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Antecedents of periventricular haemorrhage in infants weighing 1250 g or less at birth

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SUMMARY Fifty infants who weighed 1250 g or less at birth were studied with serial real time cerebral ultrasound to evaluate the temporal relation of various perinatal factors to the onset and progression of periventricular haemorrhage (PVH). The significant antecedents of PVH were severe bruising at birth, low birthweight, short gestation, ratio of arterial oxygen pressure (PaO_2) to fractional inspired oxygen (FiO_2), and haematocrit on admission, hyaline membrane disease, assisted ventilation, pneumothorax, administration of tubocurarine, hypercapnia, hypoxaemia, and hypotension. Case control studies, in which infants with PVH at 26 weeks' and 28 weeks' gestation were compared with matched infants without PVH, confirmed that the antecedents identified were independent of gestational influences. A multivariate discriminant analysis for the antecedents of PVH showed that hyaline membrane disease, hypercapnia, and short gestation correctly classified presence or absence of PVH in 78% of the study group. A similar analysis comparing infants with germinal layer haemorrhage or intraventricular haemorrhage with those who developed intracerebral extension of haemorrhage showed that three factors found on admission (hypothermia, a low PaO_2: FiO_2 ratio, and severe bruising) combined to classify correctly 90% of the haemorrhages. Our data suggest that prevention of perinatal trauma and asphyxia as well as respiratory illness, especially hyaline membrane disease, and stabilisation of blood gas tensions, blood pressure, and haematocrit within the physiological range, are likely to be the most effective ways of preventing PVH in extremely preterm infants.

Many of the early studies on factors associated with periventricular haemorrhage (PVH) were retrospective and dealt with infants who had clinically apparent haemorrhage or whose haemorrhage was diagnosed at necropsy.[1] Though useful, their value is somewhat limited because only half of the cases with PVH can be diagnosed clinically,[2] and necropsies provide data only in those infants who have died. The use of computed tomography allowed all surviving infants with PVH to be identified, but timing of the haemorrhage was inevitably imprecise as early and repetitive scanning was not possible.[3–6] Even in serial real time ultrasound studies done with minimal disturbance of the infant, difficulty in distinguishing causal factors from abnormalities developing as a result of PVH may persist.[7 8] Only one previous study distinguished antecedents—defined as variables present before PVH was detected—from associates, which included all developments in the early neonatal period.[9] If PVH is to be prevented its timing and antecedents must first be clearly defined. The timing and evolution of PVH in infants weighing 1250 g or less at birth have been reported separately.[10] The purpose of this study is to describe the factors found to predispose extremely low birthweight infants to the development of PVH.

Patients and methods

Details of the 50 infants weighing 1250 g or less have been described elsewhere.[10] All were scanned at least daily for the first four days after birth and weekly thereafter until discharge or death. The mean age at the time of the first scan was 10 hours. All infants with PVH were scanned before 12 hours of age except two infants born elsewhere who were admitted after that age. All those infants with PVH were actually scanned every 12 hours until 72 hours of age except two who were scanned every 12 hours until only 48 hours of age. This enabled the timing of haemorrhage to be established within 12 hour blocks.

A Toshiba SAL 120 real time linear array scanner with a 5 MHz transducer was used to obtain images

in coronal, saggital, and axial planes as previously described.[10] A study of correlation at necropsy previously reported by us showed 90% diagnostic accuracy of PVH[11] similar to the previous experience of one of us (WS).[12] The limit of resolution of haemorrhage by ultrasound imaging was 3 mm.

