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Antecedents and Outcomes of Cerebral Ventricular Enlargement in the Absence of Prior Germinal Matrix – Intraventricular Hemorrhage in Low Birth Weight Infants

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ANTECEDENTS AND OUTCOMES OF CEREBRAL VENTRICULAR ENLARGEMENT IN THE ABSENCE OF PRIOR GERMINAL MATRIX – INTRAVENTRICULAR HEMORRHAGE IN LOW BIRTH WEIGHT INFANTS

By

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ABSTRACT

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Background and methods: Cerebral ventricular enlargement in low birth weight infants predicts poor neurodevelopmental outcome. The etiology or outcomes of ventricular enlargement (VE) in absence of intraventricular hemorrhage (IVH) are unclear. In the neonatal brain hemorrhage (NBH) study, timed, cranial ultrasound (US) scans were performed in 1,105 infants with birth weights ≤2 kg. We searched the NBH database to determine the prevalence, etiology and outcomes of infants with VE.

Results: VE was identified in 23 of 1088 (2.1%) infants with US scans. Infants with VE had similar gestational age, birth weight and head circumference as infants with normal scans. Mothers of VE infants were more likely to be unemployed and to use drugs. VE and VE+HE were significantly associated with increased risk of overall mortality and of disabling cerebral palsy in survivors.

Conclusion: Maternal social factors may play a role in VE; VE and VE+HE are associated with increased risk of death and disabling cerebral palsy.

DEDICATION

To my wife and friend Adesuwa, and our sons Nosa, Noma, Etin, Osa and IK,

for your love, patience, prayers and encouragement.

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CHAPTER 1

VENTRICULAR ENLARGEMENT IN THE FETUS AND LOW BIRTH WEIGHT PRETERM INFANT

Introduction

Cerebral ventricular enlargement (VE) in very low birth weight (birth weight < 1,500 g) newborn infants is always cause for concern as it is often associated with an increased risk of motor, sensory and cognitive impairments[1]. VE often occurs as a sequel to germinal matrix-intraventricular hemorrhage (GM-IVH)[2], which is the most common form of intracranial injury in very low birth weight (VLBW) infants[3]. The germinal matrix is the site of hemorrhage in most cases of GM-IVH[4]; it is also the site of origin of oligodendrocytes and astrocytes precursors[5], cells that are critical to normal cerebral white matter and cortical development. However, while GM-IVH is an important risk factor for VE in VLBW infants, ventricular enlargement is also seen in the absence of intraventricular hemorrhage. Enlargement of the cerebral ventricles, whether or not associated with GM-IVH, may reflect damage to the periventricular white matter and adjacent neural tissues. Enlargement of the cerebral ventricles also causes injury to the periventricular microvasculature further increasing the risk of adverse motor, sensory and cognitive outcomes in VLBW infants with GM-IVH.

In this introductory chapter, I will discuss:

- Ventricular enlargement in the fetus
  - Definition

- Epidemiology and neurologic outcomes of ventricular enlargement in the fetus

- Ventricular enlargement in the VLBW infant
  - Post hemorrhagic ventricular enlargement
    - 'Normal pressure' ventricular enlargement
    - Post hemorrhagic hydrocephalus
  - Ventricular enlargement without prior GM-IVH (*'isolated ventricular enlargement'*)

Ventricular enlargement in the fetus

Enlargement of one or both lateral ventricles is one of the most common fetal abnormalities detected by prenatal ultrasound [6]. Therefore assessment of the size of the fetal lateral cerebral ventricles is an important part of routine prenatal ultrasound evaluation of the developing fetus. Furthermore, 3% to 12% of fetuses with VE have chromosomal anomalies while 30% to 60% have other anomalies [6]. Detection of fetal VE therefore, calls for careful evaluation of the fetus for other congenital anomalies, and for investigation of the fetus and mother for possible explanations.

Definition of fetal ventricular enlargement

The width of the atria of the lateral ventricles measured in the axial plane remains the easiest and most reproducible method of detecting fetal VE[7]. The lateral

ventricles are relatively large compared to the size of the cerebral hemispheres during late embryonic and early fetal life; however, the lateral ventricular width relative to that of the cerebral hemispheres decreases from approximately 70% at 15 weeks gestation to about 30% at 20 weeks. The absolute diameter of the lateral ventricles at the level of the atrium remains stable through most of second and third trimesters of pregnancy [8, 9] (Table 1.1).

Table 1.1: Ventricular width according to gestational age in 427 normal pregnancies (Almog et al, 2003[9])

Gestational Age (weeks)	Number of Cases	Ventricular Width (mm)			
		Mean (SD)	Percentile		4SD>Mean
			5th	95th	
20-21	38	5.89 (1.12)	4.79	8.50	10.37
22-23	106	5.66 (0.72)	4.50	7.06	8.54
24-25	77	6.04 (0.97)	4.60	7.77	9.92
26-27	35	6.01 (1.21)	3.90	9.00	10.85
28-29	52	6.38 (1.26)	4.35	9.11	11.42
30-31	30	6.57 (1.02)	4.28	7.80	10.65
32-33	26	6.77 (1.46)	4.20	8.90	12.60
34-35	31	7.22 (1.12)	5.46	9.28	11.71
36-40	32	6.92 (1.50)	4.00	9.80	12.92

A measurement of 10 mm, which represents 2.5 to 4 SDs above the mean, is accepted as the upper limit of normal [7, 10, 11]. In a prospective cohort study to establish the range of cerebral ventricular size in normal gestation, Almog et al[9]

measured fetal ventricular size at the level of the atrium in utero, in 427 pregnancies at gestational ages ranging from 20 to 40 weeks and found a mean ventricular width of 6.2 ± 1.2 mm. The ventricular size did not change significantly from 20 to 40 weeks of gestation (Table 1.1). The authors, in a review of 8 previous studies, reanalyzed additional 7789 fetal ventricular measurements and found that the pooled mean of 6.4 mm ± 3 SDs correspond to 10 mm, the widely accepted upper limit of normal fetal ventricular atrial diameter (Table 1.2).

Table 1.2: Lateral Ventricular Atrium Measurements in Different Populations of Fetuses Without Abnormalities [9]

Authors (Year)	Number of Cases	Ventricular Width (mm)		
		Mean (SD)	3SD > Mean	4SD > Mean
Hilpert et al (1995)	608	6.5 (1.5)	11.0	12.5
Cardoza et al (1988)	100	7.6 (0.6)	9.4	10.0
Pilu et al (1989)	171	6.9 (1.3)	10.8	12.1
Heiserman et al (1991)	52	6.5 (1.3)	10.4	11.7
Achiron et al (1993)	5400	6.6 (1.2)	10.2	11.4
Patel et al (1995)	219	6.1 (1.3)	10.0	11.3
Farrell et al (1994)	739	5.4 (1.2)	9.0	10.2
Alagappan et al (1994)	500	6.6 (1.4)	10.8	12.2
Almog et al (2003)	427	6.2 (1.2)	9.8	11.0
Calculated Average	**8216**	**6.4 (1.2)**	**10.0**	**11.2**

Ventricular enlargement in the fetus is therefore defined as a transverse diameter of the lateral ventricle, measured at the level of the ventricular atrium, which is greater than 10 mm. Fetal ventricular enlargement is mild when the atrial width is 10 – 15 mm; and severe when greater than 15 mm.

A ventricular atrial width greater than 10 mm at the time of delivery of a LBW, preterm infant may represent fetal ventricular enlargement. Ventricular enlargement without evidence of prior GM-IVH is reported in up to 16% of LBW infants delivered at or less than 34 weeks gestation [12, 13]. Infants with ventricular enlargement on initial scans in these studies were delivered at significantly earlier gestational ages and were of smaller birth weights. Ventricular enlargement detected in the immediate postnatal period in LBW infants likely represents fetal ventricular enlargement in some cases. The prevalence of ventricular enlargement reported in these studies however appear higher than that in earlier studies described below; this may be because the studies below defined ventricular enlargement as an axial diameter greater than 8 mm[12, 13].

Epidemiology and neurologic outcome of fetal ventricular enlargement

Mild fetal ventricular enlargement is the most common abnormality found on prenatal ultrasound scans [6]. The reported prevalence vary widely: 1.48 per 1000 births in a low risk population, 22 per 1000 births in a high-risk population [11, 14] and about 7 per 1000 in unselected pregnancies [8].

Mild fetal ventricular enlargement is described as 'isolated' when no associated cerebral or extracranial ultrasound abnormalities are detected at the time of initial

presentation; however, cases may subsequently be shown to have other anomalies. Isolated mild fetal ventricular enlargement may be unilateral, bilateral or asymmetrical; it is mostly non-progressive and the fetal head is usually of normal size. Isolated mild fetal ventricular enlargement on prenatal ultrasound is often a dynamic process – about 30% resolve spontaneously, 55% - 60% remain stable and in about 10% -15% of cases, progressive ventricular enlargement develops [15-25].

The neurologic outcomes in infants with isolated mild fetal ventricular enlargement have only been reported in case series, case reports and a couple of case control studies. The studies involved small numbers of infants and utilized mostly non-standardized methods of developmental assessments done at widely varying postnatal ages. A systematic review of such studies with a total of 577 cases, found an overall survival rate of 92.7%. Of 485 cases followed, 413 (85.2%) were developmentally normal, 38 (7.8%) had mild developmental delay and 34 (7.0%) had moderate or severe delay [26]. Another review of studies with more than 20 survivors to follow-up indicated the overall incidence of developmental delay range from 0% to 36%; 88.2% of the evaluated infants had normal development [Table 1.3] [6]. The neurologic outcome is more favorable when fetal ventricular enlargement is unilateral [22] and when there is prenatal resolution [23, 27]. However, the risk of developmental delay is higher in infants with

Table 1.3: Neurologic outcome of isolated mild fetal ventriculomegaly [adapted from Kelly et al [6]]

Authors (Year)	IMV (n)	Survived (n)	Followed (n)	Screening Test	Age at Testing (Months)	Normal (%)[b]
Arora et al (1998)	30	27	27	DDS	1.5-72	19 (70)
Bloom et al (1997)	62	60	22	BSID	21.6±17.4	14 (64)
Bromley et al (1991)	27	26	26	Unknown	3-18	21 (81)
Lipitz[a] et al (1998)	26	26	26	NA	Unknown	25 (96)
Patel et al (1994)	42	37	34	Unknown	1.5-70.3	28 (82)
Pilu et al (1999)	27	27	21	Interview / Phone	21-72	21 (100)
Robson et al (1998)	50	37	37	NA	Newborn	37 (100)
Vergani et al (1998)	45	45	45	M-C&G	3-72	45 (100)
Totals	**309**	**285**	**238**	---	**0-72**	**210 (88)**

[a] Unilateral ventriculomegaly; [b] Percentage of cases followed;

IMV – Isolated mild ventriculomegaly, BSID – Bayley Scales of Infant Development;

DDS – Denver Development Screening; M-C&G – Milani-Comparetti &Gidon;

NA – Not available

atrial width greater than 12 mm [24] and when other anomalies are detected on subsequent evaluations [22, 23].

Ventricular enlargement in low birth weight infants

Enlargement of the cerebral ventricles is present in 10 to 30% of VLBW infants evaluated with cranial ultrasound or magnetic resonance imaging in the first 2 to 4 days of life [1, 12, 13, 28]. An even higher proportion of VLBW infants have ventricular enlargement when imaging studies are repeated at term equivalent age [12, 13, 29]. In up to 50% of these infants, no radiologic evidence of prior GM-IVH is demonstrable. Factors associated with increased risk of VE in VLBW infants include extreme prematurity (28 weeks gestation or less), severe intraventricular hemorrhage, chronic lung disease and white matter injury [12, 13]. Ventricular enlargement in low birth infants may or may not be preceded by germinal matrix – intraventricular hemorrhage (GM-IVH).

