Early and Late Complications of Germinal Matrix-Intraventricular Haemorrhage in the Preterm Infant: What Is New?

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Key Words

Cranial ultrasound · Germinal matrix-intraventricular haemorrhage · Low-grade/severe germinal matrix-intraventricular haemorrhage · Magnetic resonance imaging · Preterm infant

Abstract

Germinal matrix-intraventricular haemorrhage (GMH-IVH) remains a serious problem in the very and extremely preterm infant. This article reviews current methods of diagnosis, treatment and neurodevelopmental outcome in preterm infants with low-grade and severe GMH-IVH. We conclude that there is still no consensus on timing of intervention and treatment of infants with GMH-IVH, whether or not complicated by post-haemorrhagic ventricular dilatation. The discrepancies between the studies underline the need for international collaboration to define the optimal strategy for these infants.

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Introduction

Cranial ultrasound (cUS) has been used since the late 70s to diagnose germinal matrix-intraventricular haemorrhage (GMH-IVH) and even though magnetic resonance imaging (MRI) is increasingly being used, cUS is still the most readily available and commonly used neuroimaging technique in the neonatal intensive care unit. The classification of Papile et al. [1] is still most often used to grade the severity of GMH-IVH, but most prefer to describe a parenchymal haemorrhage as a periventricular haemorrhagic infarction (PVHI) or venous infarction rather than a grade IV haemorrhage. Most studies regarding GMH-IVH are about preterm infants with a severe haemorrhage (grade III and PVHI), and this is likely for two reasons. Firstly, these lesions are reliably recognised with cUS [2]. Secondly, these larger lesions are more often related to an adverse neurological outcome [3].

The smaller lesions (grade I–II) are more difficult to diagnose with cUS and the inter-observer agreement tends to be poor with a κ of 0.20–0.26 [2]. Associated subtle white matter injury may be present, but is not always recognised with cUS. Kuban et al. [4] reported that the presence of ventriculomegaly was common in preterm infants with an IVH and more recently van Wezel-Meijler

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Fig. 1. Coronal view using the anterior fontanelle (**a**) and parasagittal view using the posterior fontanelle during the 1st week (**b**). The axial T2-weighted MRI at TEA no longer shows a dilated occipital horn and just a small amount of blood (seen as low signal intensity in both occipital horns; **c**).

et al. [5], using serial cUS and term equivalent age (TEA)-MRI, reported that the presence of a low-grade GMH-IVH was highly predictive of white matter abnormalities on TEA-MRI. The true impact of low-grade GMH-IVH on the neurodevelopment of extremely and very preterm infants is therefore not well known and the few available studies in the literature looking at neurodevelopmental outcome show conflicting data [6–9].

This review will discuss how low-grade GMH-IVH can be diagnosed more reliably and will review recent outcome data. Subsequently, we will discuss the diagnosis of severe GMH-IVH, the role of additional diagnostic methods, timing of intervention and neurodevelopmental outcome [10].

Low-Grade GMH-IVH

Any haemorrhage in the preterm infant typically has its onset in the germinal matrix, also known as the ganglionic eminence, which is the source of future neuronal and glial cells in the immature brain [11, 12]. The vasculature in the germinal matrix is very fragile and combined with the lack of cerebral autoregulation in many of these sick preterm infants and fluctuations in cerebral blood flow, it is not surprising that these vessels will rupture, which results in haemorrhage either restricted to the germinal matrix but more often also extends to the lateral ventricle [13].