For most infants an obstetrical estimate of gestation was available, which was confirmed either by an early ultrasound fetal measurement or by clinical bimanual examination of the uterus by an experienced obstetrician. A clinical examination of gestation was also made after admission with a Dubowitz score and vascularity of the anterior lens. Neonatal assessment was relied on only in those few instances where the clinical and obstetrical assessments varied by over two weeks, or when dates were unknown. Hyaline membrane disease was diagnosed clinically if certain criteria were present—namely, repiratory distress not attributable to other causes; retraction and poor air entry during spontaneous respiratory efforts; chest radiograph showing diffuse, finely granular infiltrates persisting at least until the third day; fractional inspired oxygen (FiO_2) 0·3 or more to maintain an arterial oxygen pressure (PaO_2) of 8 kPa (60 mm Hg) or more beginning during the first 12 hours and lasting at least three days; and a maximum FiO_2 requirement of 0·4 or more. Ventilation was instituted for severe apnoea or when arterial carbon dioxide pressure ($PaCO_2$) was 8 kPa (60 mm Hg) or more, pH less than 7·2, and PaO_2 6·7 kPa (50 mm Hg) or less in FiO_2 0·6 or more. Tubocurarine was used in conjunction with ventilation when air leak syndromes or persistent pulmonary hypertension developed. Metabolic acidosis was corrected for a pH less than 7·25 in association with a base deficit 6 mmol/l or more. A bolus of sodium bicarbonate ($NaHCO_3$) was only given in cardiac arrest. If base was required, a slow infusion of 2·8% $NaHCO_3$ was given over a period of 1–3 hours for total or partial correction. Routine monitoring of arterial blood pressure was started on admission via umbilical artery or radial artery catheters. Slow infusions of 10–15 ml/kg of blood or plasma were given over 1–3 hours when the systolic blood pressure was less than 35 mm Hg.

All obstetric, intrapartum, and neonatal data were recorded prospectively during the study period. In infants with PVH, neonatal data that preceded the diagnosis of haemorrhage by no more than 12 hours were used for analysis. Results in this report were tabulated as mean and standard deviation or number and percentage of infants in the respective groups. Students *t* test, χ^2 with Yates's correction, and Fisher's exact test were used to test the significance of differences between the groups. To exclude the influence of gestation, birthweight, and mortality, pairs of infants with and without PVH were matched at 26 and 28 weeks' gestation and antecedents of PVH were again analysed. A multivariate discriminant analysis of the antecedent factors for PVH was done to determine the most significant contributing factors.

Results

The overall incidence of PVH was 60%. Of the 30 infants with PVH, germinal layer haemorrhage was found in 27 infants. Intraventricular haemorrhage developed in 24 infants, of whom 21 also had a germinal layer haemorrhage. Eight of the infants with intraventricular haemorrhage also developed an intracerebral haemorrhage.

Obstetric and intrapartum data from 30 infants with PVH were compared with data from 20 infants without PVH (Table 1). In addition, drugs taken by the mother before delivery were analysed. Salbutamol, betamethasone, oxytocin, antihypertensives, chloral hydrate, and pethidine were not found to be significantly related to PVH. Birth trauma, as evidenced by severe bruising, was the only significant obstetric factor. The birthweights and lengths of gestation of infants with PVH were significantly lower than those without PVH. Seventeen (81%) of 21 infants born at 26 weeks' gestation or less had PVH compared with 13 (45%) of 29 infants of more than 26 weeks' gestation ($P<0·005$). The admission pH, PaO_2:FiO_2, and haematocrit were also significantly lower in the group with PVH. The effect of birth outside the perinatal centre and neonatal

Table 1 *Obstetric and intrapartum factors in PVH*

	PVH (n = 30)	*No PVH (n = 20)*
Presence of labour	24 (80%)	17 (85%)
Antepartum haemorrhage	7 (23%)	4 (20%)
Membranes ruptured >24 hours	9 (30%)	7 (35%)
Mode of delivery:		
Vaginal vertex	14 (47%)	7 (35%)
Vaginal breech	7 (23%)	4 (20%)
Caesarean section	9 (30%)	9 (45%)
Severe bruising at birth	9 (30%)	1 (5%)†
Birthweight (g) (mean (SD))	862 (210)	967 (186)*
Gestation (weeks) (mean (SD))	27 (2)	29 (2)‡
1 minute Apgar score (mean (SD))	4·3 (2·6)	5·0 (2·6)
5 minute Apgar score (mean (SD))	7·8 (1·9)	8·1 (1·4)
Endotracheal intubation at birth	18 (60%)	10 (50%)
Sodium bicarbonate treatment at birth	3 (10%)	4 (20%)
Cardiac massage at birth	3 (10%)	3 (15%)
Data on admission (mean (SD)):		
pH	7·22 (0·13)	7·29 (0·08)*
$PaCO_2$ (mm Hg)	51 (16)	47 (12)
HCO_3 (mmol/l)	20 (3)	21 (4)
PaO_2:FiO_2	154 (113)	261 (136)‡
Haematocrit (%)	46 (9)	51 (8)
Temperature (°C)	35·1 (1·3)	35·5 (1·2)
Systolic blood pressure (mm Hg)	34 (11)	36 (10)

*$P<0·05$, †$P<0·025$, ‡$P<0·005$.

transport could not be assessed as 46 (92%) of the study population were born in this hospital.