Post hemorrhagic ventricular enlargement in low birth weight infants

Enlargement of the cerebral ventricle in the low birth weight infant occurs most often in infants with GM-IVH. A direct relationship exists between the severity of GM-IVH and the risk of ventricular enlargement; infants with moderate to severe GM-IVH have a higher risk of ventricular enlargement than infants with minor or no bleeds. While there is currently no universally accepted or satisfactory classification of the severity of GM-IVH, the Papile and Volpe classifications are most commonly used (Tables 1.4 & 1.5).

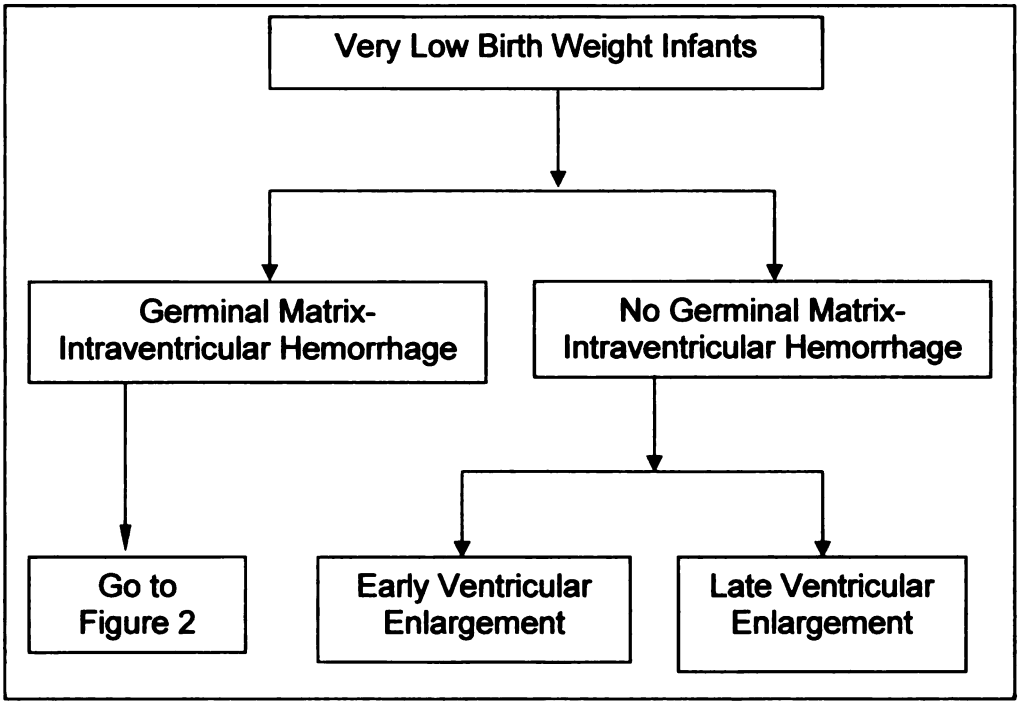
Table 1.4: Papile Classification of Germinal Matrix-Intraventricular Hemorrhage in Premature Infants[30]

SEVERITY	DESCRIPTION
Grade 1	Germinal matrix hemorrhage
Grade 2	Germinal matrix-intraventriventricular hemorrhage with blood within the lateral ventricles but no distention
Grade 3	Germinal matrix-intraventriventricular hemorrhage with blood filling and distending the lateral ventricles
Grade 4	Germinal matrix-intraventriventricular hemorrhage with parenchymal 'extension'

Table 1.5: Grading of Severity of Germinal Matrix-Intraventricular Hemorrhage by Ultrasound Scan ('Volpe classification')[31]

SEVERITY	DESCRIPTION
Grade 1	Germinal matrix hemorrhage with no or minimal intraventricular hemorrhage (10% of ventricular area on parasagittal view)
Grade 2	Intraventricular hemorrhage (10%-50% of ventricular area on parasagittal view)
Grade 3	Intraventricular hemorrhage (>50% of ventricular area on parasagittal, view usually distends lateral ventricle)
Separate notation	Periventricular echodensity (location and extent)

Figure 1.1: Ventricular enlargement in very low birth weight infants



The natural history of ventricular enlargement following GM-IVH has been well characterized (Figure 1.2) and extensively reviewed [31-33]. Infants with moderate to severe GM-IVH may experience an immediate, transient distension of the lateral ventricles by intraventricular blood – the so-called 'grade III IVH' on the Papile classification [30]; this may or may not be followed by progressive ventricular dilatation within days to weeks.

In about 65% of cases, a period of progressive ventricular dilatation often ensues after the initial diagnosis of GM-IVH; this is followed by spontaneous arrest and subsequent complete or partial resolution of ventricular dilatation. In these cases ventricular dilatation is not associated with excessive increase in occipito-frontal circumference or increased intracranial pressure ('normal pressure ventricular enlargement').

In another 30% of cases, an initial phase of slow ventricular dilatation is followed, in about 2 - 4weeks, by the development of post-hemorrhagic hydrocephalus

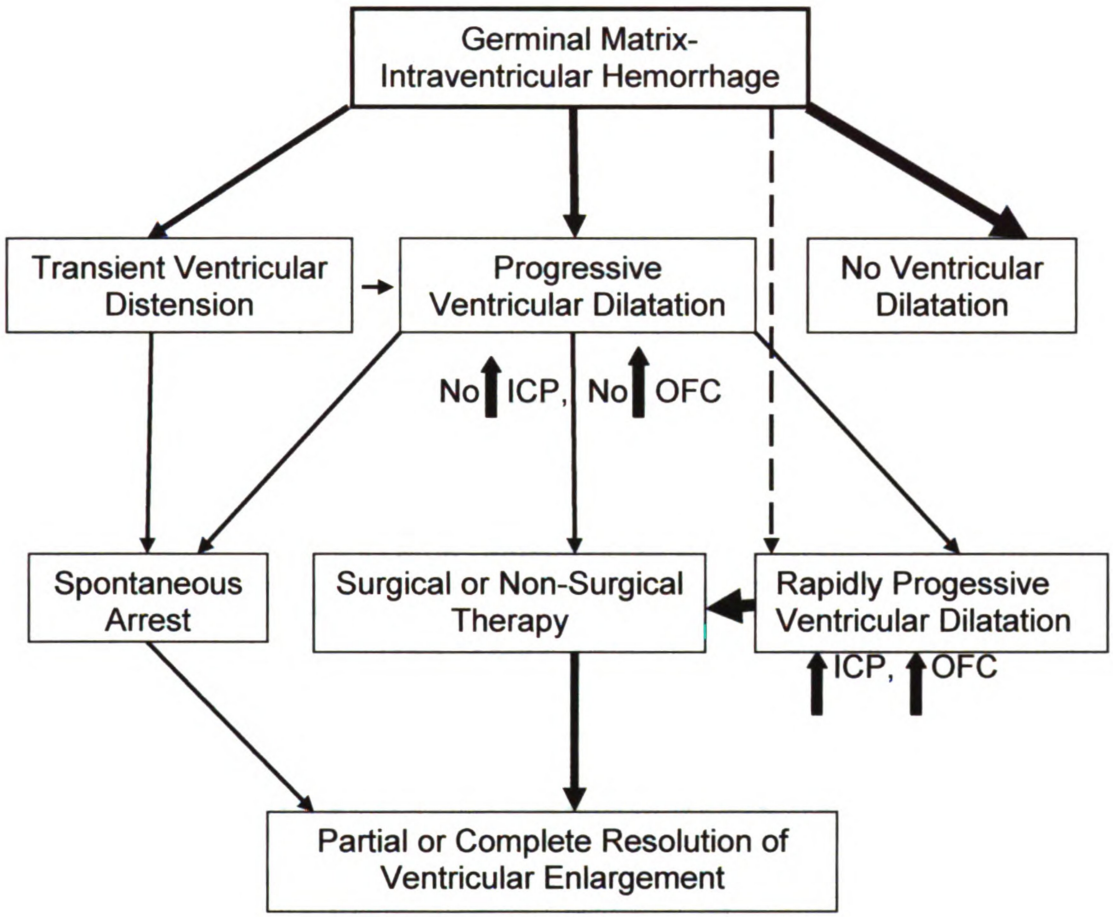
characterized by accelerated ventricular distension associated with raised intracranial pressure and greater than normal growth in occipito-frontal circumference requiring surgical and/or nonsurgical intervention for management. Lastly, in about 5% of cases, rapidly progressive ventricular enlargement ensues within days of the initial detection of GM-IVH in infants with the most severe grades of hemorrhage.

'Normal pressure' ventricular enlargement

In her original autopsy study of intraventricular hemorrhage in preterm low birth weight infants, Larroche found several infants with ventricular enlargement and normal head growth [34]. This phenomenon was later confirmed in vivo by several investigators who demonstrated the presence of ventricular dilatation by CT scan or ultrasonography prior to any increase in occipito-frontal head circumference or the onset of clinical features indicative of raised intracranial pressure in infants with intraventricular hemorrhage [35-37]. This phenomenon may occur after any grade of intraventricular hemorrhage and probably results from partial obstruction to the normal flow and absorption of cerebrospinal fluid (CSF) within the ventricular system (Figure 1.3). The obstruction is probably caused in part by an obliterative arachnoiditis affecting principally the posterior fossa; less commonly, the obstruction may also be due to blood clot and other cellular debris [34].

Studies of the natural history of GM-IVH indicate that normal pressure ventricular enlargement occur in 15% to 30% of LBW infants with GM-IVH (Table 1.6).

