom testing gross and fine motor function with the BSID was not feasible and/or resulted in test scores that were too low to determine developmental indices, were also classified as severe developmental delay.

Parents were asked to complete the Dutch version of the Child Behavior Checklist (CBCL) (26). The questionnaire yields three summary indexes (internalizing, externalizing and total problems) with associated, age-standardized *T* scores. Higher scores indicate increasing behavioral problems. Scale scores were dichotomized: *T* scores in the borderline clinical range (≥84th percentile but <90th percentile) were defined as mild and in the abnormal clinical range (≥90th percentile) as severe behavioral problems (27).

Mildly abnormal neurodevelopmental outcome was defined as presence of simple MND, a GCMFS score of 1, mild developmental delay on the BSID and/or mild behavioral problems. Severely abnormal neurodevelopmental outcome was defined as moderate or severe CP, complex MND, severe developmental delay on the BSID and/or severe behavioral problems.

Data analysis

Statistical analysis was performed using SPSS software (version 17.0; SPSS inc., Chicago, Illinois, USA). Frequency counts and percentages were used to summarize categorical variables. Mean and SD were reported for continuous variables.

We compared perinatal and postnatal factors, and presence of supratentorial injury between infants with and without small CBH, using a chi-square or Fisher's exact test for categorical variables and a *t* test for continuous variables. We calculated odds ratios (OR) and 95% confidence intervals (95% CI) by univariate logistic regression to determine factors associated with small CBH and performed backward multivariate

logistic regression analysis to determine which factors detected by univariate analysis (p <.05) were independently related to small CBH.

Baseline characteristics of infants with and without follow-up were compared to assess if selective loss to follow-up occurred. Chi-square and Fisher's exact test were used to assess the relationship between small CBH and neurodevelopmental outcome. Subsequently backward logistic regression was performed adjusting for known risk factors for adverse outcome including GA, gender and supratentorial brain injury (severe IVH and WMI). A p value less than .05 was considered statistically significant.

Results

Patients and MRI findings

A cohort of 132 very preterm infants was enrolled in the neuroimaging study; 112 infants underwent MRI at TEA. Reasons for not obtaining MRI at TEA were described previously (14). Mean GA and BW were 28.9 (range, 25-31) weeks and 1204 (range, 520-1960) grams. Four infants had a large hemispheric CBH in combination with cerebellar atrophy. Sixteen had small, punctate, or streak-like CBH on MRI at TEA. All small CBH measured 1-3 mm. Eight infants had a single hemispheric hemorrhage, one a single vermian hemorrhage, three multiple hemorrhages in one hemisphere (two in combination with a hemorrhage in the vermis), and four had multiple hemorrhages in both hemispheres. In none of the infants cerebellar atrophy or destruction of the cerebellar parenchyma was seen (Figure 1).

We excluded infants without MRI and/or with large CBH from further analyses. Data of the remaining 108 infants were used for this study.

Perinatal and postnatal factors

Table 1 shows the association between perinatal or postnatal factors and the occurrence of small CBH. In univariate analysis small CBH was associated with GA and respiratory failure needing HFO ventilation as rescue strategy. In multivariate analysis, HFO ventilation remained an independent predictor of small CBH (OR, 4.6 [95%CI: 1.5-14.0]; p =.007).

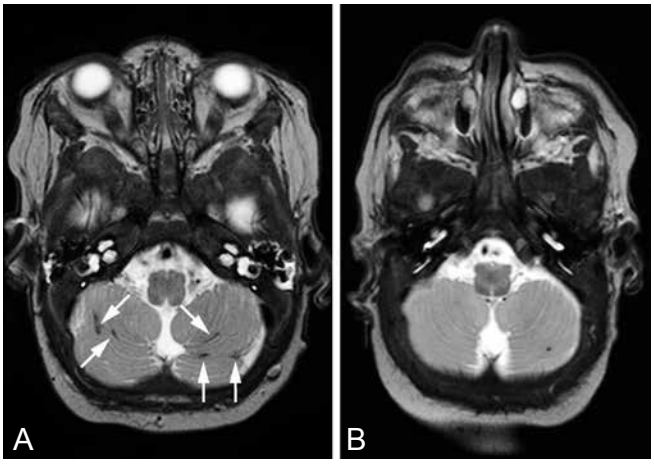

Figure 1. (A) T2-weighted MR image obtained at term age in a preterm male neonate born at 29 weeks GA. While CUS was normal, MRI showed multiple small streak-like hemorrhages in both cerebellar hemispheres (arrows). **(B)** T2-weighted MR image obtained at term age in a preterm female neonate born at 29 weeks GA. CUS was normal, MRI showed a single small hemorrhage in left cerebellar hemisphere.

