Factors associated with periventricular haemorrhage in very low birthweight infants

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SUMMARY Periventricular haemorrhage was diagnosed *in vivo* in 20 of 39 consecutively admitted infants of birthweight below 1500 g using an ultrasound scanner. Ten (51 %) infants with haemorrhages survived. Mortality was related to the extent of the bleeding. Statistically significant associations with respiratory distress, ventilator therapy, metabolic acidosis, and hypercapnia were observed, lending support to their role in the pathogenesis of periventricular haemorrhage.

Periventricular haemorrhage (PVH) is a common cause of death in infants of very low birthweights. Clinical diagnosis is often difficult, and most studies concerning pathogenesis of PVH have been of cases diagnosed at necropsy. The introduction of computerised tomography (CT) scans has allowed *in vivo* diagnosis of PVH to be made, and has shown a much higher incidence than had been expected.^{1 2} Two-dimensional ultrasound scanning has also been used successfully to visualise PVH *in vivo*.^{3 4} Portability of the equipment and lack of ionising radiation, make this method ideal for studying newborn infants in an intensive care unit.

Previous studies of factors associated with PVH in low birthweight infants have used clinical diagnosis or examination at necropsy to define a 'haemorrhage group' which was then compared with a remaining 'non-haemorrhage' group.^{16 17} As the non-haemorrhage group will inevitably contain some infants with non-fatal haemorrhages, such a comparison may fail to demonstrate differences. In the present study diagnosis of PVH was made using an ultrasound sector scanner. Infants with PVH were then compared with infants in whom no bleeding was detected.

Methods

Thirty-nine preterm infants weighing <1500 g at birth, and consecutively admitted to the neonatal unit at this hospital, were studied. Data concerning birthweight, birth order, method of delivery, gestation, and need for resuscitation at birth were recorded. Each day after admittance the occurrence of respiratory disease, pneumothorax, convulsions, or sudden deteriorations was noted, together with details of ventilatory support and inspired oxygen

administered. Blood gas data were recorded as the lowest oxygen saturation (So₂), lowest pH, highest PCO₂, and lowest base excess measured each day. Up to 8 blood gas measurements determined on arterial or arterialis capillary blood were made each day depending on clinical need. No measurements were made for the purpose of this study. A daily haematocrit was also recorded.

The first ultrasound scan was made between the 5th and 10th day of life in infants who did not have clinical signs that suggested PVH. If a clinical diagnosis of haemorrhage was made before age 5 days, an earlier scan was made. If a PVH was seen, regular follow-up scans were made until the infant was discharged home, or died. CT scans were performed too on some infants with clinical evidence of PVH at the discretion of the managing paediatrician.

Ultrasound scans were made using an Advanced Technology Labs 850 A sector scanner with a 3.5 or 5 MHz head. Scans were made through the fontanelle in both a right and left parasagittal position and coronally, when the scan plane was 'swept' from an anterior to posterior position. Scans were recorded in real-time on videotape, and photographed from a monitor screen on play-back. This technique has several advantages when compared with CT scans and other ultrasound techniques. Firstly the infant remains undisturbed in his incubator and the entire examination lasts 2 or 3 minutes. Secondly, by using the fontanelle as a 'window', and employing a sector type of ultrasound scanner rather than a linear array type, the bones of the skull are avoided, greatly increasing the quality of image. Theoretically, lateral resolution at the depth scanned is less than 2 mm, and in practice germinal layer haemorrhages of 3-4 mm could be clearly distinguished. Thirdly,

the ability to record 'sweeps' in real time on videotape, enables the images to be reviewed at leisure, and an almost infinite number of 'cuts' to be seen. A suspected haemorrhage can be viewed in 3 dimensions and distinguished from the other bright echoes in the region of the lateral ventricles originating from the fornix.

Results

Incidence and extent of PVH. Using the technique described it was possible to detect PVH in 20 (51%) of the 39 infants. The haemorrhages were graded in a similar manner to that used by Papile *et al.*² for CT scans of neonatal PVH: grade 1, confined to germinal layer or minimal intraventricular bleeding; grade 2, intraventricular haemorrhage; grade 3, intraventricular haemorrhage with ventricular distension; grade 4, parenchymal haemorrhage.