Figure 1.2: Natural history of germinal matrix – inrtraventricular hemorrhage in very low birth weight infants

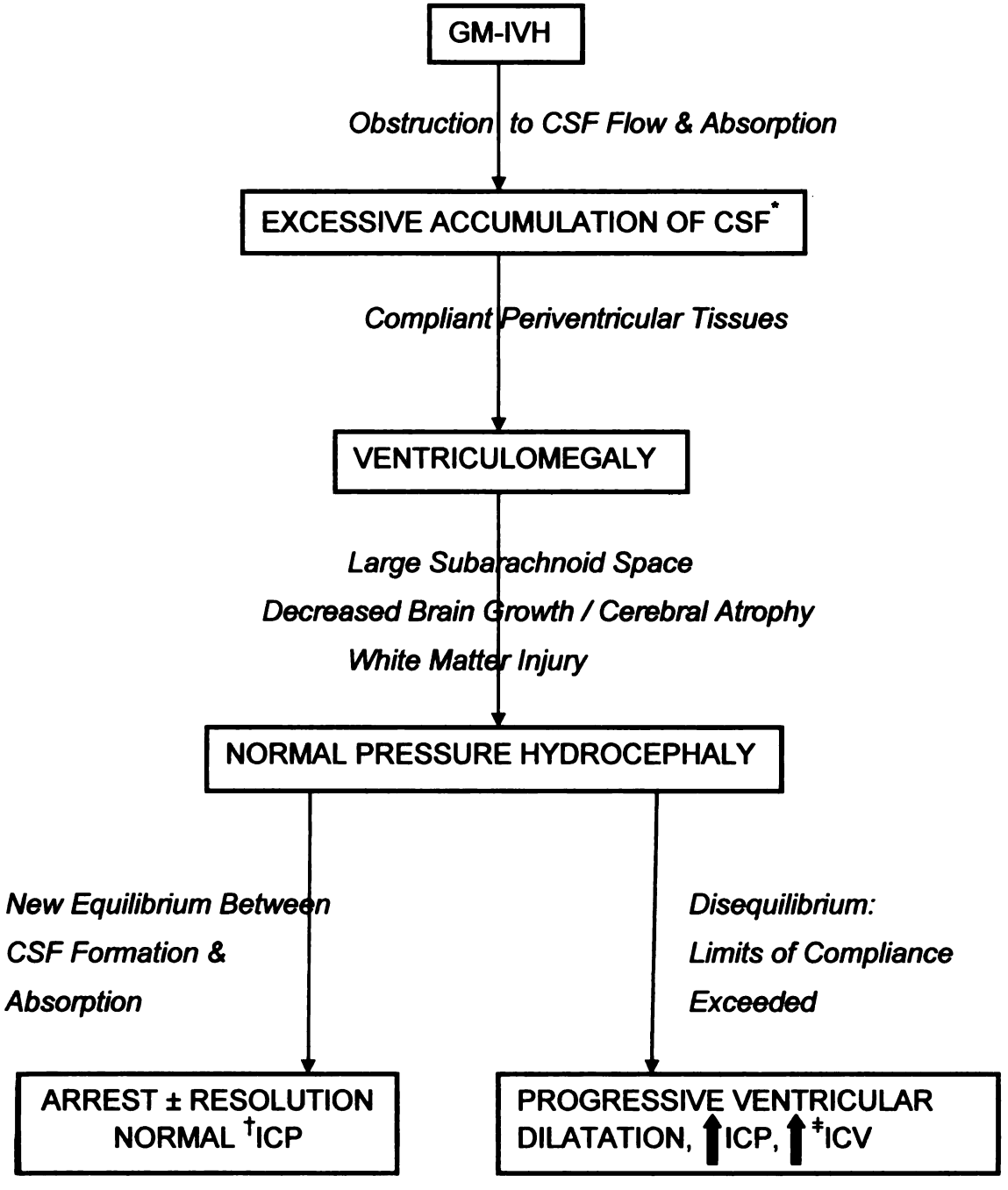


ICP- Intracranial pressure, OFC – Occipito-frontal circumference

Normal pressure ventricular enlargement (Figure 1.3) is thought to result from:

1) Increased compliance of the periventricular tissue due to the immature state of development and possible prior hypoxic-ischemic or compressive injury to the immature brain.

Figure 1.3: Evolution of ventricular dilatation following GM-IVH [Modified from Hill et al 1983[33]]



*CSF – Cerebrospinal fluid, †ICP – Intracranial pressure, ‡ICV – Intracranial volume

Table 1.6: Frequency of normal pressure ventricular enlargement in low birth weight infants with germinal matrix – intraventricular hemorrhage

Author (Year)	GM-IVH (n)	No Ventricular enlargement (%)	NP Ventricular enlargement (%)
Hill et al (1981)	87	47 (54)	20 (23)
Ahmann et al (1980)	77	35 (45)	12 (16)
Dykes et (1989)	409	254 (62)	125 (30)
Levene et al (1981)	68	24/39 (62)	11/39 (28)
Enzmann et al (1985)	115	90 (78)	22 (19)

NP – normal pressure, GM-IVH – germinal matrix – intraventricular hemorrhage

2) The presence of a large subarachnoid space over the cerebral convexities in preterm infants may also be contributory. The continued accumulation of CSF within the ventricular system leads to progressive ventricular enlargement with normal intracranial pressure (ICP) until the limits of periventricular compliance are exceeded (Figure 1.3).

3) Ventricular enlargement associated with neonatal intracranial hemorrhage may not be explained by obstruction to CSF flow and absorption alone. Decreased brain growth and cerebral atrophy as a result of injuries to the cerebral white matter, cortical and deep cortical gray matter have been described even in infants with uncomplicated [38] and mild grades (I & II) of IVH [39]. The ventricles enlarge to replace tissue loss from parenchymal brain injury, hence ventricular enlargement.

Post hemorrhagic hydrocephalus

Post hemorrhagic hydrocephalus (PHHC) has been defined as "the progressive accumulation of cerebrospinal fluid (CSF) in the ventricles and/or subarachnoid space resulting from obstruction to the normal CSF pathways directly due to hemorrhage into the CSF space" [32]. Thus, in PHHC the ventricles are distended (*not merely enlarged*) by accumulation of CSF (*not simply by large volume of intraventricular blood*). These changes may be accompanied by clinical signs of raised intracranial pressure, excessively rapid increase in occipito-frontal head circumference associated with rapidly progressive enlargement of the cerebral ventricles necessitating medical and / or surgical intervention. These changes may be delayed for days to weeks following the initial detection of intraventricular hemorrhage. In a review of studies of GM-IVH in preterm low birth weight infants, the rate of PHHC ranged from 3 – 15%; when all the studies were pooled, the rate of PHHC following any GM-IVH was about 10% (Table 1.7).

Factors associated with increased risk of PHH in these studies include:

1) Gestational age of the infant at birth - the more premature the infant, the higher the risk of posthemorrhagic ventricular enlargement;

2) Timing of the bleed – the earlier bleeds, especially bleeds in the first 24 hours of life, tend to be more severe and are associated with higher rates of posthemorrhagic ventricular enlargement.

3) The severity of initial bleed – this is the most important determinant of PHHC; bleeds of grades III or worse are more likely to be complicated by PHHC than grades I and II bleeds.

Table 1.7: Frequency of GM-IVH, GM-IVH associated mortality and PHH following GM-IVH in very low birth weight infants.

Author (Year)	Study & Infant Characteristics	GM-IVH Rate	GM-IVH Mortality Rate	*PHH Rate
Ahmann PA, (1980)	N=191, GA < 35 wks, Single center,	77/191 (40%)	22/77 (28%)	8/77 (10%)
Smith WL et al, (1983)	N=92, Bt wt < 2kg, Single center	29/92 (31%)	8/29 (28%)	1/29 (3%)
Ment LR, (1984)	N= 438, Bt Wt ≤1250g, Single center,	95/228** (42%)	27/133 (20%)	5/95*** (5%)
Enzmann D, (1985)	N=377, Bt Wt ≤1500g, Prospective, single center	115/377 (30.5%)	19/115 (16%)	22/377 (6%)
Murphy BP, (2002)	N=1127, Bt Wt ≤1500g, Multi-hospital study	248/1127 (22%)	54/248 (22%)	37/248 (15%)
Larroque B (2003)	N=2667, GA 23-32wks, Multi-hospital study	613/2667 (23%)	84/613 (14%)	80/613 (13%)
Total		**1177/4682 (25%)**	**214/1215 (17%)**	**145/1439 (10%)**

** - Survived first 36 postnatal hours *** - Survived first postnatal week

Ventricular enlargement without prior GM-IVH ('isolated ventricular enlargement)

Data from cranial ultrasound [40], computed tomography scans [41], and more recently, magnetic resonance imaging (MRI) studies [12] indicate that ventricular enlargement occurs in preterm low birth weight infants without prior GM-IVH.

In a recent survey of very low birth weight infants born between 23 and 30 weeks gestation, 119 infants were studied with serial MRI scans [12]. Thirty-six infants (30%) had ventricular enlargement identified on the initial scan carried out on the second day of life, raising the possibility that some cases of ventricular enlargement are prenatal in origin. Twenty of the 36 infants (55%) with ventricular enlargement had no prior IVH. The proportion of infants with ventricular enlargement increased from 30% to 39% (36/119 to 47/119) on the final scan done at term equivalent age; 22 (47%) of these infants did not have prior IVH [12] indicating that VE may also develop postnatally in VLBW infants in the absence of a history or neuroradiographic evidence of GM-IVH. The explanation for the higher estimate of VE reported by Dyet et al compared to the other reports listed in Table 1.8 is not exactly clear. It may be related to several factors including:

a) The use of MRI in their study - the other studies listed in the table utilized CT or ultrasound scans. MRI scans have been shown to be more sensitive than ultrasound scans in the identification of white matter injury and ventricular enlargement in VLBW infants[42].

Table 1.8 – Prevalence of ventricular enlargement in absence of germinal matrix - intraventricular hemorrhage

Author (Year)	Infant & Study Characteristics	Prevalence	Criteria for diagnosis of VE
Ancel P, (2006)	N=1929, GA 22-32 wk, CUS, Multicenter cohort	98/1929 (5.1%)	Judgment
Larroque B, (2003)	N=2667, GA 23-32 wk, CUS, Multicenter hospital study	133/2667 (5.0%)	Judgment
De Felice C, (2001)	N=483, Bt Wt 500-3850g, CUS, Single center	35/483 (7.2%)	Measurement*
Kuban K, (1999)	N=1310, Bt Wt 500-1500g, CUS, Multicenter hospital study	10/1310 (0.8%)	Judgment
Smith WL, (1983)	N=92, Bt wt < 2kg, CUS, Single center	4/92 (4.3%)	Judgment
Aziz K, (1995)	N=669, Bt Wt 500-1249g, Survivors to 1yr, CUS, Population based study	8/669 (1.2%)	Measurement**
Ment LR, (1984)	N=228, Bt Wt ≤ 1250g, CUS, Single center	5/228 (2.2%)	
Dyet, LE et al (2006)	N=119	20/119 (16.8%)	Measurement†
Total	**N=7454**	**313/7454 (4.2%)**	

CUS – Cranial ultrasound; GA – Gestational age

*Lateral ventricle width greater than 97th centile for postconceptual age

**Lateral ventricle greater than 2 SDs above the mean for gestational age[43]

† Axial diameter >8mm at GA ≤25 wk; axial diameter >10mm at GA >25 wk[12]

b) Dyet et al used lateral ventricle axial diameter > 8mm at GA ≤25 week or diameter >10mm at GA >25 week [12]as criteria for VE; this is different from the criteria used in the other studies listed,

c) A large proportion of the infants evaluated in data reported by Dyet had diffuse white matter abnormalities and widened extracerebral space. The pathogenesis of these changes is likely multi-factorial and the lesions could have contributed to the higher prevalence of VE in the cohort,

d) The study was hospital based and was conducted in a quaternary medical center; there may have been an unduly high representation of very sick VLBW infants in the study population.

It has been suggested that ventricular enlargement without prior GM-IVH may be as common as ventricular enlargement associated with GM-IVH [41, 44]. Ventricular enlargement in VLBW infants without documented GM-IVH has not been systematically studied. In a case control follow-up study of outcomes in newborns with abnormal cranial ultrasound findings, Garfinkel et al [40] performed serial cranial ultrasounds at less than 24 hours of age and on the third and seventh day of life. They identified a subset of infants with ventricular enlargement with no evidence of hemorrhage. The outcomes for infants with ventricular enlargement and no prior GM-IVH were comparable to the outcomes in infants with grades III and IV periventricular – intraventricular hemorrhage. Several cranial US and more recently MRI studies indicate the prevalence of VE in VLBW infants range from 1 to 5 percent [45-51]. From these studies, factors that appear to contribute to VE include degree of prematurity; perinatal asphyxia, severity of initial and later

respiratory illness, multiple gestation and perinatal infection. The numbers of infants with VE in these studies have been small and the maternal, prenatal and perinatal risk factors for VE were not determined. This is important because VE is widely accepted as a marker of white matter injury (WMI) and there is a direct correlation between WMI on brain imaging studies and the risk of cerebral palsy in VLBW infants. Furthermore, there have been few population based studies of the long-term cognitive and neuromotor outcomes of infants with VE.

