Ultrasonically detectable cerebellar haemorrhage in preterm infants

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ABSTRACT

Objective To determine the frequency and pattern of cerebellar haemorrhage (CBH) on routine cranial ultrasound (cUS) imaging in infants of ≤32 weeks gestation, and to investigate how extremely preterm infants with CBH differ from those with severe intraventricular haemorrhage (IVH).

Methods 672 infants of ≤32 weeks gestation were prospectively examined for CBH on serial cUS imaging. In a separate case–control analysis, the clinical features, ultrasound findings and outcome of preterm infants with CBH were compared to those of infants with isolated severe IVH (grade III–IV).

Results Nine cases of CBH were identified among 53 infants with severe IVH. The incidence of CBH in infants of ≤32 weeks gestation was 1.3%. Five infants had bilateral CBH involving both hemispheres, three had unilateral left sided CBH and one had a right hemispheric lesion. Infants with CBH were male, significantly more preterm (24.4 vs 27.0 weeks) and of lower birth weight (692 g vs 979 g). Vaginal births predominated in the CBH group (89% vs 50%). The median time to identification of haemorrhage for both groups was 3 days. Mortality in the CBH group was 100% (9/9) compared to 43% (19/44) in the severe IVH group.

Conclusions Extensive CBH in preterm infants is rare and devastating. It appears to be confined to very preterm, extremely low birthweight infants and may have a male predominance. The co-existence of severe IVH and extensive CBH on routine cot-side cUS in the early neonatal period is an ominous finding.

What is already known on this topic

- Extreme prematurity is a risk factor for cerebellar haemorrhage (CBH) with most cases occurring in infants of <28 weeks gestation.
- Use of the mastoid fontanelle has improved visualisation of the posterior fossa structures in neonatal cranial ultrasound (cUS).

What this study adds

- The co-existence of severe intraventricular haemorrhage (IVH) and extensive CBH detectable on early cUS is uncommon and associated with a grave prognosis.
- Compared to infants with severe IVH, preterm infants with life threatening CBH are more likely to have been delivered vaginally, have lower birth weights, are more premature and may be predominantly male.

INTRODUCTION

Cerebellar haemorrhage (CBH) is an important but poorly understood complication of preterm birth. The first reports, based on autopsy findings, were published in the 1970s. Martin *et al*[1] described six infants with destruction of at least one third of their cerebellar tissue on postmortem examination. Grunnet *et al*[2] reported 12 cases of CBH among 144 brains of preterm infants at autopsy. In these infants blood was noted in the cerebellar germinal plate in the roof of the fourth ventricle. This germinal plate was evident on postmortem up to 28–30 weeks gestation. Extreme prematurity was documented as an associated risk factor for CBH with 75% of cases occurring in infants under 28 weeks gestation and none in infants over 32 weeks.

With the advent of cranial ultrasound (cUS), Perlman *et al*[3] published what they described as the first demonstration of ultrasound for the diagnosis of CBH. Reeder *et al*[4] reported a single case of CBH. It became apparent that the anterior fontanelle did not provide sufficiently clear images of the posterior fossa, which were obstructed by the highly echogenic nature of the tentorium and the cerebellar vermis. The mastoid fontanelle, an additional acoustic window, was introduced which enabled axial and coronal views of the posterior fossa. It is the view of choice for visualising the cerebellum on cUS.

Merrill *et al*[5] used the mastoid fontanelle to examine 525 infants including 250 infants with a birth weight of <1500 g. Over a 2-year period they identified 13 cases of CBH on cUS compared with only two cases of CBH in the preceding 3 years before the mastoid fontanelle was incorporated into routine imaging. They described a "new pattern of CBH" which was clinically silent and not associated with a significant amount of supratentorial bleeding. Limperopoulos *et al*[6] reviewed 35 preterm infants with CBH on cUS. The overall reported incidence of CBH in their series was 2.8% of infants of <1500 g. Overall, 23% had isolated CBH with no associated intraventricular haemorrhage (IVH). Morbidity and mortality were significantly higher in infants with CBH compared to preterm controls.