Diagnosis

With the use of cUS it can be difficult to make a distinction between an isolated GMH and an associated small IVH. Sometimes, the presence of blood in the ventricle may become clear after some time due to either mild post-haemorrhagic ventricular dilatation (PHVD) or due to increased echogenicity of the lining of the ependyma. Using the posterior fontanelle as an additional acoustic window, the diagnosis can be made more reliably [14]. This distinction can also be made with MRI and more small GMHs may be recognised, especially in the temporal horn, where it may be more difficult to have a good field of view using cUS. A relatively new MR sequence, susceptibility-weighted imaging (SWI), has also been reported to be very useful in the diagnostic process of these GMHs. Using cUS, 15 out of 60 infants were considered to have a GMH, but using MRI including SWI, 25 out of 60 were diagnosed to have a GMH [15]. A similar observation was reported by Intrapiromkul et al. [16]. In addition to a GMH, it is not uncommon to find additional, usually more subtle white matter lesions, mostly punctate white matter lesions using MRI. While these lesions are easy to recognise with MRI, they are often, but not always, recognised as inhomogeneous echogenicity on cUS [17]. One should also be aware of the fact that an MRI at TEA may no longer be able to assess the initial grade of the GMH-IVH. It is not uncommon to see no or only a very small amount of blood in the occipital horn with or without some degree of ventriculomegaly (fig. 1).

Fig. 2. MRI, coronal T2-weighted image (a), showing an IVH of grade II with mild PHVD but extensive haemorrhagic lesions in the cerebellum, which are also clearly seen with SWI (b).

Fig. 3. MRI, coronal T2-weighted images. **a** Preterm infant, GA 29 weeks, MRI day 10, showing a grade III haemorrhage with PHVD and ballooning shape of the ventricles. Note the lack of extracerebral space. **b** Preterm infant, GA 28 weeks, MRI day 14, showing a PVHI with the typical triangular shape with the apex at the border of the right ventricle.

Relation to Neurodevelopmental Outcome

Most of the studies relating low-grade GMH-IVH with outcome are about preterm infants in whom the initial diagnosis was made using cUS. It is not clear from these studies whether the diagnosis, low-grade GMH-IVH, also took into account whether there were associated white matter lesions. The latter may have been more important with regard to later outcome than the GMH itself, but may be easily overlooked in the absence of an additional MRI. It is possible that these infants also had small cerebellar lesions, which may have played a role, but were not diagnosed using cUS. In one study, the diagnosis of a low-grade GMH-IVH was made with cUS, and the TEA-MRI showed reduced cortical volume [18].

In the EPIPAGE study, 6.8 and 8.1% of infants with a grade I and II GMH-IVH, respectively, developed cerebral palsy (CP) based on cUS rather than MRI data [7]. In another large cohort, no difference was found between those without a haemorrhage and those with a grade I–II GMH-IVH [8]. In this study, there was quite a high percentage of infants who developed CP, 8 and 9% of infants without or with a grade I and II GMH-IVH, respectively, which was likely to be explained by associated white matter injury not recognised with cUS. A third study reported outcome on an Australian cohort consisting of more than 2,000 preterm infants, with 515 (21.3%) infants with a grade I–II GMH-IVH diagnosed with cUS. The authors reported increased rates of neurosensory impairment, developmental delay, CP (10.4%) and deafness at 2–3 years of corrected age in those with a grade I–II GMH-IVH. The CP rate was quite high (6.8%) in those without cUS abnormalities [9]. Compared to these studies, the CP rate of 35 and 55% for preterm infants with a gestational age (GA) below 28 weeks with a grade I and II GMH-IVH, respectively, was very high in the study by Klebermass-Schrehof et al. [19]. Even for those with a GA of 28–32 weeks, the CP rates of 12.5 and 23.0% for grade I and II GMH-IVH, respectively, are higher than reported so far. In our own cohort of 705 infants (2008–2011) with a GA of 30 weeks or less, 78 (26.0%) showed a grade I or II haemorrhage on cUS and 0 and 4.0%, respectively, developed CP. In 1 of the 3 infants with CP, this could be explained by associated cystic periventricular leukomalacia not seen with cUS, the second had moderate PHVD (fig. 2) and in the third, adverse motor outcome could be explained by non-cystic white matter injury.

Looking at these studies, it is clear that we need to look at a prospectively enrolled cohort of preterm infants, studied with serial cUS and early MRI, in order to study the effect of an isolated GMH-IVH and to find out how many of such a cohort do indeed have an isolated low-grade GMH-IVH and how many have a low-grade GMH-IVH with associated subtle white matter and/or cerebellar lesions.