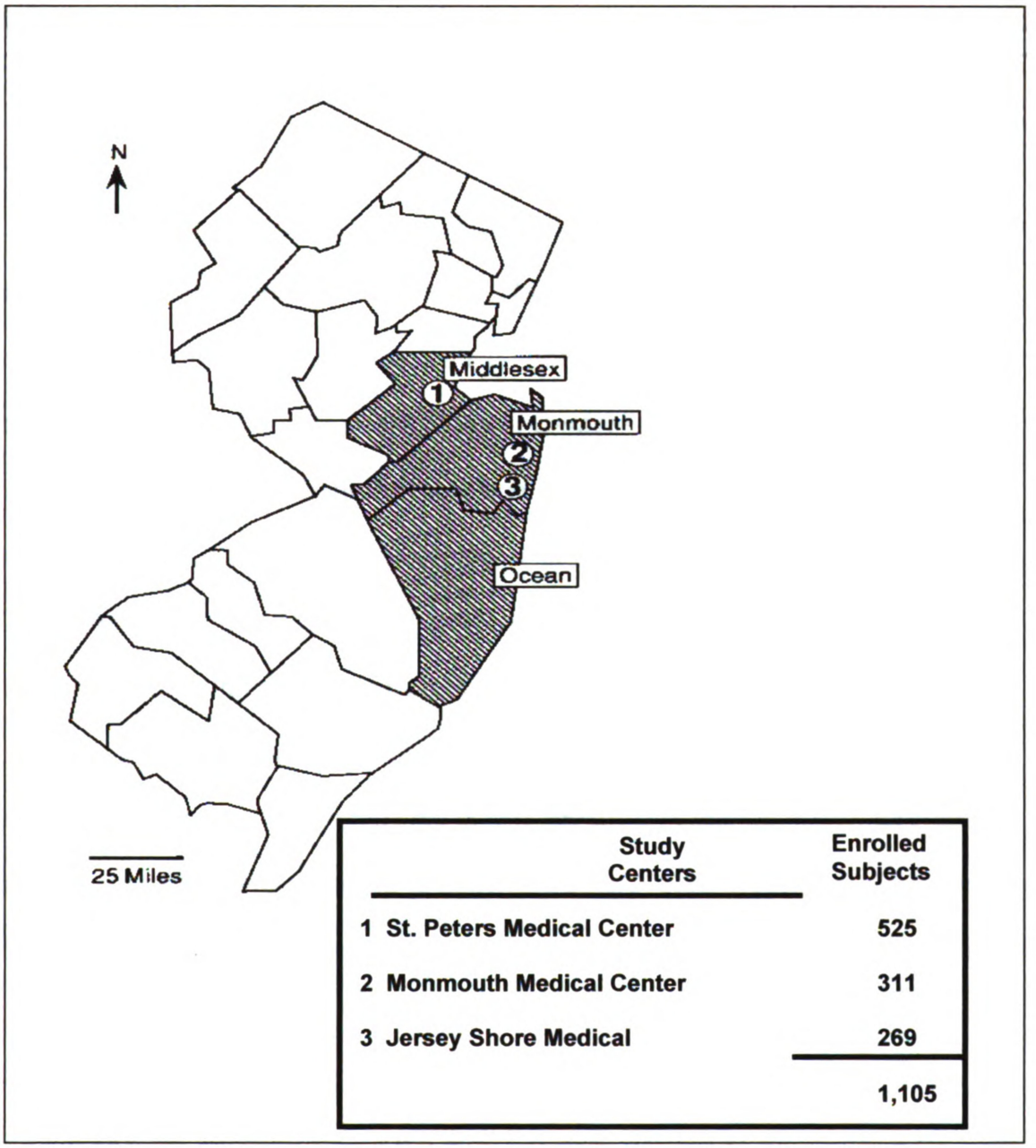
The Newborn Brain Hemorrhage (NBH) study, a large population-based study of intraventricular hemorrhage in preterm low birth weight infants (birth weight ≤ 2000 g), presents an opportunity for in-depth study of VE as a number of infants in the study were noted to have ventricular dilatation prior to the documentation of any intraventricular hemorrhage.

CHAPTER 2

i) THE NEONATAL BRAIN HEMORRHAGE STUDY

Brief description

Figure 2.1: New Jersey counties served by the NICUs in the NBH study[52].



	Study Centers	Enrolled Subjects
1	St. Peters Medical Center	525
2	Monmouth Medical Center	311
3	Jersey Shore Medical	269
		1,105

The Central New Jersey Neonatal Brain Hemorrhage (NBH) Study was designed

to determine the antecedents and consequences of germinal matrix intraventricular hemorrhage (GM-IVH) in a large cohort of unselected low birth weight infants. The study also explored correlations of cranial US and neuropathologic findings in infants that succumbed in the neonatal period. Details of the NBH study have been described in several previous publications [1, 52-55].

Infant enrolment and study sites

Over a period of 34 months from August 1984 to June 1987, live-born infants that met the study birth weight criteria of 501 to 2000g were enrolled prospectively into the NBH study at three participating neonatal intensive care units. The three units are located at Jersey Shore Medical Center (JSMC) in Neptune, Monmouth Medical Center (MMC), Long Branch, and St Peter's Medical Center (SPMC) New Brunswick in the three New Jersey counties of Middlesex, Monmouth and Ocean respectively [see Figure 2.1]. Prior to the study, an analysis of hospital admission data along with New Jersey birth certificates for the above three counties, indicated that 85 % of infants with birth weight 501 – 2000 g were born at or cared for at the three study sites. Moreover, 90% of infants with birth weight of 1500 g or less were cared for at the study sites[52]. However, while 7-8% of the three counties population were noted to be African-Americans in the 1980 and 1990 census data, 26% of the study population were African-Americans[52]. Furthermore, about 25% of infants enrolled were products of multiple gestations but not all such infants entered the study as some co-twins were above the birth weight criterion or were still born[52]. The high proportions of African-American

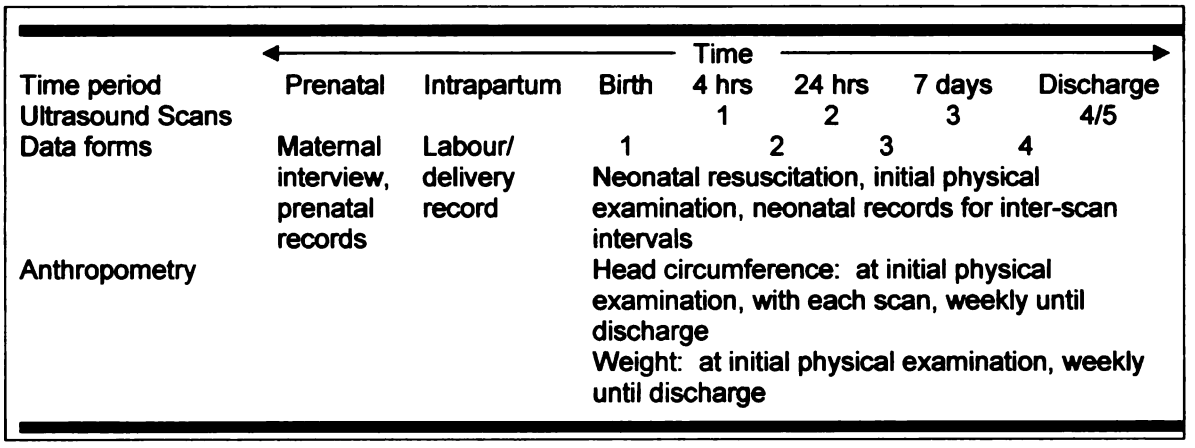
infants and products of multiple gestation in the study population is in line with the known contributions of race and multiple gestation to the high rates of low birth weight[56].

Maternal interviews, maternal and neonatal chart abstraction

The design of the NBH study has been described in detail elsewhere [52, 53]. In summary, 1105 infants with birth weights 501 - 2000g managed in the study hospitals were enrolled into the study. Of this number, 982 (89%) were delivered at the study hospitals while 123 (11%) were transferred to the study hospitals from elsewhere. Variables relevant to brain hemorrhage in low birth weight infants were obtained from maternal interviews conducted by trained nurses soon after delivery, and from abstraction of the mothers' and infants' medical records. At the maternal interview, information was requested on reproductive and contraceptive history; history of the index pregnancy including illnesses, medication, tobacco, alcohol and drug use by trimester of pregnancy, and feelings and attitudes towards the pregnancy and delivery[53].

Trained research nurses abstracted maternal prenatal, labor and delivery records onto data forms designed for the study. Data obtained from the infants' medical records included neonatal resuscitation data, initial physical examination, postnatal physical signs, physiologic measurements, diagnoses and pertinent laboratory findings. The later data were separately recorded for each interval between cranial ultrasound scans [see Figure 2.2] [53].

Figure 2.2: Data collected in the neonatal period in the NBH study[52].



Cranial ultrasound procedures and interpretation

All the CUS scans in the NBH study were performed by trained, hospital based ultrasound technologists (sonographers). The sonographers participated in a special training session, prior to recruitment of study subjects, to become familiar with neonatal neuroanatomy and learn the proper techniques for obtaining the protocol images. Details of the cranial ultrasound protocol and interpretation in the NBH study have been published elsewhere [52, 57].

In the NBH study, cranial ultrasound scans (US) were performed prospectively on 1,088 of the 1,105 (98.5%) infants in the cohort. The scans were performed as closely as possible to ages 4 hours, 24 hours and 7days [53]. Scans were obtained using Diasonic DFR sector scanners (Diasonics Inc., San Francisco) equipped with 5 - 7.5 MHz transducers. Ultrasound technologists obtained six coronal and six parasagittal views through the anterior fontanel using acoustic gel to couple the transducer to the skin to improve transmission of the sound beam.

While no explicit criteria were developed for the identification of ventricular enlargement in the NBH study, study ultrasound technicians were requested to judge enlargement separately for the third, fourth and each lateral ventricle and to grade any enlargement as mild, moderate or severe on each cranial ultrasound scan.

All study cranial US scans were initially read by one of five radiologists based at the hospital from which the film originated. All films were independently read again either by one of two outside readers who were consultants to the study or by another of the participating radiologists but from a different hospital. Both readers recorded ultrasound data on a form that reported observations ('normal', 'abnormal echodensity', 'abnormal echolucency' and 'structure not visualized') and interpretations ('ventricular enlargement', 'germinal matrix hemorrhage' and 'ventricular hemorrhage') separately. Concordance on presence or absence, location and laterality of an observed and interpreted lesion or ventricular enlargement constituted agreement and the accepted interpretation. Scans were submitted to a third reader in case of disagreement as to the presence or absence or time of onset of a lesion for a consensus as described elsewhere [53]. The radiologists were provided the infants' birth weight but were blinded to the infants' clinical information and to previous ultrasound reading(s).

Several months after initiation of the study, a predischarge CUS scan was added to the protocol; infants hospitalized for long enough periods also had CUS at 5 weeks and at about monthly intervals until discharged [1]. This allowed for

improved detection of white matter damage and monitoring of ventricular enlargement in the study infants.

Head circumference measurements

Study neurologists trained the ultrasound technologists to measure head circumferences of study infants. The technologists measured the Infants' head circumference at each cranial ultrasound scan. The attending neonatologist or pediatric resident physician also measured the infants' head circumference on admission. The reliability of head circumference measurements by ultrasound technologists has been reported elsewhere[58]. The Pearson correlation coefficient between measurements obtained by technologists and admitting physicians on initial physical examination was 0.93.