Much of the subsequent research on CBH has employed MRI. These studies differ in that they tend to be undertaken later beyond the critical early neonatal period. Thus they may refer to a different population of infants. Messerschmidt *et al*[7] examined MR images carried out between 2 months

and 6 years of life on a series of 28 ex-preterm infants weighing <1500 g. They described three morphological MRI patterns of "cerebellar growth disruption" as a consequence of extreme prematurity. In a comparative study of ultrasound and MRI, Steggerda *et al*[8] reported cerebellar injury in 19% of infants of <32 weeks gestation. Seven infants were diagnosed with CBH on serial cUS in the neonatal period. On term equivalent MRI, a further six cases were identified with punctate cerebellar lesions which had not been visible on ultrasound.

The number of case series of CBH in acutely ill very preterm infants is relatively small. The aim of this ultrasound study was to determine the frequency and pattern of CBH in the current era with increased survival of extremely preterm infants. We also attempted to determine how preterm infants with CBH may differ clinically from those with severe IVH only.

METHODS

Patients

From January 2005 to December 2008 we prospectively examined all very preterm infants admitted to the neonatal intensive care unit (NICU) at the National Maternity Hospital (NMH), Dublin for CBH and IVH. All infants of ≤32 weeks gestation underwent serial cot-side cUS imaging as part of their routine neonatal care. Each scan was undertaken by the same experienced consultant radiologist (VD). To visualise both the supra- and infratentorial structures, all imaging incorporated views through the anterior and mastoid fontanelles. Clinical data and sonographic findings were recorded. Patient characteristics are shown in table 1.

Using a case–control design, we compared all preterm infants with a sonographic diagnosis of CBH to a control group of infants of ≤32 weeks gestation who had severe IVH (grade III or IV) but who did not have CBH. The two groups were compared in terms of clinical features, ultrasound findings and outcome. Univariate analysis was performed to identify significant differences between the two groups using the Pearson χ^2 test. Statistical significance was defined as $p \leq 0.05$.

Table 1 Patient characteristics of infants with CBH and severe isolated (grade III–IV) IVH

Infants (n=672)	CBH (n=9)	Grade III–IV IVH (n=44)	p Value
Sex			
Male	9 (100%)	22 (50%)	<0.01
Female	0 (0%)	22 (50%)	
Multiple pregnancy	4 (44%)	16 (36%)	
Twins	4	14	
Triplets	0	1	
Quads	0	1	
Gestational age (weeks)	24.4 (23+6 to 25+1)*	27.0 (23+5 to 32+0)*	<0.01
Birth weight (g)	692.7 (520–860)*	979.9 (510–2060)*	<0.01
Complete ANS	2 (22%)	19 (43%)	>0.2
Mode of delivery			
Vaginal	8 (89%)	22 (50%)	<0.05
Caesarean	1 (11%)	22 (50%)	
Place of delivery			
In-born	4 (44%)	33 (75%)	
Out-born	5 (54%)	11 (25%)	
Apgar score at 5 min	7 (5–7)*	7 (0–9)*	>0.2

*Data are shown as mean and range or as number of cases (%).
ANS, antenatal steroids; CBH, cerebellar haemorrhage; IVH, intraventricular haemorrhage.

cUS imaging

In the NMH all infants of ≤32 weeks gestation routinely undergo at least two cUS in the first week of life. The first scan takes place, where possible, within the first 24 h and the second at 48–72 h. Further scans are often carried out at 1 week and at 1 month of age, or more frequently if clinically indicated. The mastoid fontanelle view has been included in routine cUS scanning in the NMH since 2004. The standard cUS examination includes sagittal and coronal views of the brain through the anterior fontanelle using a 7.5 MHz transducer and coronal and axial views of the posterior fossa through the mastoid fontanelle, see figure 1.