As 50% of germinal layer haemorrhages, 67% of intraventricular haemorrhages, and 85% of intracerebral haemorrhages developed after 12 hours of age events in the neonatal course must play an important part in the development of PVH. Table 2 shows that hyaline membrane disease, pneumothorax, administration of tubocurarine, and hypercapnia were very significant antecedents of PVH. Hypoxaemia, mechanical ventilation, and systemic hypotension were also significant antecedents. Other neonatal factors were analysed but were not found to be related to PVH. These included pulmonary haemorrhage, pulmonary interstitial emphysema, persistent pulmonary hypertension, patent ductus arteriosus, thrombocytopenia, disseminated intravascular coagulation, volume expansion, administration of $NaHCO_3$, tolazoline, pancuronium, ventilation variables of maximum ventilatory rates or maximum peak inspiratory pressure, maximum and mean PaO_2, minimum $PaCO_2$, maximum and minimum serum osmolality, and sodium, calcium, potassium, and maximum serum bilirubin concentrations.

As the gestation periods and birthweights of infants with PVH were significantly lower than those without PVH, a case control study was carried out to compare the incidence of risk factors in subgroups of a similar gestation and birthweight. Five extremely preterm infants with PVH (mean (SD) gestation 26·0 (0·7) weeks, birthweight 827 (71) g) were matched with five control infants without PVH (gestation 25·8 (0·4) weeks, birthweight 886 (56) g). Table 3 lists the significant antecedents of PVH at this degree of extreme prematurity. In addition, 6 more mature infants with PVH (gestation 28·3 (0·5) weeks, birthweight (1002) (199) g) were matched with 6 control infants without PVH (gestation 28·5 (0·5) weeks, birthweight 1015 (153) g). Table 4 shows significant antecedents of PVH in this group.

Of the 24 infants with intraventricular haemorrhage, 10 developed the haemorrhage before 24 hours, 9 between 24 and 48 hours, and five after 48 hours. Table 5 shows that infants who developed intraventricular haemorrhage early had had significantly shorter gestations, lower pH and PaO_2:FiO_2 ratio on admission, and lower minimum arterial oxygen pressures compared with those with late intraventricular haemorrhage. Other antecedents of PVH had occurred with equal frequency in the three groups.

A multivariate discriminant analysis for the

Table 2 *Significant neonatal factors in PVH*

	PVH (n = 30)	*No PVH (n = 20)*	*P value*
Hyaline membrane disease	23 (77%)	8 (40%)	<0·005
Pneumothorax	9 (30%)	0	<0·005
Administration of tubocurarine	12 (40%)	0	<0·005
Maximum $PaCO_2$ (mm Hg) (mean (SD))	71 (19)	52 (19)	<0·005
$PaCO_2$ (mm Hg) (mean (SD))	51 (11)	40 (7)	<0·005
Minimum PaO_2 (mm Hg) (mean (SD))	40 (15)	53 (21)	<0·025
Assisted ventilation	26 (87)	11 (55)	<0·025
Blood pressure (mm Hg) (mean (SD))	38 (8)	44 (9)	<0·01

Table 3 *Case control study in group of 26 weeks' gestation*

	PVH (n = 5)	*No PVH (n = 5)*	*P value*
Severe bruising	3 (60%)	0	<0·05
Data on admission (mean SD):			
pH	7·17 (0·09)	7·28 (0·09)	<0·005
PaO_2:FiO_2	66 (30)	236 (120)	<0·005
Temperature (°C)	34·8 (0·7)	35·8 (1·0)	<0·005
Systolic blood pressure (mm Hg)	25 (4)	39 (6)	<0·005
Hyaline membrane disease	5 (100%)	1 (20%)	<0·05
Administration of tubocurarine	3 (60%)	0 (0%)	<0·05
Maximum $PaCO_2$ (mm Hg) (mean (SD))	74 (17)	41 (12)	<0·005
Minimum PaO_2 (mm Hg) (mean (SD))	23 (15)	50 (8)	<0·005
Blood pressure (mm Hg) (mean (SD))	32 (5)	41 (5)	<0·005
Maximum peak inspiratory pressure (cm H_2O) (mean (SD))	28 (8)	16 (3)	<0·005
Administration of $NaHCO_3$ (mmol) (mean (SD))	4.8 (2.0)	2·5 (2·5)	<0·01