Follow-up examination

Follow-up assessment was obtained at 2 years corrected age (based on mother's last menstrual period) on 777 (86.2%) of the 901 survivors: 721 (80%) by examination while clinical information was obtained by mail or phone interview in 56 (6.2%) children who had moved out of state. Details of the results and procedures of the 2-year follow-up evaluation have been published elsewhere [1]. In brief, the 2-year assessment focused on detection of major developmental handicaps especially cerebral palsy (CP). Initial assessment of motor development, hearing, vision, and neurologic status were performed by a pediatric nurse practitioner specially trained for the project. Study infants' motor

tone, extrapyramidal movements and tendon reflexes in all limbs were assessed quantitatively and scored on an ordinal scale. The nurse also documented the preservation of primitive reflexes and measured the range of hip abduction and extension, popliteal extension and ankle dorsiflexion. When abnormalities were suspected, infants were referred to one of four consultant child neurologists who were unaware of the nurse's specific findings, for further evaluation and classification of CP by subtype [1].

Objective of the present analysis

While the NBH study was designed to study the prenatal and perinatal antecedents and outcomes of GM/IVH in infants with birth weights 501 to 2000 g, some infants were found with ventricular enlargement with or without GM/IVH. Of the 1019 infants with cranial US diagnoses in the neonatal period, 171(16.8%) had isolated GM/IVH with no ventricular enlargement. One hundred and twelve infants (11%) had parenchymal echodensities / echolucencies or ventricular enlargement, in either case with or without GM/IVH. This latter group of infants likely had sonographic appearances consistent with damage to the white matter [1]. At the two-year follow-up evaluation, this group of infants had a 15-fold increased risk of disabling cerebral palsy (DCP) compared to infants with normal scans [1]. However, infants with VE in the absence of GM/IVH in the NBH study have neither been identified nor studied separately and little is known of the perinatal risk factors, approximate time of onset and long-term outcomes of low birth weight infants with VE without prior GM/IVH. This is an important group of

infants to study because VE is widely regarded as a sonographic evidence of focal and / or diffuse white matter injury [59, 60], and white matter injury is associated with a significantly increased risk of poor neurodevelopmental and cognitive outcomes [1].

Ventricular enlargement without prior GM/IVH is becoming an increasingly recognized pattern of brain injury in low birth weight and very low birth weight infants. For example, in a recent brain MRI study of a sequential cohort of VLBW infants at a median age of 2 days, about 15% of the infants had VE without prior GM/IVH [28]. A clear understanding of the perinatal risk factors associated with this complication of prematurity is imperative in order to plan effective preventive strategies.

This analysis of the NBH study data was therefore undertaken with the following objectives:

1) To identify the prevalence of ventricular enlargement without prior intraventricular hemorrhage ('isolated ventricular enlargement') in a population of low birth weight infants
2) To identify the prenatal and perinatal antecedents of isolated ventricular enlargement in low birth weight infants
3) To determine the 2-year neurodevelopmental outcomes in infants with isolated ventricular enlargement.

Suitability of the NBH data set for the study of isolated ventricular enlargement

The NBH data was obtained from a large population study carried out in three centers located in the three New Jersey counties of Middlesex, Monmouth and Ocean. The study enrolled a large number of infants with birth weights 501 to 2000gm. From previous census data, it was estimated that approximately 85% of infants that met the birth weight criterion for enrolment into the study in the three study counties, were delivered and / or cared for at the study centers. Enrolment of infants from the three study centers therefore provided for a good opportunity to obtain a representative sample of the target study population.

Secondly, the NBH study utilized a rigorous CUS protocol that paid close attention to infants' age at time of study. The first protocol scan was obtained at close to 4 hours of age. This is relevant to this analysis as ventricular enlargement detected at this age is likely to be related to prenatal and / or perinatal factors. Furthermore, accurate timing of the initial and subsequent scans allowed for rational evaluation of the antecedents and factors associated with the progression or non-progression of early cranial ultrasound abnormalities in the study infants.

Thirdly, the antecedents, risk factors and neurocognitive outcomes of ventricular enlargement following GM/IVH (post hemorrhagic ventricular enlargement) have been studied extensively and are well described [31-33]. There are so far, very limited numbers of studies of low birth weight infants with ventricular enlargement in the absence of a prior GM/IVH. A good number of infants in the NBH study

also had ventricular enlargement following GM/IVH. Therefore, the NBH data set provides an excellent opportunity to study the prenatal, perinatal and postnatal correlates and long-term neurocognitive outcomes in infants with isolated ventricular enlargement; it also provides us with the opportunity to compare and contrast infants with VE and GM/IVH and infants with VE without prior IVH.

ii) METHODS

Identification of infants with isolated ventricular enlargement (cases) and selection of comparison groups (controls) from the NBH dataset

We performed a search of the archived, electronic NBH database to identify infants in whom any ventricular enlargement (VE) had been documented. VE was said to be present when there was **any** enlargement (mild, moderate or severe) of at least one lateral ventricle based on the consensus of two study radiologists. The assessment of ventricular enlargement in the NBH study was therefore by *judgment* and not by an objective *measurement.*

Infant classification

Infants with ventricular enlargement were classified as having *isolated ventricular enlargement* (VE) if there was no associated GM/IVH prior to, or at the time of, initial identification of ventricular enlargement.

Infants were classified as *ventricular enlargement with hemorrhage* (VE+HE) if CUS demonstrated any GM/IVH prior to or at the time of initial detection of VE. On the other hand, infants with GM/IVH and no ventricular enlargement at any time were classified as *hemorrhage only* (HE).

Infants with neither ventricular enlargement nor GM/IVH at any time were classified as *normal scans* (Normal) and served as another comparison group.

Data collection

We pulled and reviewed the original data forms of the infants with VE including prenatal forms, pregnancy and delivery history, neonatal data forms and ultrasound interpretation forms. Data extracted from the sheets included:

1) Maternal history and demographic information – including age, maximum educational level attained, history of smoking, alcohol and illicit drug use;

2) History and complications of pregnancy – including infections, hypertensive disorders of pregnancy, vaginal bleeding;

3) Labor and delivery data including mode of delivery, duration of membrane rupture, duration of labor, Apgar scores at 1 and 5 minutes, chorioamnionitis, placental and umbilical cord abnormalities; and

4) Infant data including birth weight, head circumference, CUS results and death; we also reviewed the follow-up records at 2 years of age for neuromotor and cognitive functions.

The same data were extracted from the archived electronic NBH database for the three comparison groups.

Statistical Methods

Characteristics of mothers and infants in the VE, VE+HE, HE and Normal groups were compared and p-values calculated. Means and standard deviations were

calculated for continuous variables and the groups compared with student t-test while categorical variables were compared with chi-square and Fishers exact test. Conditional logistic regression was used to estimate effect of perinatal factors on the occurrence of VE, VE+HE and HE for matched pairs. Mortality, cerebral palsy (CP) and disabling cerebral palsy (DCP) rates were compared among the three groups. Risks of death, CP and DCP by exposure to VE, VE+HE or HE were estimated. Statistical analysis was with SAS statistical software (SAS Institute Inc., Cary, NC,).

CHAPTER 3

RESULTS – ANTECEDENTS AND OUTCOMES OF ISOLATED VENTRICULAR ENLARGEMENT IN THE NEONATAL BRAIN HEMORRHAGE (NBH) STUDY

A search of the archived electronic NBH database, and review of the stored forms, showed that 23 of 1088 infants (2.1%) that had at least one protocol CUS scan met our definition of isolated ventricular enlargement (VE). These constituted the study subjects. Eighty-seven infants (8.0%) had ventricular enlargement noted either at the time of initial identification of GM-IVH or at subsequent cranial US scans (VE+HE). One hundred seventy infants (15.6%)

Table 3.1: Frequency distribution of infants in the NBH study by cranial ultrasound results

Cranial Ultrasound Results	Frequency (%)
Isolated ventricular enlargement (VE)	**23 (2.1)**
Isolated germinal matrix – intraventricular hemorrhage (HE)	170 (15.6)
Germinal matrix – intraventricular hemorrhage and ventricular enlargement (HE+VE)	87 (8.0)
Normal scans (Normal)	808 (74.3)
Total	**1088 (100)**

Table 3.2: Some characteristics of infants with ventricular enlargement in the absence of germinal matrix intraventricular hemorrhage (VE)

Infant ID	Gender	Best Gestational Age (wks)	Birth Weight (gm)	Head Circumference (cm)*	5 min Apgar Score
84102700	Female	27.3	800	24	7
84300500	Male	28.3	1035	27	7
84301300	Male	30.7	1295	26.5	6
84303900	Male	28.0	1020	26	7
85105500	Male	27.6	1280	27.5	4
85107100	Male	26.6	1070	25.2	9
85109600	Male	30.3	1800	29.5	8
85110000	Male	33.9	1765	28	9
85112100	Male	31.6	1795	29	5
85207500	UTD†	30.0	1332	23.5	2
85313400	Female	36.4	1850	30	6
86116000	Male	30.4	1500	29	0
86116300	Male	29.1	1134	27	8
86118700	Female	29.9	1430	28	8
86119500	Female	27.7	.	.	.
87121600	Male	36.6	1380	30.2	5
85110602	Male	35.4	1775	33.8	8
85311702	Male	23.0	590	21	3
86119802	Male	33.1	1580	30.5	7
86217102	Female	28.9	1430	28	6
86336202	Male	29.0	1600	30	7
87344702	Female	31.7	1820	31	9
87345802	Female	31.6	1500	29.5	8

*Head circumference measured at initial physical exam

†UTD – Unable to determine

had germinal matrix – intraventricular hemorrhage without documented ventricular enlargement (HE) in any CUS scan. Eight hundred and eight infants (74.3%) had neither ventricular enlargement nor GM/IVH at any time (Normal Scans). The latter three groups constituted our comparison groups (Table 3.1). Of the 23 infants with VE, 15 (65.2%) were male and 8 (34.8%) had 5-minute Apgar score less than 7 (Table 3.2). Three of the 23 infants with VE subsequently developed GM-IVH (late onset GM-IVH) after the identification of ventricular enlargement; the other 20 infants remained free of GM/IVH. The infants with 'late onset GM-IVH' were all males, and their gestational age, birth weight and 5-minute Apgar scores are shown in Table 3.3.

Table 3.3: Some characteristics of infants with initial IVE, but later developed germinal matrix intraventricular hemorrhage

Infant ID	Gender	Best Gestational Age (wks)	Birth Weight (gm)	Head Circumference (cm)*	5 min Apgar
86116000	Male	30.4	1500	29	0
85311702	Male	23.0	590	21	3
86336202	Male	29.0	1600	30	7

Note: Head circumference measured at initial physical exam.

Seven (30.4%) of the cases of VE were products of multiple gestation; they were all the 2nd of a pair of twins. There were no higher order multiples among the cases. The cases that were products of twin gestation had similar birth weight and gestational age to the singleton cases (Table 3.4). Among the infants with

normal scans, 22.8% were products of twin gestation while 2.4% were of higher order multiple gestations, giving a multiple gestation rate of 25.1%. On the other hand, of the infants with HE+VE, 19.5% were twins while 4.6% were higher order multiples, with a multiple gestation rate of 24.1%. The multiple gestation rate was similar in the cases and comparison groups.