Examination of the cerebellum consisted of visualisation of the vermis and both cerebellar hemispheres. We defined CBH as an echo dense lesion in the cerebellar hemisphere(s) or vermis. The extent and distribution of the CBH, where present, was documented. The presence of IVH, periventricular leukomalacia (PVL) or posthaemorrhagic ventricular dilatation (PHVD) was also noted. The severity of the IVH was graded from I to IV according to established criteria.[9] PVL was defined as echogenicity in the white matter adjacent to the lateral ventricles evolving into echolucent cysts and was graded according to the sonographic classification of de Vries.[10]

RESULTS

Incidence of CBH and IVH in infants of ≤32 weeks gestation

During the 4-year study period, 778 infants of ≤32 weeks gestation were admitted to the NICU in the NMH. A total of 106 infants died or were transferred out of the NICU to specialist cardiac and surgical centres before a cUS was carried out. Among the 672 infants who underwent routine cot-side imaging in the early neonatal period, we encountered nine cases of CBH. There were 53 infants with severe (grade III–IV) IVH, 44 of whom had isolated extensive IVH with no CBH. In our centre the overall incidence of sonographic CBH was 1.3% and the incidence of severe IVH was 7.9% of those infants of ≤32 weeks gestation who underwent routine imaging.

Patterns of CBH on cUS

Table 2 demonstrates the timing of the cUS scans and the ultrasound findings for all infants diagnosed with CBH. Each infant had two cot-side cUS scans within the first 72 h of life. All nine infants had associated severe supratentorial haemorrhage. We did not identify any cases with isolated CBH on cUS. Five infants were found to have bilateral CBH involving both hemispheres. Three had unilateral left sided CBH, in two of which extended from the left hemisphere into the vermis. A right hemispheric haemorrhage was identified in one infant. Three infants had increased echogenicity in the periventricular white matter on cUS on day 2 of life. These infants died before further imaging could be undertaken. Three of the four infants who survived beyond the first week of life developed PHVD.

It is difficult to comment on the exact timing of the CBH and IVH in each case. On serial cUS imaging in the first week of life, the majority of the CBH infants (6/7) scanned had a normal cUS on day 1. One infant had a small subependymal haemorrhage. The subsequent scan on day 2 or day 3 of life showed severe IVH in all nine infants. In six of the nine infants with CBH, the cerebellar lesion was noted at the same time as the supratentorial haemorrhage, in two infants it was noted on a second scan within 24 h and in one case there was

Table 2 Timing of cranial ultrasound and sonographic findings of infants with CBH

Infant	Day 1 cUS	Day 2 cUS	Day 3 cUS	Day 7 cUS (or nearest day)
1	Normal		Bilateral grade III IVH, echogenic lesion in right cerebellar hemisphere	(Day 8) Bilateral grade III IVH, CBH of right cerebellum
2	Normal	Bilateral grade IV IVH, increased echogenicity throughout periventricular white matter bilaterally, haemorrhage of left cerebellar hemisphere and vermis, blood in the fourth ventricle		
3	Normal	Bilateral grade IV IVH, a few areas of increased echogenicity in periventricular white matter on right, bilateral extensive CBH in both hemispheres and vermis, marked haemorrhage and dilatation of third and fourth ventricles		
4		Bilateral grade III IVH	Bilateral grade III IVH, CBH of left hemisphere extending to vermis	(Day 5) Increased size of lateral ventricles, left CBH, significant enlargement of fourth ventricle – PHVD
5	Small SEH	Bilateral grade III IVH	IVH grade III left and IV right, mild ventricular dilatation	(Day 5) Findings as for day 3. (Day 11) IVH grade III left, IV right and PHVD, extensive CBH of both hemispheres and vermis
6	Normal	IVH grade III left, II right, bilateral echogenicity of both cerebellar hemispheres in keeping with haemorrhage	Bilateral grade III IVH, bilateral CBH, increased echogenicity in region of the thalami	(Day 10) Bilateral grade III and PHVD, some reduction in echogenicity of thalami, bilateral CBH
7		Bilateral grade IV IVH	Bilateral grade IV IVH, bilateral extensive echogenicity of both cerebellar hemispheres consistent with haemorrhage	
8	Normal	Bilateral grade III IVH, bilateral increased echogenicity in deep periventricular white matter, large area of haemorrhage in left cerebellar hemisphere		
9	Normal	Bilateral grade IV IVH, extensive echogenic lesion in fourth ventricle, vermis and both cerebellar hemispheres		

CBH, cerebellar haemorrhage; cUS, cranial ultrasound; IVH, intraventricular haemorrhage; PHVD, posthaemorrhagic ventricular dilatation; SEH, subependymal haemorrhage.