Fig. 1 shows a normal coronal and parasagittal

Fig. 1a Normal coronal section through fontanelle in a 900-g infant. (b) Normal parasagittal section through fontanelle in a 1200-g infant.

scan; Fig. 2 shows the 4 grades of PVH as seen in coronal plane. Fig. 3 shows a parasagittal view of an intraventricular haemorrhage with a CT scan view taken on the same day.

Table 1 shows the distribution of grades, and rate of survival after PVH.

Table 2 shows the birthweight, gestation, distribution of haemorrhage, and occurrence of ventricular dilatation after the PVH.

In all infants sustaining an intraventricular haemorrhage, and surviving the immediate incident, ventricular dilatation took place. Enlargement of the lateral ventricle was mainly in a vertical direction and towards the occiput (Fig. 4). Gross ventricular enlargement was present in 5 infants, 4 of whom died; 3 of them showed clinical hydrocephalus.

Of the 19 infants not sustaining PVH, 6 died: 4 of necrotising enterocolitis, 1 of respiratory causes, and 1 from *Candida* sp. and septicaemia, each of them after the first week of life.

Factors associated with PVH. Of the 39 infants examined, 20 (51%) had evidence of PVH on ultrasound scan and were designated as the haemorrhage (H) group. The remaining 19 infants formed the non-haemorrhage (NH) group. Clinical details and events relating to the two groups are shown in Table 3. The statistical differences between the groups have been determined by the Mann-Whitney U test or Fisher's exact test as appropriate. There was no statistically significant difference in gestational age, birthweight, the occurrence of premature rupture (>48 hours) of amniotic membranes, mode of delivery, or the need for resuscitation at birth between the two groups. There was no significant difference in the recorded frequency of administration of hypertonic alkaline solutions at delivery. After admission to the unit only 2 infants received infusions of sodium bicarbonate, but each was known at the time to have had a PVH.

The H group had a higher incidence of respiratory distress ($P = 0.0008$) with a correspondingly higher incidence of respiratory support (CPAP or mechanical ventilation) on the first day of life ($P = 0.0025$) and during the first week ($P = 0.00045$), Table 4. There was however, no significant difference in the

Table 1 Survival after PVH according to grade of haemorrhage

Grade	Lived	Died
1 (n=5)	5	0
2 (n=8)	4	4
3 (n=4)	0	4
4 (n=3)	1	2

Fig. 2 Coronal sections: (a) grade 1, (b) grade 2, (c) grade 3, and (d) grade 4 PVH.

Table 2 Clinical data, type of PVH, and outcome for infants with PVH

Grade	Birthweight (g)	Gestation (weeks)	Extent of PVH	Ventricular dilatation	Outcome
1	960	29	SEH/SEH	—	Lived
	1210	30	SEH/SEH	—	Lived
	800	28	SEH/—	—	Lived
	750	27	SEH/—	+	Lived
	1460	32	SEH/—	—	Lived
2	1130	28	IVH/IVH	++	Died, 9 days
	1350	35	IVH/IVH	++	Lived
	950	29	IVH/IVH	+	Lived
	910	28	IVH/SEH	+	Lived
	1250	30	IVH/SEH	+	Died, 15 days
	1440	30	IVH/IVH	+	Lived
	675	31	IVH/IVH	—	Died, 2 days
	1210	30	IVH/IVH	—	Died, 3 days
3	1250	28	IVH/IVH	++	Died, 8 days
	800	27	IVH/SEH	++	Died, 9 days
	1330	30	IVH/IVH	++	Died, 2 months
	970	28	IVH/IVH	+	Died, 8 days
4	950	28	IVH/IVH + parietal haematoma	—	Died, 3 days
	990	28	IVH/IVH + parietal haematoma	—	Died, 4 days
	1000	32	IVH/— + frontal haematoma	+	Lived

Fig. 3a Parasagittal section through lateral ventricle after IVH. (b) CT scan of same infant.

Table 3 Perinatal data on infants with and without evidence of PVH

	Haemorrhage group (n=20)	Non-haemorrhage group (n=19)	P
Gestational age (weeks) (median + range)	29 (27-35)	31 (26-34)	NS
Birthweight (g) (median + range)	995 (675-1460)	1290 (725-1500)	NS
Male/female	11/9	9/10	
Premature rupture of membranes	4	3	NS
Mode of delivery, caesarean section/vaginal	5/15	6/13	NS
Resuscitation at birth	8	5	NS
Bicarbonate given at birth	4	2	NS
Died	10	6	NS

incidence of pneumothorax or the need for inspired oxygen concentration of $>60\%$ during the first week. Except in cases of massive haemorrhage, clinical signs and symptoms were often equivocal, and did not reliably predict PVH. A fall in haematocrit in 24

Fig. 4a Coronal section showing ventricular dilatation after IVH. (b) Parasagittal scan on same infant.