Table 4 *Case control study in group of 28 weeks' gestation*

	PVH (n = 6)	*No PVH (n = 6)*	*P value*
Data on admission (mean (SD))			
pH	7·24 (0·13)	7·31 (0·08)	<0·05
PaO_2:FiO_2	113 (70)	244 (100)	<0·01
Pneumothorax	4 (67%)	0	<0·01
Administration of tubocurarine	4 (67%)	0	<0·01
Maximum $PaCO_2$ (mm Hg) (mean (SD))	75 (17)	48 (8)	<0·005
Median $PaCO_2$ (mm Hg) (mean (SD))	53 (9)	40 (3)	<0·01
Minimum PaO_2 (mm Hg) (mean (SD))	41 (10)	55 (11)	<0·02
Assisted ventilation	6 (100%)	2 (33%)	<0·01
Maximum peak inspiratory pressure (cm H_2O) (mean (SD))	28 (13)	9 (10)	<0·02
Volume expansion (ml) (mean (SD))	24 (18)	0	<0·01

Table 5 *Significant antecedents that differed between early and late intraventricular haemorrhage (IVH)*

	IVH <24 hours (n = 10)	*IVH 24–48 hours (n = 9)*	*IVH >48 hours (n = 5)*
Gestation (mean (SD))	25·5 (1·4)	26·7 (2·2)	29·0 (2·0)*
Admission pH (mean (SD))	7·10 (0·12)	7·31 (0·10)*	7·30 (0·07)*
Admission PaO_2/FiO_2 (mean (SD))	80 (45)	170 (199)	166 (113)*
Minimum PaO_2 (mean (SD))	30 (10)	38 (9)	57 (7)*

*Compared with group with IVH <24hr. P<0·005.

antecedents of PVH showed that hyaline membrane disease, hypercapnia, and short gestation correctly indicated the presence or absence of PVH in 39 (78%) of the study group. The most significant antecedent of PVH was hyaline membrane disease (contributing 43% to the discriminant function), followed by hypercapnia (29%), and short gestation (28%). The discriminant function analysis erred in classification only when a small germinal layer haemorrhage developed or when acute deterioration was followed quickly by death. A discriminant function analysis was also done comparing 22 infants with germinal layer haemorrhage with or without intraventricular haemorrhage with 8 infants with intracerebral and intraventricular haemorrhage. The variables that combined to classify correctly 90% of cases were hypothermia and low PaO_2:FiO_2 ratio on admission and severe bruising at birth. Hypothermia contributed 41% to the discriminant function followed by a low PaO_2:FiO_2 ratio (37%) and severe bruising (22%).

Discussion

To date, only one other published study has examined antecedents of PVH in a similar fashion.[9] The study population included infants weighing up to 2500 g at birth, all of whom were of less than 33 weeks' gestation. Ultrasound scans were done often enough in 83% of their infants with PVH to determine timing of haemorrhage within one day. They concluded that short gestation and severe respiratory illness, particulary hyaline membrane disease, necessitating ventilation and complicated by pneumothorax, were the most significant antecedents. Other significant antecedents included hypothermia, abnormal pH and blood gas tensions, hypotension, bicarbonate infusion, administration of tolazoline, and abnormal clotting times. The study population of infants weighing 1250 g or less at birth in the present report is the largest real time ultrasound study group for these extremely preterm infants (mean gestation 27 weeks, mean birthweight 888 g) to be reported on. Our frequent scanning enabled the timing of PVH to be established within at least 12 hour blocks (range 2–12 hours) in all infants.

Severe bruising at birth, probably reflecting the degree of birth trauma, was the only significant obstetric factor. Eight of the 9 infants with severe bruising developed PVH before 24 hours of age, and all were of 26 weeks' gestation or less. Although caesarean section has been proposed for delivering these extremely preterm infants in optimal condition with the least physical or biochemical trauma,[13] and although a significantly lower incidence of PVH has been reported in babies born by caesarean section compared with vaginally in previous studies,[5 8] this association could be explained by the fact that mostly more mature infants who had the lower incidence of PVH were selected for delivery by caesarean section. In our study, no protective effect of caesarean section was shown. It was the degree of birth trauma and not mode of delivery itself that was the significant factor.