Table 3 Cranial ultrasound findings and outcomes of infants with CBH and severe (grade III–IV) IVH

	CBH (n=9)	Grade III–IV IVH (n=44)	p Value
Timing of haemorrhage seen on cUS (days)	3.5 (2–11)*	3.8 (1–9)*	
Severity of IVH			
Grade III	5 (55%)	20 (45%)	
Grade IV	4 (45%)	24 (55%)	>0.2
Posthaemorrhagic dilatation	3 (33%)	21 (48%)	
Cystic PVL on serial cUS	0 (0%)†	12 (27%)	
Outcome			
Discharge	0 (%)	25 (57%)	<0.01
Death	9 (100%)	19 (43%)	<0.01
Withdrawal of care	4/9	12/19	
Age at death (days)	16 (3–54)*	10.9 (2–43)*	

*Data shown as mean and range or as number of cases (%).
†3 of the 9 infants with CBH had periventricular white matter opacification but died before follow-up scans could be carried out.
CBH, cerebellar haemorrhage; cUS, cranial ultrasound; IVH, intraventricular haemorrhage; PVL, periventricular leukomalacia.

an interval of 9 days between the diagnoses of IVH and CBH. The median time to identification of haemorrhage on ultrasound was 3 days in both the CBH and isolated IVH groups. Examples of CBH are shown in figures 2 and 3.

Clinical characteristics of patients and controls

Table 1 shows the patient characteristics of the nine infants with CBH and the 44 infants with isolated severe IVH. There are a number of differences between the two groups. All nine infants with CBH were male, while there was an equal sex distribution in the severe IVH group (22/44). Infants with CBH were significantly more preterm (24.4 weeks, range 23+6 to 25+1) compared to infants with isolated severe IVH (27 weeks, range 23+5 to 32) and were of much lower birth weight (692.7 g, range 520–860 g vs 979.9 g, range 510–2060 g). Vaginal births occurred more frequently in the CBH group (eight infants, 89%), while there were equal numbers of caesarean and vaginal births in the control group. Factors such as multiple pregnancies, out-born births, Apgar scores and completed courses of antenatal steroids were statistically comparable between the two groups.

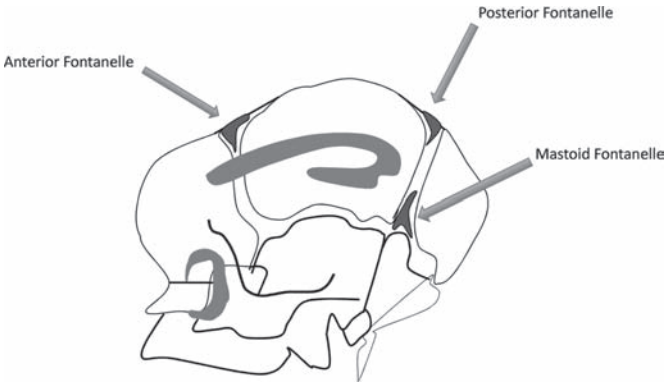

Figure 1 Line drawing of the neonatal skull (lateral view) with arrows demonstrating the anterior, posterior and mastoid fontanelles.