Table 3.4: Low birth weight infants with isolated ventricular enlargement: comparison of singletons and products of twin gestations

Characteristics	Singletons (N=15)	Twin Gestations (N=7)	P-Value
Best gestational age (wks)	30.3±3.0	30.4±3.9	NS
Birth weight (gm)	1365±326	1470±412	
Head circumference (cm)	27.3±2.0	29.1±3.9	
Males (%)	11/15 (73)	4/7 (57)	
5 min Apgar (median)	7	7	

Characteristics of cohort infants by cranial ultrasound findings

The characteristics of the four groups of cohort infants that had CUS scans are shown in Table 3.5. The mean gestational age, birth weight and head circumference at birth were significantly different among the 4 groups: the VE+HE group had the lowest gestational age, birth weight and smallest head circumference at birth (P<0.0001). The frequency of small weight for gestational age (SGA) was also different between the groups. Of the infants with ventricular enlargement, small weight for gestation was more frequent among infants with

GM-IVH than among infants with isolated ventricular enlargement. Of note, infants with Normal US scans had the highest rate of SGA.

Table 3.5: Characteristics of all cohort infants with IVE, VE+HE, HE and Normal CUS scans

Characteristics		VE (n=23)	VE+HE (n=87)	HE (n=170)	Normal Scans (n=808)	P-value
Gestational age (wks)		30.3 ± 3.0	28.7 ± 3.8	29.6±3.3	31.5 ± 3.4	<0.0001
Birth wt (gm)		1399 ± 349	1126 ± 364	1248±382	1464 ± 392	<0.0001
OFC[f] (cm)		27.9 ± 2.8	26.1 ± 2.7	26.5±2.8	28.1 ± 2.8	<0.0001
Percent *SGA		13.0	24.1	18.8	31.2	<0.0001
5 minute Apgar	Median	7.0	7.0	7.0	8.0	<0.0001
	< 7 (%)	40.9	46.9	28.8	18.2	<0.0001
Male Gender (%)[†]		65.2	59.7	55.3	49.6	0.007
Ventilation days (median)[‡]		3	9	4	0	0.01
Oxygen days (median)[‡]		5	10	6	1	0.0007
Cord pH ≤ 7.25 (%)		36.4	36.3	27.2	29.2	0.45
First CO_2 ≤ 30 (%)		19.0	33.7	35.6	35.4	0.48
[π]BPD (%)		13.0	24.1	16.4	7.8	<0.0001

[†]Fisher's Exact Test, [‡] Among infants with durations greater than 0, *Small for gestational age [π] Bronchopulmonary dysplasia, [f]Occipito-frontal circumference

Infants with VE tends to be more mature, have higher birth weight and head circumference at birth compared to infants with VE+HE and HE only. All these measurements tended to be greater in infants with Normal scans compared to the other 3 groups. There was a slight male preponderance among infants with abnormal CUS scans compared with infants with normal scans. The proportion of infants with 5-minute Apgar score less than 7 was higher among infants with VE and VE+HE than in infants with HE and Normal scans.

Infants with VE were more likely to be males compared to the other groups but infants with VE+HE were more likely to require assisted ventilation and supplemental oxygen for more days compared to the other groups. They also had a higher rate of bronchopulmonary dysplasia compared to the other groups. However, there was no significant difference between cord pH and initial $PaCO_2$ in all 4 groups.

Rate of detection of ventricular enlargement in the VE and VE+HE groups

Proportion of infants with ventricular enlargement was higher at each of the first three scans in the HE+VE group compared with infants with VE. (Table 3.6). There was a sharp increase in the proportion of infants with ventricular enlargement on the 3rd scan in the group with VE+HE (Figure 3.1). The frequency of detecting new onset ventricular enlargement was similar in both groups at the 4th and later scans. The second CUS obtained at 13 – 48 hours of life yielded only one new VE case; however, there was a sharp increase in detection of new cases on the 3rd scan. In infants with GM-IVH, the rate of detection of new ventricular enlargement was similar on the 1st and 2nd scans,

followed by a significant increase on the 3rd scan. By the 4th and subsequent scans, the rate of detection dropped off in the VE+HE group but continued to rise in the infants with isolated ventricular enlargement.

Table 3.6: Frequency of isolated ventricular enlargement (VE) and ventricular enlargement associated with GM-IVH (VE+HE) at each CUS

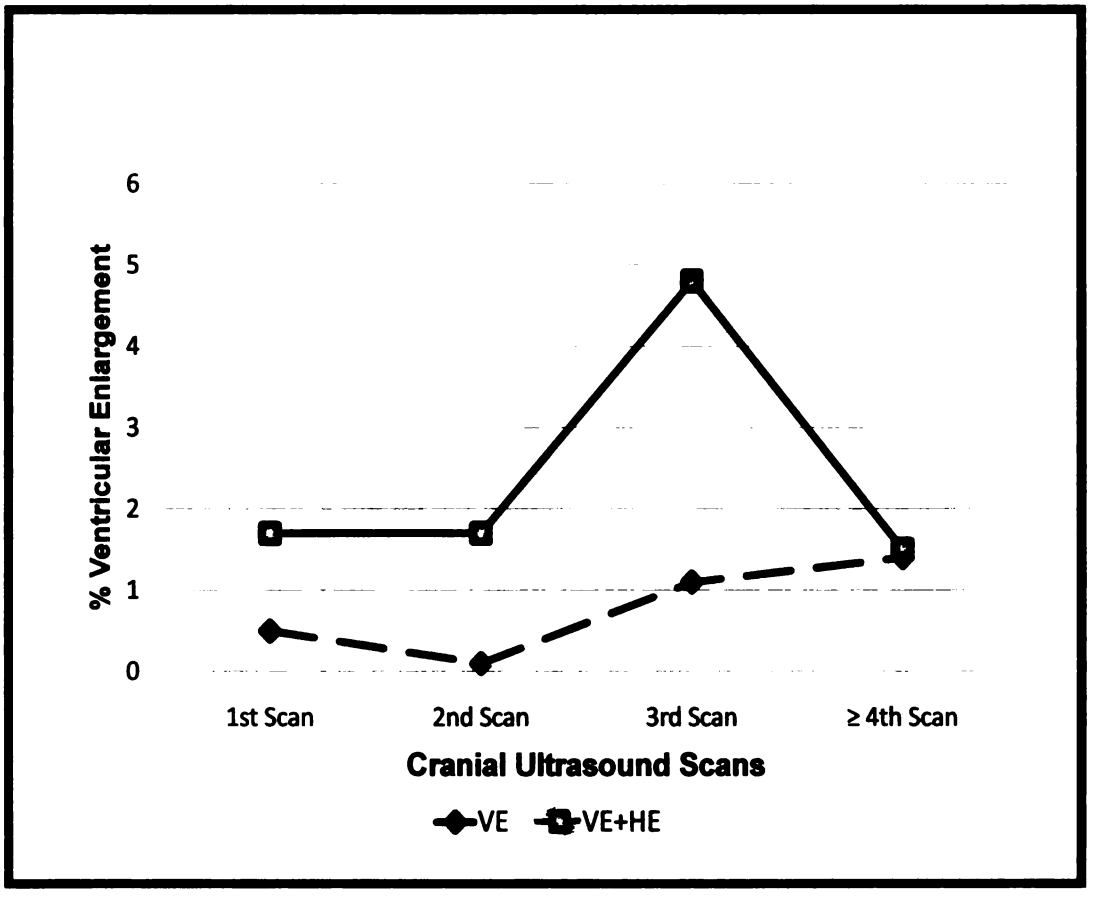
CUS Scans	Total Scanned (N)	Rate of Detection	
		IVE (%)	VE+HE (%)
1st Scan (0-12hrs)	1015	5 (0.5)	17 (1.7)
2nd Scan (13-48hrs)	1001	1 (0.1)	17 (1.7)
3rd Scan (49hrs – 7days)	926	10 (1.1)	45 (4.8)
≥ 4th Scan (>7days)	517	7 (1.4)	8 (1.5)
Totals	1015	23 (2.3)	87 (8.5)

Maternal characteristics

Maternal characteristics including age, highest educational attainment, smoking and alcohol use were similar in the 4 groups (Table 3.7). However, mothers of infants with Normal scans were least likely to use illicit drugs compared to mothers in the other groups. The proportion of mothers with addiction to social (alcohol, tobacco, marijuana) or hard (cocaine, heroin) drugs was similar in all 4

groups; however, the proportion of unemployed parents was highest among the infants with VE.

Figure 3.1: Prevalence of VE and VE+HE at each ultrasound scan.



Hypertensive disorders of pregnancy including pregnancy induced hypertension, preeclampsia and chronic hypertension were significantly more frequent in mothers whose infants had Normal CUS scans compared to mothers whose infants had ventricular enlargement with or without hemorrhage (Table 3.8). The proportion of mothers with vaginal bleeding and infectious complications was

similar in all 4 categories. However, chorioamnionitis was more frequent among mothers of infants with VE+HE and HE than in mothers of infants with Normal scans (Table 3.9). There was also a trend towards less frequent rupture of fetal membranes for greater than 18 hours before delivery among mothers of infants

Table 3.7: Maternal characteristics: demographic data

Characteristics		VE (N=23)	VE+HE (N=87)	HE (N=170)	Normal (N=808)	P-Value
Maternal age (yrs)		26.55	26.92	25.77	26.91	0.2907
Education (yrs)		12.20	12.74	12.98	12.99	0.4157
Smoking (%)		30.43	16.09	16.47	19.78	0.3328
Alcohol use (%)		43.48	26.44	31.18	33.01	0.3985
Drug[1] use[4] (%)		4.35	4.60	5.88	2.18	0.0327
Any addiction[2] (%)		65.22	42.53	46.47	46.84	0.2864
Race	White (%)	69.57	62.07	62.72	69.33	0.1672
	Black (%)	17.39	34.48	30.18	25.00	
	Other (%)	13.04	3.45	7.10	5.67	
Unemployed[3] (%)		34.78	10.34	12.35	13.47	0.0198

[1] Drug includes any use of marijuana, cocaine or heroine.

[2] Any addiction includes addiction to tobacco, alcohol, marijuana, cocaine or heroin.

[3] Unemployed: both mother and father are unemployed.

[4] Fisher exact test used for P-value.

with VE compared to the other 3 groups. Rates of cesarean section delivery and the frequency of placental and umbilical cord abnormalities were similar in the 4

groups of mothers. We explored the influence of different pregnancy and delivery complications on the risk of developing ventricular enlargement in the absence or presence of GM/IVH (Table 3.10). Pregnancy induced hypertension was

Table 3.8: Maternal characteristics: medical and pregnancy complications (entire cohort)

Complications	VE (N=23)	VE+HE (N=87)	HE (N=170)	Normal (N=808)	P-value
Pregnancy induced hypertension (%)	4.35	8.05	12.35	22.45	0.0001
Preeclampsia (%)	4.35	3.45	2.94	9.59	0.0087
Chronic hypertension (%)	4.35	3.45	2.94	8.86	0.0208
Vaginal bleeding[1] (%)	39.13	25.29	33.53	35.07	0.3038
Infectious complications[2] (%)	60.87	51.72	57.65	58.86	0.6294

[1]Includes placenta previa and abruptio placenta

[2]Include all respiratory and urinary tract infections

significantly associated with a decreased risk of ventricular enlargement in infants with VE+HE but not in infants without hemorrhage. Preeclampsia was also associated with a tendency towards reduction of the risk for ventricular enlargement in infants with GM-IVH; this however did not achieve statistical significance. On the other hand, chorioamnionitis was associated with a nearly 3-fold increased risk of ventricular enlargement in infants with GM-IVH. The role of chorioamnionitis in VE could not be estimated, probably because of the small

Table 3.9: Maternal characteristics: mode of delivery and delivery complications (entire cohort)

Characteristics	VE (N=23)	VE+HE (N=87)	HE (N=170)	Normal (N=808)	P-value
Cesarean section (%)	47.83	40.23	45.88	48.06	0.5605
‡ROM > 18hours (%)	8.70	22.99	30.59	23.06	0.0585
†MSAF* (%)	4.35	6.90	4.71	5.70	0.9109
Oligohydramnios (%)	0	0	0.59	1.21	0.6175
Placental abnormalities (%)	8.70	5.75	9.41	9.47	0.7218
Cord abnormalities (%)	4.35	8.05	11.18	10.68	0.6598
Chorioamnionitis* (%)	0	9.20	8.82	3.52	**0.0044**

*Fishers exact test for P-value ‡Rupture of membranes †Meconium stained amniotic fluid

number of infants in this category. Maternal smoking or alcohol use during pregnancy, placental abnormalities, prolonged rupture of membranes for greater than 18 hours before delivery were not associated with increased risk of ventricular enlargement in low birth weight infants with or without GM-IVH.