Secondary analysis on respiratory morbidity showed that infants with small CBH required longer assisted ventilation (conventional and/or HFO) than infants without small CBH (11.5±10.1 days versus 5.6±7.1 days; p=.005) but did not require longer oxygen treatment. There was no relation between small CBH and moderate or severe BPD at 36 weeks GA or treatment with postnatal steroids for severe lung disease.

CBH and supratentorial brain injury

Table 2 shows the association between small CBH and supratentorial injury. Grade III IVH and/or PVHI was independently associated with small CBH (OR, 11.9 [95%CI: 2.3-61.7]; p =.003). There was no relation between small CBH and moderate or severe WMI.

CBH and neurodevelopmental outcome

Follow-up was available for 84 (78%) of 108 children. There was no difference in baseline clinical parameters or supratentorial brain injury between the groups with and without follow-up. Fourteen infants with small CBH (88%) were seen at 2 years of age. In one child the parents gave no permission for psychological testing and

Table 1. Perinatal and postnatal factors in infants with and without small cerebellar hemorrhage (CBH)

	CBH (*n*=16)	no CBH (*n*=92)	OR (95% CI)	*P* value
GA (weeks), mean±SD*	27.9±1.6	29.2±2.0	1.40 (1.05-1.87)	.02
BW (g), mean±SD**	1122±347	1239±368	2.50 (0.54-11.36)	.24
Male (%)	9 (56)	55 (60)	1.16 (0.40-3.38)	.79
Antenatal steroids (%)	11 (69)	70 (76)	0.69 (0.22-2.21)	.54
Vaginal delivery (%)	11 (69)	54 (59)	1.55 (0.50-4.82)	.45
Apgar (5 min), mean±SD	6.9±1.7	7.7±2.0	1.18 (0.93-1.50)	.17
Perinatal infection (%)	10 (63)	39 (42)	2.27 (0.76-6.76)	.14
RDS (%)	11 (69)	46 (50)	2.20 (0.71-6.83)	.16
HFO ventilation (%)	9 (56)	20 (22)	4.63 (1.53-13.98)	.01
Hypotension (%)	7 (44)	23 (25)	2.44 (0.78-6.97)	.14
5-day minimum platelet count 10^3/μL, (mean±SD)	130±70	166±80	0.99 (0.99-1.00)	.09
Postnatal sepsis (%)	4 (25)	38 (41)	0.47 (0.14-1.58)	0.22
NEC ≥ stage 2 (%)	1 (6)	2 (2)	3.00 (0.26-35.18)	0.39
PDA (%)	5 (31)	20 (22)	1.64 (0.51-5.26)	0.52

GA=gestational age, BW=birth weight, RDS=respiratory distress syndrome, HFO=high-frequency oscillation, NEC=necrotizing enterocolitis, PDA=patent ductus arteriosus.
* OR is for 1 week decrease in gestational age. ** OR is for 1.0 kg decrease in birth weight.

Table 2. Supratentorial brain injury in infants with and without small cerebellar hemorrhage (CBH)

Supratentorial brain injury	CBH (*n*=16)	no CBH (*n*=92)	OR (95% CI)	*P* value
IVH (%)	9 (56)	19 (21)	4.94 (1.63-14.98)	.005
Grade I-II IVH (%)	4 (25)	16 (17)	1.58 (0.45-5.55)	.49
Grade III and/or PVHI (%)	5 (31)	3 (3)	13.49 (2.83-64.33)	.002
Moderate WMI (%)	8 (50)	54 (59)	0.70 (0.24-2.04)	.52
Severe WMI (%)	5 (31)	13 (14)	2.76 (0.83-9.25)	.14

IVH=intraventricular hemorrhage, WMI=white matter injury, PVHI= periventricular hemorrhagic infarction.