Table 4 Postnatal illness in infants with and without evidence of PVH

	Haemorrhage group (n=20)	Non-haemorrhage group (n=19)	P
Respiratory distress	17	6	0.0008
Severe recurrent apnoea	3	0	NS
Pneumothorax	4	1	NS
Respiratory support (CPAP/mechanical ventilation)			
1st day	16	6	0.0025
1st week	20	8	0.00045
$F_{iO_2} > 60\%$ ever	8	3	NS
Haematocrit fell more than 10 points in 24 hours ever	13	7	0.056
Haematocrit fell more than 10 points in 24 hours after first day of life	10	2	0.001

Fig. 5a CT scan 1 week after small IVH in 1200-g infant. (b) Coronal ultrasound scan on same day showing residual germinal layer haemorrhage not seen on CT.

hours of more than 10 points however, was associated with PVH if it occurred after the first day of life ($P = 0.001$).

Blood gas data for both groups on each of the first 7 days of life are summarised in Table 3. Medians and range for each variable are given, and the significance of differences tested non-parametrically using the Mann-Whitney U test.

Lower values for SO_2 in the H babies were seen, but the differences were not statistically significant. Infants in the H group had a significantly lower pH on the first 6 days of life. This was associated with a significantly lower base excess during the first 72 hours, and a significantly higher PCO_2 during the first week.

Discussion

Recent *in vivo* diagnosis of PVH in very low birthweight infants using CT scans, showed a high incidence among surviving infants.² If PVH in these infants has the same aetiology as in those who die, analysis of perinatal factors and events must be based on *in vivo* diagnosis rather than diagnosis at necropsy. Attempts at timing PVH have shown the highest incidence to be between 24 and 48 hours, indicating that early events are likely to be the most important.^{5, 6} The use of a portable ultrasound scanner for diagnosis allowed examinations to be rapidly performed in the intensive care unit with little disturbance to the patient. Although a small pilot study has shown good comparability between ultrasound and CT scans, further comparisons within the study group were made in 7 infants on whom both forms of scan were performed on the same day. In all cases the grading was the same, although the differences in scan planes made the precise appearances differ. The resolution of the ultrasound scanner appeared rather better, as in the CT scan of a 1-week-old, 1200-g infant (Fig. 5a). A coronal scan by ultrasound, made at the same time (Fig. 5b), shows the same degree of ventricular dilatation but shows too the germinal layer haemorrhage which a few days earlier had caused a small IVH, not seen in the CT scan.

The incidence (51%) of PVH in this study is similar to that in the study of Papile *et al.*² (44%) in a similar group of infants. The distribution of the PVHs seen was also similar (Table 1). Mortality in grades 3 and 4 was much higher than in grades 1 and 2 and this was due mainly to the higher incidence of death at the time of the PVH or to the development of hydrocephalus later.

It is of interest to note that all infants with ventricular bleeding developed ventricular enlargement if they survived the initial incident, although this was not often clinically evident as hydrocephalus. In the survivors this enlargement reached a maximum at about 1 week after the event, and subsided slowly during the next 2 months, although 2 infants still had evidence of dilatation on discharge. The presence and degree of ventricular dilatation appears to be related to the presence and amount of blood released into the ventricular system, although dilatation was seen in 1 infant in whom only a germinal layer bleed was noted. Alternatively, it could be, at least in part, related to a degree of cerebral atrophy after hypoxia.