After adjusting for gestational age and birth weight, only chorioamnionitis remained significantly associated with increased risk of ventricular enlargement in infants with GM-IVH (Table 3.11); pregnancy induced hypertension was no longer associated with increased risk of ventricular enlargement in this group of infants. None of the factors evaluated was associated with increased risk of VE in infants with no GM-IVH after adjusting for gestational age and gender.

Table 3.10: Unadjusted odds ratios (OR) and 95% confidence intervals (CI) for the influence of different pregnancy and delivery characteristics on the occurrence of VE and VE+HE compared to infants with Normal CUS scans

Risk factors	VE vs. Normal OR (95% CI)	P-values	VE+HE vs. Normal OR (95% CI)	P-values
PIH	0.15 (0.02, 1.17)	0.071	0.30 (0.13, 0.66)	0.003
Preeclampsia	0.42 (0.05, 3.22)	0.410	0.33 (0.10, 1.09)	0.069
Smoking	1.77 (0.71, 4.38)	0.214	0.77 (0.42, 1.41)	0.409
Alcohol use	1.56 (0.67, 3.6)	0.297	0.72 (0.44, 1.20)	0.214
Placenta abnormality	0.91(0.21, 3.95)	0.900	0.58 (0.23, 1.48)	0.257
ROM > 18 hrs	0.31 (0.07, 1.36)	0.123	0.99 (0.58, 1.68)	0.998
Chorioamnionitis	UTE	UTE	2.77 (1.22, 6.28)	0.014

PIH = Pregnancy induced hypertension

ROM = Rupture of membranes

UTE = Unable to estimate

Mortality and neurodevelopmental outcomes at 2 years

The overall mortality and mortality within 28 days were significantly higher in infants with VE and VE+HE compared to infants with Normal CUS scans (Table 3.12). While the rates of non disabling cerebral palsy was similar in all three groups, infants with VE and VE+HE had significantly higher rates of disabling cerebral palsy compared with infants with normal CUS scans.

Table 3.11: Adjusted[‡] odds ratios (OR) and 95% confidence intervals (CI) for the influence of different pregnancy and delivery characteristics on the occurrence of VE and VE+HE compared to infants with Normal CUS scans

Risk factors	VE vs. Normal OR (95% CI)	P-Value	VE+HE vs. Normal OR (95% CI)	P-Value
PIH	0.18 (0.02, 1.38)	0.099	0.46 (0.20, 1.05)	0.065
Preeclampsia	0.52 (0.06, 3.98)	0.529	0.54 (0.16, 1.79)	0.317
Smoking	1.79 (0.72, 4.45)	0.206	0.78 (0.42, 1.44)	0.436
Alcohol use	1.61 (0.69, 3.74)	0.262	0.77 (0.46, 1.29)	0.324
Placental abnormality	0.94 (0.21, 4.13)	0.943	0.65 (0.25, 1.69)	0.383
ROM > 18 hours	0.30 (0.07, 1.31)	0.112	0.93 (0.54, 1.61)	0.819
Chorioamnionitis	UTE	UTE	2.43 (1.03, 5.77)	**0.042**

[‡]Adjusted for best gestational age and gender; UTE = Unable to estimate

Using a multivariate logistic regression model, VE and VE+HE were associated with increased risk of both overall mortality and mortality in the first 28 days of life (Table 3.13). While neither VE nor VE+HE were associated with nondisabling cerebral palsy, both lesions were significant risk factors for disabling cerebral

Table 3.12: Mortality and neurodevelopmental outcomes at age 2years in infants with ventricular enlargement (VE, VE+HE) compared with infants with Normal CUS scans

	Independent Variables			
Outcome Measures	VE N (%)	VE+HE N (%)	Normal N (%)	*P-Values
Mortality within 28 days	9 (39.1)	23 (26.4)	95 (11.5)	< 0.0001
Overall Mortality	10 (43.5)	35(40.2)	120 (14.6)	< 0.0001
Non Disabling Cerebral Palsy	2 (8.7)	5 (5.8)	39 (4.8)	0.5119
Disabling Cerebral Palsy	6 (26.1)	25 (28.7)	17 (2.1)	< 0.0001

* Exact test

palsy. Following adjustment for best gestational age and birth weight, VE but not VE+HE remained a significant risk factor for mortality within 28days (Table 3.14); both lesions remained significant risk factors for disabling cerebral palsy but not for nondisabling cerebral palsy.

Table 3.13: Unadjusted odds ratios (OR) and 95% confidence intervals (CI) for the risk of outcome measures in infants with ventricular enlargement (VE, VE+HE) compared to infants with normal CUS scans.

Outcome Measures	VE OR (95% CI)	P-Value	VE+HE OR (95% CI)	P-Value
Mortality within 28 days	4.93 (2.07, 11.71)	0.0003	2.75 (1.63, 4.64)	0.0001
Overall mortality	4.51 (1.93, 10.52)	0.0005	3.94 (2.46, 6.31)	< 0.0001
Non Disabling Cerebral Palsy	1.91 (0.43, 8.46)	0.3905	1.22 (0.47, 3.20)	0.6751
Disabling Cerebral Palsy	16.75 (5.87, 47.75)	< 0.0001	19.14 (9.81, 37.33)	< 0.0001

Table 3.14: Adjusted[‡] odds ratios (OR) and 95% confidence intervals (CI) for the risk of outcome measures in infants with ventricular enlargement (VE, VE+HE) compared to infants with normal CUS scans.

Outcome Measures	VE OR (95% CI)	P-Value	VE+HE OR (95% CI)	P-Value
Mortality within 28 days	4.83 (1.84, 12.63)	0.0013	1.25 (0.69, 2.26)	0.4473
Mortality	4.28 (1.67, 10.98)	0.0025	1.98 (1.16, 3.38)	0.0122
Non Disabling Cerebral Palsy	1.80 (0.40, 8.01)	0.4396	1.07 (0.39, 2.89)	0.8939
Disabling Cerebral Palsy	15.67 (5.43, 45.19)	< 0.0001	21.83 (10.56, 45.11)	< 0.0001

[‡]Adjusted for best gestational age and gender

CHAPTER 4

VENTRICULAR ENLARGEMENT, PERIVENTRICULAR WHITE MATTER INJURY AND NEUROLOGIC OUTCOMES IN THE NEWBORN BRAIN HEMORRHAGE (NBH) STUDY – DISCUSSION

Summary of findings

Ventricular enlargement without prior germinal matrix – intraventricular hemorrhage (VE) was identified in 23 of 1088 (2.1%) infants by protocol cranial ultrasound (CUS) scans in the NBH study. Pregnancy induced hypertension (PIH) was significantly more frequent in mothers of infants with normal CUS scans compared mothers of infants with abnormal scans. Furthermore, PIH was associated with decreased risk of ventricular enlargement in infants with GM-IVH. The protective effect of maternal high blood pressure against the development of ventricular enlargement in infants with GM-IVH was lost after adjustment for best gestational age (BGA) and gender. On the other hand, chorioamnionitis was more frequently seen in infants with VE+HE and HE compared to infants with Normal scans; chorioamnionitis was also associated with increased risk of ventricular enlargement in infants with GM-IVH, this association persisted after adjustment for BGA and gender. Overall mortality, death within 28days and disabling cerebral palsy (DCP) were more frequent in infants with ventricular enlargement with or without GM-IVH compared to infants with Normal scans. These abnormal CUS findings were also associated with increased risk of mortality and DCP; however, after adjustment for BGA and gender, VE+HE was

no longer associated with increased risk of mortality within 1st 28 days. Ventricular enlargement associated with GM-IVH was associated with a greater risk of DCP compared to VE, this relationship persisted after adjustment for BGA and gender.

Significance of VE in LBW infants

Advances in obstetric and neonatal care in the last three decades, including the use of antenatal steroids, exogenous surfactant therapy, improved monitoring technologies and ventilatory methods have led to increased survival of smaller and less mature VLBW infants[61, 62]. These advances also contributed to a steady decline in the prevalence and severity of GM-IVH, the most common form cerebral abnormality detected on cranial ultrasound scan in the VLBW premature infant [63, 64]. However, the improved survival rates of VLBW infants in the 1990s was not accompanied by improvement in the rates of neurodevelopmental impairment[65], and some studies of long-term outcomes reported increased rates of neurodevelopmental problems including cerebral palsy in surviving VLBW infants[66, 67]. Cerebral white matter injury (WMI) is now widely regarded as the major form of brain injury and the leading cause of long-term neurologic disability in surviving VLBW infants[68]. Cranial ultrasound (CUS)[50 48] and magnetic resonance imaging (MRI)[12, 69] studies indicate VE is a frequent marker of WMI and may be seen in association with focal, cystic and diffuse white matter lesions as well as with intraventricular hemorrhage in VLBW infants.

Frequency of isolated ventricular enlargement in low birth weight infants

The NBH study presents one of the first opportunities to take a close look at VE in a cohort of unselected, population based study of LBW infants. There are no comparable population studies of GM-IVH that utilized timed cranial ultrasound scans starting from very early after delivery. The study provided an opportunity to estimate the approximate time of onset of intracranial abnormalities detected by CUS in LBW infants.

However, a review of some other studies of unselected low birth weight infants for the frequency of VE on early cranial US scans revealed a wide range with figures ranging from 1.2% to 27%[12, 51]. In a study of a Provincial cohort of very preterm infants, birth weight 500 – 1250 g, Aziz et al[51] found VE by CUS scan in 8 of 669 (1.2%) infants that survived to 1-year adjusted age. Lower rates of cranial ultrasound (CUS) abnormalities in this study may be explained by the fact this was an unselected population study and not a study of sick infants in tertiary centers. Furthermore, the study radiologists only reviewed and reported scans that were initially read as abnormal by hospital radiologists that did not participate in the study. Therefore, lesions that could have been considered abnormal by study radiologists may have been missed at the initial, non-protocol reading stage, contributing to the rather low frequency of abnormal CUS scans. On the other hand, Dyet et al[12] carried out a hospital based study of 119 consecutively recruited preterm infants born at < 30 weeks gestational age. They obtained serial cranial MRI scans, starting as soon as possible after birth, at a median age of 2 days. Scan timing was however, not standardized and depended on infants'

clinical stability. Twenty (16.8%) and 22 (18.5%) of 119 infants with no intraventricular hemorrhage had VE on the first and final scans respectively. Ancel et al[48] found a frequency of VE in 98 of 1929 (5%) evaluated by CUS scans in a population study of preterm infants of 22 to 32 weeks gestational age (the EPIPAGE Study). In that study, the observed frequency of VE was not related to gestational age but was higher in products of multiple than singleton gestations; infants with intrauterine growth restriction were not at a higher risk of VE[47]. However, in the EPIPAGE study, there was no standardized protocol for obtaining cranial ultrasound scans; the scans evaluated were those obtained for routine surveillance of perinatal brain injury during routine neonatal care. The timing, technique, quality and reading of the scans were not standardized. This calls to question the accuracy of the reported frequency of VE in the study; a recent audit of clinical neonatal ultrasound scan interpretations indicate low frequencies of accurate identification of cerebral abnormalities including ventricular dilatation and white matter lesions[70].