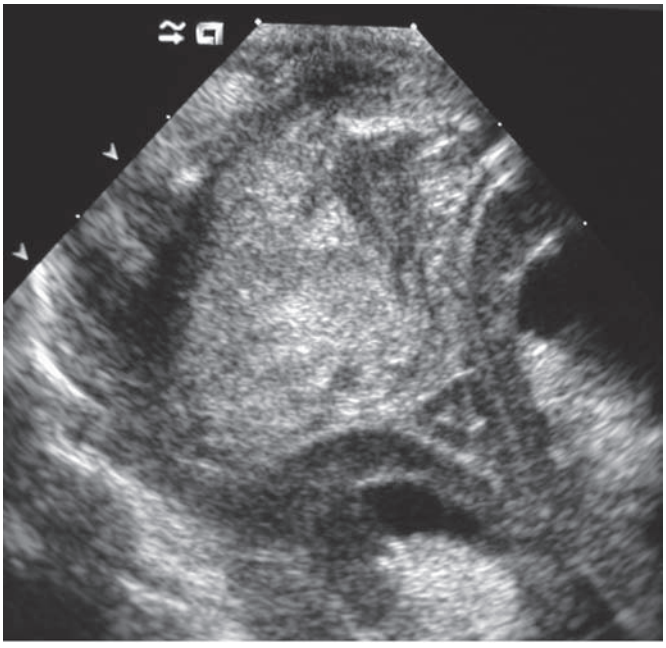

Figure 2 Cranial ultrasound image through the mastoid fontanelle demonstrating a large left sided cerebellar haemorrhage involving the vermis on day 3 of life.

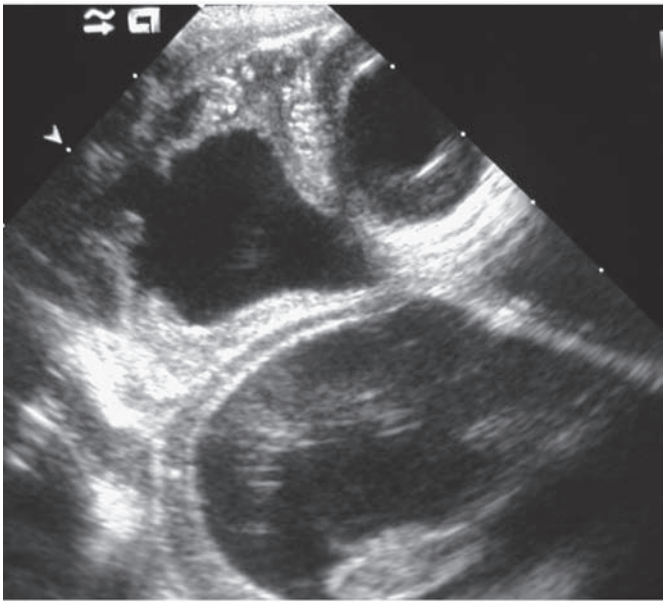

Figure 3 Axial cUS view of the posterior fossa depicting a cerebellar haemorrhage in the left cerebellar hemisphere extending to the midline. There is significant posthaemorrhagic ventricular dilatation with the enlarged fourth ventricle compressing the surrounding cerebellar tissue.

Outcome

The outcome of all infants with CBH and severe IVH is outlined in table 3. All of the infants in the CBH group died. Each one was extremely preterm and critically unwell. To varying extent, their neonatal course was complicated by respiratory distress syndrome, hypotension, metabolic acidosis, electrolyte imbalance, anaemia, thrombocytopenia and sepsis. Seven infants with CBH had clinical seizures and were treated with anticonvulsants. Following discussion with their parents, four infants died after intensive care was withdrawn. These infants were very unstable, with grossly abnormal findings on cUS and multi-organ failure and were deteriorating despite the escalation of intensive care. The remaining five infants died while receiving maximal treatment.

There were two late neonatal deaths. One infant died at 28 days from *Escherichia coli* sepsis and suspected necrotising enterocolitis. The other died on day 54 of life following an acute cardiorespiratory deterioration. This was the only infant in our CBH cohort who had an autopsy which revealed severe bronchopulmonary dysplasia. Postmortem examination of the brain demonstrated PVL and cerebral ischaemia with cystic haemorrhagic necrosis of the right cerebellar hemisphere. These findings were consistent with the infant's antemortem cUS reports. The mortality in the IVH group was significantly less with 25 (57%) infants surviving to discharge. The mean age of death of infants with CBH was 16 days compared to 10.9 days in infants with isolated severe IVH.