In the one long-term survivor of a grade 4 bleed, a large loculated cerebral cyst persisted at the site of the initial frontal lobe haematoma, and neurological examination at 3 months was abnormal. All other

Table 5 Median values (with range) for extreme values of blood gas data in haemorrhage and non-haemorrhage infants during the first 7 days of life

	Day						
	1	2	3	4	5	6	7
So₂(%)							
Haemorrhage	83 (26-100)	84 (21-98)	85 (55-98)	90 (55-150)	90 (22-99)	86 (57-100)	84 (58-91)
Non-haemorrhage	89 (44-100)	92 (80-100)	93 (84-100)	95 (49-100)	94 (85-100)	94 (68-97)	90 (42-100)
P	NS	NS	NS	NS	NS	NS	NS
pH							
Haemorrhage	7.18 (6.92-7.53)	7.15 (6.77-7.39)	7.17 (6.93-7.39)	7.21 (7.04-7.37)	7.20 (7.02-7.39)	7.18 (7.00-7.35)	7.22 (7.11-7.33)
Non-haemorrhage	7.29 (7.13-7.36)	7.32 (7.23-7.40)	7.27 (7.01-7.35)	7.27 (7.06-7.38)	7.26 (7.15-7.38)	7.27 (7.18-7.33)	7.28 (7.01-7.41)
P	<0.05	<0.001	<0.001	<0.05	<0.025	<0.025	NS
Pco₂ (mmHg)							
Haemorrhage	63 (38-141)	62 (41-110)	60 (39-106)	50 (42-80)	54 (41-97)	56 (38-85)	53 (35-79)
Non-haemorrhage	47 (36-62)	44 (29-62)	46 (33-77)	44 (31-65)	43 (36-52)	44 (32-92)	44 (29-78)
P	<0.001	<0.001	<0.01	<0.01	<0.001	<0.01	<0.01
Base excess (mmol/l)							
Haemorrhage	-9 (-18-+1)	-11 (-25-+1)	-10 (-15-+1)	-9 (-14-0)	-8 (-15-+3)	-7 (-14-+2)	-8 (-13-+5)
Non-haemorrhage	-4 (-11-0)	-4 (-10-+1)	-5 (-14-+3)	-6 (-11-+3)	-6 (-14-+2)	-6 (-10-0)	-5 (-12-+2)
P	<0.001	<0.001	<0.01	NS	=0.05	NS	NS

surviving infants appeared neurologically normal at discharge, although only long-term follow-up will confirm this.

Because only infants of <1500 g birthweight were studied, an association of PVH with prematurity and low birthweight⁷ was not observed. The principal differences between the H and NH groups concerned the occurrence of respiratory problems. Of the 23 infants developing symptoms of respiratory distress in the first 24 hours, 17 were found to have PVH ($P = 0.0008$). The requirement for inspired oxygen concentrations of >60%, and the arterial oxygen saturations measured were not significantly different during the first week. H babies were nevertheless significantly more acidotic during the first 6 days, with a greater degree of metabolic acidosis during the first 3 days, indicating that oxygen delivery to peripheral tissues was less adequate than the arterial oxygen saturations would suggest.

The most pronounced difference between the two groups is the Pco₂ which remained significantly higher in H infants for the first 7 days. Since all of the haemorrhages had occurred by the end of the first week and probably most of them by between 24 and 72 hours, part of this difference could have been due to hypoventilation secondary to PVH. However, all the H infants had received ventilatory support of some kind by the end of the first week making the high Pco₂ more likely to have been due to severe lung disease which the H infants clearly had, than

simply central nervous system depression. Thus, hypercapnia is more likely to be an associated cause, than the result of PVH. The association between PVH and respiratory distress, in particular hyaline membrane disease, has been demonstrated in necropsy studies.⁸⁻⁹ Moriette *et al.* found that in studies at necropsy on infants with hyaline membrane disease, PVH was associated with hypothermia, metabolic acidosis, and respiratory assistance.¹⁰ Papile *et al.* however, in an *in vivo* study,² found no association with any perinatal factors including respiratory assistance. Wigglesworth¹¹⁻¹² has suggested that hypercapnia and acidosis, because of their known vasodilator effects, could be important in the pathophysiology of PVH. Experimental evidence with newborn goats has shown cerebral blood flow to be related independently of both hydrogen ion concentration and Pco₂.¹³ In newborn infants respiratory distress has been shown to be associated with high cerebral blood flow if hypercapnia and normal blood pressure are present,¹⁴ and that sudden variations in flow occur with apnoea. Lou *et al.*¹⁵ have also shown disturbed cerebral blood flow in newborn infants, in the form of low flow rates after 'asphyxia' when hypotension was present.

The demonstration in this study of a clear association of PVH with both metabolic acidosis and hypercapnia lends further support to their role in the causation of PVH. Greater attention to maintenance of normal acid/base balance and

normocapnia in the first few hours and days of life may reduce the incidence of PVH in low birthweight infants.

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