Intrauterine growth and VE

Infants with VE in our study were significantly less likely to be small for gestational age than infants with Normal CUS scans. No consistent relationship between VE and intrauterine growth in preterm infants has been established. A review of the relevant literature reveals studies that have variously reported increased frequency[71], no change in frequency[72] and decreased frequency[69, 73] of ventricular enlargement in infants with intrauterine growth restriction when

compared with gestational age matched, appropriate for gestational age preterm infants.

In a small retrospective review, Kriss and Desai[71] found a significantly higher frequency of non-pathologic, mild isolated ventriculomegaly on CUS scans in asymmetric IUGR infants compared to appropriate for gestational age (AGA), matched controls. In the report, ventricular enlargement was found to have resolved without intervention on follow-up CUS scans obtained 4 to 12 weeks after the initial scan. Furthermore, IUGR infants with mild isolated ventricular enlargement were asymptomatic and remained normal on follow up evaluations at ages ranging from 3 to 5 years.

On the other hand, Inder et al[69] carried out a qualitative MRI study of 100 consecutive VLBW preterm infants at term equivalent age. They found IUGR had a significant protective effect on the risk of moderate to severe white matter injury and VE in preterm infants. This protective effect was lost after controlling for gestational age and mode of delivery. The finding in this analysis of the highest frequency of SGA among infants with Normal CUS scans may be reflective of the protective effect of IUGR on ventricular enlargement in infants without GM-IVH.

Apgar scores and VE

Compared to infants with normal CUS scans, a higher proportion of infants with VE have a 5-munite Apgar score less than 7 in this report. Although the reason for this is not obvious from this analysis, chronic sublethal hypoxia in an experimental animal model[74] and perinatal asphyxia in human neonates with or

without intracranial hemorrhage[41] are associated with cerebral ventriculomegaly. Low birth weight preterm infants are at a higher risk of cardiopulmonary depression and therefore frequently require active neonatal resuscitation and have lower Apgar scores compared to their term counterparts[75].

Hypertensive disorders of pregnancy and VE

Hypertensive disorders of pregnancy including pregnancy induced hypertension, preeclampsia and chronic hypertension were significantly more frequent in mothers with Normal CUS scans compared to mothers of infant with ventricular enlargement, with or without prior GM-IVH.

The placenta in hypertensive disorders of pregnancy is characterized by inadequate invasion and replacement of the endothelial layers of the uterine spiral arteries by cytotrophoblast cells [76]. The process of cytotrophoblast invasion results in the transformation of the spiral arteries from thick walled muscular vessels into saclike, low resistance flaccid vessels that eventually accommodate the 10-fold increase in uterine blood flow required to meet the demands of the growing fetus [77]. Failure of vascular remodeling of the spiral arteries leads to a state of progressive placental ischemia and hypoxia believed to be the trigger for the systemic maternal vascular endothelial dysfunction and inflammation seen in preeclampsia as pregnancy progresses [78, 79]. Inadequate remodeling of the uterine spiral arteries in preeclampsia may lead to a state of chronic placental underperfusion and fetal hypoxia that could contribute to impaired fetal growth.

In this analysis, infants with Normal CUS scans also had a significantly higher frequency of SGA than infants with VE. Furthermore, pregnancy induced hypertension was associated with a reduced risk of ventricular enlargement in infants with GM-IVH. Although this association was lost after adjusting for gestational age and gender, the data suggest that hypertensive disorders of pregnancy are associated with intrauterine growth restriction and protective against ventricular enlargement in low birth weight infants with GM-IVH. Several reports indicate that very low birth weight preterm infants born to women with preeclampsia and pregnancy induced hypertension are at a lower risk of cerebral palsy [80, 81] and intraventricular hemorrhage [82, 83]. However, there are no direct studies of the influence of preeclampsia on the size of the cerebral ventricles in preterm infants, and reports on the association between white matter injury and preeclampsia have been conflicting: while some investigators report that preeclampsia is associated with a reduced risk of ventriculomegaly and white matter damage in VLBW infants[72, 73, 84-86], others have found preeclampsia / eclampsia is associated with a higher risk of cystic PVL in infants of 33 to 35 weeks GA[87] and yet other investigators found no influence of preeclampsia / eclampsia on the risk of brain injury in VLBW infants[88]. A neuropathologic and cranial ultrasound study found no association between preeclampsia and prenatal ischemic brain injury but a significant association between preeclampsia and postnatal ischemic cerebral damage[89]. These varied results indicate the etiology of VE and white matter injury in VLBW infants is multifactorial and likely

includes factors that are operative in the prenatal, perinatal and postnatal periods.

Chorioamnionitis and VE

The relationship between chorioamnionitis and VE could not be estimated from the data because of the absence of chorioamnionitis from this group. However, chorioamnionitis was associated with increased risk of ventricular enlargement in infants with GM-IVH. This association remained statistically significant after controlling for gestational age and gender. This finding is in agreement with what has been demonstrated by several investigators that chorioamnionitis is associated with increased risk of GM-IVH, white matter injury and ventricular enlargement [49, 90, 91]

Timing of VE in LBW infants

The distribution in the rate of detection of ventricular enlargement in infants with no prior GM-IVH is different from that noted in infants with prior GM-IVH. In both groups of infants, ventricular enlargement was noted on the 1st scan, but with a higher frequency in infants with GM-IVH. In the both groups, this may include contribution from fetal ventriculomegaly; however, the higher rate in the VE+HE suggest ventricular dilatation associated with early IVH – the so-called grade III IVH on the Papille classification. In this regard, it has been shown in several studies that up to 40% of intraventricular hemorrhage in very low birth weight preterm infants occurs within the first 24 hours of life[92, 93]. In the NBH study, over

35% of IVH occurred on the 1st U/S scan obtained at the age of 4.9 ± 2.2 hours[54]. The 2nd scan obtained at 13 – 48 hours of life (mean age 25.5 ± 4.8 hours)[53] revealed only 1 new case of VE, while the rate of detection in the VE+HE group was still as high as in the first scan. The timing of the 2nd scan corresponds to the age at which low birth weight infants are very susceptible to developing intraventricular hemorrhage as a number of the risk factors for this complication, including respiratory distress syndrome, pneumothoraces, cardiovascular and hemodynamic instability are quite prevalent at this age. The persistently high rate of detection of ventricular enlargement in the VE+HE group on the second scan likely represent ventricular dilatation associated with new onset GM-IVH at this age.

The 3rd scans obtained between ages 49 hours to 10 days (mean age of 7.2 ± 0.8 days) shows an increase in the rate of detection of ventricular enlargement in both the VE and VE+HE groups, with a sharp increase in the VE+HE group. In the VE+HE group, the ventricular enlargement likely represent a combination of progressive posthemorrhagic ventricular dilatation and cerebral white matter and cortical injury[32, 50]. In the VE cases, ventricular enlargement detected on the 3rd scan most likely represents diffuse white matter injury. In the NBH study, neuropathologic evaluation of infants that came to autopsy, and in whom three or more CUS scans had been performed before death, showed that ventricular enlargement on ultrasound was a marker of white matter damage in infants that survived six days or longer[60].

The 4th and later scans were predischarge studies added to the protocol several months into the NBH study. In keeping with the pattern of posthemorrhagic ventricular dilatation after GM-IVH, fewer instances of new onset ventricular enlargement were noted in the VE+HE group. On the other hand, there was still a modest increase in the proportion of infants in the VE group that had new onset ventricular enlargement at the 4th and later scans. This is in keeping with serial CUS and MRI studies which show increases in the proportion of VLBW infants with ventricular enlargement without prior GM-IVH at term equivalent age[12, 94].

Neonatal and 2 year outcomes of infants with VE

Infants with VE and VE+HE had significantly increased risk of overall mortality and mortality in the 1st 28days of life compared to infants with normal CUS scans. This increased risk persisted for infants with VE but not in those with VE+HE after adjusting for gestational age and gender. The increased risk of early mortality in infants with VE suggests the underlying cause of ventricular enlargement in this group of infants may have been present prenatally. This may be related to factors other than hypertensive disorders of pregnancy which has been shown to be associated with a lower risk of ventriculomegaly[86].

However, infants in both groups had significantly higher risks of disabling cerebral palsy (DCP) compared to infants with normal scans, even after adjusting for gestational age and gender.

The higher frequency of cerebral palsy in the VE and VE+HE groups is in keeping with the neuropathologic changes of ventricular dilatation that occur in

the context of cerebral white matter injury. Cerebral white matter injury includes a spectrum of cerebral pathologic changes that range from focal injury to diffuse, extensive cerebral white matter lesions.

The focal lesions are characterized by well circumscribed necrotic or cystic lesions that occur commonly in the subventricular zone adjacent to the lateral ventricle and involve injury to all cellular elements (periventricular white matter injury, PVWMI). The lesions are often accompanied by reduction in white matter volume secondary to cyst formation or ventricular dilatation[5, 95]. PVWMI results from selective vulnerability of the periventricular white matter in the preterm neonate to ischemic, infectious or metabolic insults and are closely correlated to spastic cerebral palsy[96].

Diffuse cerebral white matter injury, on the other hand, is characterized by areas of poor myelination and diffuse gliosis in the deep cerebral white matter. The injured cell type that provokes the gliosis in diffuse white matter injury is presumably the ologidendrocyte progenitors[5]. The later cells are destined to develop into mature oligodendrocytes which form the myelin of the cerebral white matter. Thus the the principal neuropathologic sequela of periventricular white matter injury is diminution of white matter volume and ventriculomegaly.

The ultrasonographic finding of ventricular dilatation in the absence of intraventricular blood is a risk factor for cerebral palsy[97] and has been shown to increase the risk of neurodevelopmental delay 4 to 5 fold[98]. In this analysis, infants with VE+HE were at a higher risk of DCP compared to infants with VE. This is consistent with result of cranial ultrasound studies in VLBW infants which

indicate that GM-IVH have a 5 to 9 fold increased risk of WMD regardless of size, laterality, or extent of lesion[50].

Isolated dilatation of the lateral ventricles identified by early or late cranial ultrasound scans in the neonatal period is a risk factor for later development of cerebral palsy [90, 97]. Furthermore, late onset ventricular enlargement without periventricular-intraventricular hemorrhage is strongly associoated with white matter injury in the forms of periventricular leukomalacia or cerebral cortical atrophy or both[99]. Because PVWMI is by far the most important brain lesion associated with later development of neurologic and cognitive impairments [1], sonographic evidence of white matter damage is now regarded as a critical piece of information in the counseling of families on the likely long-term neurodevelopmental outcomes of their LBW infants.

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