did not complete the CBCL. Eight of these infants (57%) had a mildly or severely abnormal neurodevelopmental outcome (Table 3). Follow up was also available for 70 (76%) of 92 children without CBH. Two of them did not undergo standard neurologic examination but completed the BSID-III and CBCL. Parents of four infants gave no permission for psychological testing, and parents of eight infants did not complete the CBCL. Of the 70 infants without CBH, 34 (48%) had a mildly or severely abnormal neurodevelopmental outcome. Table 4 shows the outcome measures specified for each test and the overall outcome. There was no relation between small CBH and mildly or severely abnormal neurodevelopmental outcome at 2 years of age. In addition, we found no relation between any abnormal test result and the presence of small CBH.

Table 3. Brain imaging findings and outcome in infants with small cerebellar hemorrhage (CBH)

Subject	IVH	WMI	Location small CBH	Outcome
1	None	Moderate	Bilateral multiple	MA
2	None	Normal-mild	Left multiple, vermis	N
3	None	Moderate	Bilateral multiple	Not available
4	None	Normal-mild	Right single	N
5	Grade III, PVHI	Severe	Vermis	SA
6	Grade II	Severe	Left single, vermis	SA
7	None	Moderate	Right single	MA
8	Grade III, PVHI	Severe	Bilateral multiple	Not available
9	Grade I	Moderate	Left single	MA
10	None	Normal-mild	Left multiple	N
11	Grade I	Moderate	Left single	N
12	None	Moderate	Right single	N
13	Grade III, PVHI	Severe	Left single	N
14	Grade III, PVHI	Severe	Left single	SA
15	Grade I	Moderate	Bilateral multiple	SA
16	Grade III	Moderate	Left single	MA

IVH=intraventricular hemorrhage, and PVHI=periventricular hemorrhagic infarction, classified according to Volpe (17); WMI=white matter injury, classified according to Leijser (15).
Outcome: N=normal, MA=mildly abnormal, SA=severely abnormal.

Table 4. Outcome measures in infants with and without small cerebellar hemorrhage (CBH)

Outcome measure, *n* (%)	Small CBH	No CBH	OR (95% CI)	*P* value
Hempel				
Any MND	7 (50)	21 (31)	2.19 (0.68-7.04)	.22
Complex MND	2 (14)	5 (7)	2.08 (0.36-11.92)	.34
GMFCS score ≥ 2	1 (7)	5 (7)	0.97 (0.10-9.00)	1.00
BSID				
Mental delay	0 (0)	5 (8)	-	.58
Motor delay	2 (15)	5 (8)	1.93 (0.33-11.24)	.60
CBCL				
Internalizing problems (*)	2 (15)	5 (8)	2.07 (0.36-12.08)	.60
Externalizing problems (*)	3 (23)	14 (23)	1.03 (0.25-4.26)	1.00
Total problems (*)	2 (15)	7 (11)	1.43 (0.26-7.82)	.65
Neurodevelopmental outcome				
Normal	6 (43)	36 (51)	0.71 (0.22-2.25)	.56
Mildly abnormal	4 (29)	21 (30)	0.93 (0.26-3.31)	1.00
Severely abnormal	4 (29)	13 (19)	1.75 (0.48-6.48)	.47

MND=minor neurologic dysfunction, GMFCS=Gross Motor Function Classification System, BSID=Bayley Scales of Infant and Toddler Development 3rd edition.
CBCL=Child behavior checklist, (*) includes children with mild or severe behavioral problems.

Discussion

This is the first paper analyzing associations between perinatal or postnatal factors and the occurrence of small CBH. The influence of small CBH on neurodevelopmental outcome was so far only scarcely studied (6).

Several mechanisms have been described in the neuropathology of preterm CBH. Primary CBH in preterm infants originates from the germinal matrices that are present in the subependymal region around the fourth ventricle and the subpial external granule layer. These structures contain vulnerable capillaries that can easily rupture, especially with the pressure passive circulation of the sick preterm newborn (28). Large CBH affects the sickest, most preterm infants (1). Small CBH occur more frequently and are often seen on MRI examinations performed in very preterm neonates (4,6).