DISCUSSION

In our experience, ultrasonically diagnosed CBH was an uncommon but devastating complication of extreme prematurity. When CBH was detectable on cUS, it was associated with a very grave prognosis as all the infants whom we encountered with CBH subsequently died. The high mortality that we observed is likely to be related to the extensive nature of the CBH and associated severe IVH. In our series, the majority of infants had haemorrhage which involved both hemispheres or, if unilateral, which extended to involve the vermis. In the ultrasound study of Limperopoulos *et al*,[6] there was a predominance of unilateral lesions with the right hemisphere (in 60% of cases) being more commonly involved than the left (in 40% of cases). Less than 10% of cases in their series displayed bilateral haemorrhages and their overall mortality was 14%.

All of our infants had concomitant extensive IVH. Although we routinely examined all very preterm infants, we did not identify any 'clinically silent' CBH on cUS despite the fact that this phenomenon has been well documented.[1 2 5 6] Another feature of this series was the male preponderance observed in the CBH group. We are uncertain whether our observation regarding male gender and extensive CBH is unique to our series or whether it is encountered more widely.

The aetiology of CBH is unknown but, like IVH, may be associated with circulatory disturbance in the preterm brain. The cerebellum's blood supply is provided by branches of the vertebral basilar system. The cerebellar cortex consists of molecular, Purkinje and granular layers.[11] The inner granular layer, which lies adjacent to the white matter, appears to be the source of cerebellar hemisphere bleeds. This granular cell layer is thickest at 24 weeks gestation and starts to involute by 30 weeks.[12] The vasculature to this subpial germinal matrix may be vulnerable to perfusion–reperfusion injury similar to that postulated for IVH. The other consideration is whether trauma could play a role. In our study we did observe a high rate of vaginal delivery compared with IVH-only infants. Studies have previously raised the potential for severe distortion and disruption of the venous structures within the compliant preterm neonatal skull.[5 9 13 14]

The types and patterns of cerebellar lesions detected by ultrasound and MRI appear to differ. There are two variables to consider. Ultrasound, due to its cot-side accessibility, can be performed at an early stage when the preterm infant is acutely

ill. The other advantage of ultrasound is that it is particularly sensitive to haemorrhage. MRI tends to be undertaken later due to the logistics of transporting an unstable infant to the scanner. In our study none of the infants with CBH and almost half of the infants with severe IVH survived long enough for an MRI to be undertaken. Our incidence, therefore, only refers to ultrasonically detectable CBH and does not include the potential additional infants with smaller haemorrhages only detectable on MRI.

It is perhaps not surprising that infants with co-existing CBH and extensive supratentorial injury are at significant risk of severe neurodevelopmental disability if they survive beyond the neonatal period. However, in the absence of IVH or PVL, several follow-up studies have described varying degrees of motor, cognitive and behavioural impairment in preterm infants with isolated CBH.[5 15] Using a different approach, Johnsen *et al*[16] performed MRI on 67 children with cerebral palsy who were born prematurely at <28 weeks gestation. Thirty of the cases were found to have cerebellar injuries. This subgroup with cerebellar pathology had a more adverse clinical picture.

There is diversity in the cerebellar injuries sustained by extremely preterm infants. Our series consisted of extensive, early onset, ultrasonically detectable haemorrhage with concomitant IVH. All the infants were sick, unstable and subsequently died. This is the pattern described in previous autopsy and ultrasound studies. Many of the MRI studies, on the other hand, show predominantly 'silent' cerebellar lesions with infarction and atrophy predominating. It is unclear whether these two contrasting patterns represent a different pathogenesis or whether they are related to the later carrying out and higher resolution of the MRI.

CONCLUSION

At the current state of knowledge it is difficult to suggest any measure that could be instituted to prevent early onset severe CBH in these vulnerable infants. In our experience it appears to be a rare and devastating event that is confined to very preterm, extremely low birthweight infants and may have a male preponderance. At a practical level, the co-existence of severe IVH and extensive CBH when detected on routine cot-side cUS is an ominous finding.

Competing interests None.

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