Decreasing gestation and birthweight were shown to be significant antecedents of PVH even within the narrow range of our study population. The least mature infants were the most vulnerable. This was not surprising as the germinal matrix, which is the most frequent origin of PVH, is most prominent in very immature infants and does not involute until almost term.[14] To control for the influence of gestation and birthweight and to exclude the possibility that the identified antecedents of PVH simply represent the descriptive characteristics of a population of more immature infants, case control studies of infants with and without PVH at 26 and 28 weeks' gestation were done. All of the previously described risk factors except one, were found to remain significant within the two subgroups, and 6 antecedents were common to both subgroups (low admission pH and PaO_2:FiO_2 ratio, administration of tubocurarine, maximum peak inspiratory pressure, maximum $PaCO_2$, and minimum PaO_2). This data analysis confirmed that perinatal asphyxia followed by severe lung disease and considerable disturbances in $PaCO_2$ and PaO_2 pressures were significant antecedents of PVH.[1]

Some previous studies have reported an association between pneumothorax and PVH,[4 15] but others have disagreed.[5 7] In all our infants the pneumothorax caused clinical deterioration accompanied by high $PaCO_2$ and low PaO_2 pressures, low pH, and fluctuations in blood pressure. These disturbances caused by a tension pneumothorax have been shown to cause an abrupt increase in cerebral blood flow.[16] In our study, pneumothorax was a significant antecedent of PVH; however, early diagnosis and treatment before acute deterioration has changed that. The varying degrees of physiological disturbances caused by pneumothorax may explain the different conclusions reached regarding its significance in the pathogenesis of PVH.

The relation between administration of tubocurarine and PVH is as yet unknown. Tubocurarine was given in response to severe hypoxaemia from persistent pulmonary hypertension and for significant air leaks. Nevertheless, tubocurarine can cause hypercapnia if ventilatory adjustments are inadequate as was the case in 9 of 12 infants treated with the drug, and also systemic hypotension mediated

by histamine release, which developed in two of 12 treated infants. The effects of tubocurarine on the cerebral vasculature are as yet unknown.

A model for PVH in the preterm infant has been proposed based on findings of germinal matrix capillary disruption at necropsy.[14] Initial hypotension or hypoxaemia might lead to ischaemic damage of the germinal matrix capillaries, and a subsequent increase in cerebral blood flow or cerebrovascular transmural pressure might disrupt the injured microvasculature and lead to haemorrhage. Asphyxia, which results in hypoxaemia, hypercapnia, and acidaemia, has been shown to impair autoregulation and to lead to increased cerebral blood flow.[17] Increased systemic pressure could then be directly transmitted to the poorly supported germinal matrix capillary beds with resultant rupture. Clinical observations have suggested an important pathogenic role for fluctuating blood pressure in PVH.[18–20]

The results of our study give strong support to the hypothesis that increased or fluctuating cerebral blood flow leads to PVH. The infants with the shortest gestation, who have the most extensive germinal matrix, have the highest risk of PVH as any factor causing an increase in cerebral blood flow would tend to over perfuse the periventricular region preferentially in these extremely preterm infants. Severe bruising at birth probably reflected the degree of physiological trauma intrapartum. Acidaemia on admission reflected the degree of perinatal asphyxia. Severe lung disease, reflected by the low ratio of PaO_2:FiO_2 on admission, need for assisted ventilation, and high peak inspiratory pressure, was often a result of hyaline membrane disease. This was responsible for episodes of hypoxaemia and hypercapnia and for the development of pneumothorax. Hypercapnia, however, remained a significant antecedent of PVH independent of hyaline membrane disease in the multivariate discriminant analysis. Low haematocrits and systemic hypotension, often corrected by volume expansion, are factors that have been shown to increase cerebral blood flow.[1] These factors were also found to be significant antecedents of PVH.

The data from our study suggest that prevention of perinatal trauma and asphyxia as well as respiratory illness, especially hyaline membrane disease, should reduce the incidence of PVH in extremely preterm infants. In particular, stabilisation within the normal range of physiological variables (PaO_2, $PaCO_2$, blood pressure, haematocrit) that affect cerebral flow and cerebrovascular transmural pressure is likely to be the most effective way of preventing the development of PVH in the immediate neonatal period.

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