The etiology of small CBH may be different from large CBH. In previous studies, large CBH was associated with circulatory events related to prematurity such as fetal distress, need for emergency cesarean section, inotropic support, PDA and low pH (1,7,8). We did not find an association between the occurrence of small CBH and mode of delivery, Apgar score, hypotension or PDA. However, we found an independent association between small CBH and HFO ventilation. This may be explained by the fact that we used HFO as a rescue strategy for severe respiratory failure. Therefore, it is likely that these infants needed higher mean airway pressures. High mean airway pressures can lead to increased cerebral venous pressure which can have impact on brain perfusion and may thus, by this route, play a role in the genesis of small CBH (1,7,29). Furthermore, the infants with HFO ventilation probably had more severe cardiorespiratory problems, acidosis, and hypercarbia which may influence cerebrovascular autoregulation and cerebral circulation. The fact that the periods of mechanical ventilation were longer in infants with small CBH may also reflect the more severe respiratory failure in this group.

In our cohort, a considerable proportion of infants with small CBH (56%) had supratentorial hemorrhage. In a multivariate model, severe IVH was independently associated with small CBH. This may be explained by the fact that the etiology of CBH in preterm infants resembles that of IVH: both originate from germinal matrix layers and can therefore occur concomitantly (8,29). Large CBH can also occur secondary to extension of intraventricular or subarachnoid blood into the cerebellum (28,30). It is unknown whether this holds true for small CBH but may be another explanation for the association we found between IVH and small CBH.

Another important finding of our study was that small CBH was not related to unfavorable short-term neurodevelopmental outcome. Several groups have shown cerebellar injury in preterm infants to be associated with a significant risk of neuromotor disabilities and cognitive and behavioral problems (3,10,12,31). This may be related to parenchymal destruction and disruption of cerebellar growth and development caused by large CBH during a highly critical period of cerebellar development (8,9). However, these groups did not study infants with small CBH detected only on MRI. Up to now, only one study reported on the outcome of preterm infants with small CBH (6). They found small CBH in 10 (8%) of 131 very preterm infants. Eight infants were tested around 5 years of age. They had a greater risk of abnormal neurological examination, but no difference in cognitive outcome as compared to infants without

CBH. In the present study, we detected small CBH in 16 (15%) of 108 very preterm infants. Follow up was available for 14 infants with small CBH. We did not find any relation with neuromotor outcome, cognitive function, or behavioral problems at 2 years of age. An explanation for the different results on neurodevelopmental outcome between our study and the study of Tam et al may be the age of testing. We assessed the infants at a relatively young age. Subtle motor abnormalities may develop later and be more difficult to detect at toddler age.

Our study has other limitations. First, the small number of infants with CBH reduces statistical power. However, we feel that the present study including 16 infants with small CBH adds important information to the literature. Probably related to our scan protocol, using a 3.0 Tesla MR system (slice thickness 1-2mm, without gap) including hemosiderin-sensitive T2* sequences, we were able to detect the smallest CBH and found more single CBH than others (6). This also explains our higher incidence, comparable to the incidence found in a recent study, using an identical MRI protocol (32). The number of cases in our study was, however, still too small to assess the effect of particular locations or number of CBH on outcome. Second, we tested only the cognitive and fine and gross motor skills with the BSID-III. To avoid overburden of the infants during testing we omitted the language scale. Comparison with the mental developmental index of the BSID-II is therefore not possible. Furthermore, the cerebellum of infants who were born prior to 32 weeks of gestation may play an important role in the development of cognitive, learning and behavioral dysfunctions (8,10,12) which are difficult to test at 2 years of age and may manifest at later age. Finally, a substantial number of infants (22%) were lost to follow-up. However, the vast majority (88%) of infants with small CBH underwent follow-up and there were no differences in baseline clinical parameters and supratentorial brain injury between infants with or without follow up.

Conclusion

Innovations in neuroimaging techniques have led to an increased detection of small CBH in very preterm infants. These hemorrhages are independently associated with complicated respiratory disease needing HFO ventilation and severe supratentorial hemorrhage. In contrast to large CBH, small CBH seem to have a favorable short-term prognosis. Future studies should address the implications of these smaller lesions on long-term cerebellar growth and neurodevelopmental outcome. Current evidence warrants reassurance of parents about the outcome of preterm infants with isolated small CBH.

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