Severe GMH-IVH

The incidence of moderate-severe GMH-IVH has remained more or less the same over the last 2 decades [20, 21]. The proportion of severe GMH-IVH is especially large among the more immature infants with the incidence being inversely related to GA and birth weight [22]. A grade III is defined as a large IVH filling the ventricle by more than 50% with blood and resulting in dilatation in the acute stage. In approximately 15% of very low birth weight (<1,500 g) infants, the GMH-IVH is associated

Table 1. Neurodevelopmental outcome: IVH grade I and II

	n	Normal cUS	Grade I–II	Outcome
Vasileiadis et al. [18], 2004	23; <1,500 g	22	11	16% reduction in cerebral CGM volume at near-term age
Scherlock et al. [47], 2005	270; <1,000 g or <28 weeks	180	72	At 8 years; CP: normal cUS: 6.7%; grade I: 6.4%; grade II: 24%
Patra et al. [6], 2006	490; <1,000 g	258	104	CP: normal cUS: 3%; grade I–II: 8%; significantly lower MDI and major neurologic abnormality (13 vs. 5%)
Beaino et al. [7], 2011	1,812; ≤32 weeks	1,153	290	CP: normal cUS: 4%; grade I: 8%; grade II: 11%
Klebermass-Schrehof et al. [19], 2012	438; <32 weeks	287	121	CP: normal cUS: 14.3%; grade I: 34.8%; grade II: 55%
Payne et al. [8], 2013	1,472; <27 weeks	1,021	270	CP: normal cUS: 8%; grade I–II: 9%
Bolisetty et al. [9], 2014	2,414; <1,000 g	1,043	336	CP: normal cUS: 6.5%; grade I–II: 10.4%
UMCU	705; ≤30 weeks	296	89 (4 died)	Grade I: none; grade II: 3.5%

CGM = Cortical grey matter; MDI = mental developmental index; UMCU = University Medical Centre Utrecht.

with parenchymal involvement of grade IV, preferably referred to as PVHI (fig. 3). There are three neuropathological consequences of IVH: (1) destruction of the germinal matrix [12], (2) associated white matter injury and (3) PHVD [22].

Post-Haemorrhagic Ventricular Dilatation

The most serious complication is the development of PHVD. PHVD occurs in 30–50% of all preterm infants with a grade III IVH or PVHI, and 25–30% of these develop progressive PHVD [23, 24]. The choice of intervention and the timing of neurosurgical intervention is still a matter of debate, as shown in a previous study [10] as well as in a European survey [25]. Currently, the prospective randomised controlled ELVIS trial (Early vs. Late Ventricular Index Study, trial No. ISRCTN43171322) is being conducted to assess the potential beneficial role of early intervention [i.e. initiated once the ventricular index (VI) has crossed the 97th centile according to Levene] over late intervention (i.e. initiated after the VI has exceeded the 97th centile by 4 mm). In this trial, the primary endpoint is death or the need for a ventriculoperitoneal (VP) shunt and the secondary endpoint neurodevelopmental outcome at 2 years of corrected age. In the ELVIS trial, timing of intervention is based on measurements, including the VI and anterior horn width, while others have looked, in a retrospective study, at the number of days after birth as a marker for early versus late treatment [26].

Neuromonitoring

Doppler ultrasound has been used to assess changes in cerebral haemodynamics in infants with ventricular dila-

tation, showing an increase in the peak systolic flow velocity, followed by a decrease or absence of the end diastolic flow velocity [27–29]. Klebermass-Schrehof et al. [30] and Olischar et al. [31] have shown that an amplitude-integrated electroencephalography background pattern may deteriorate with progressive PHVD even before clinical deterioration occurs and before cUS measurements indicate the need for neurosurgical intervention. Only 23.5% of their infants showed a normal amplitude-integrated electroencephalography trace prior to intervention compared to 58.8% after the intervention. We were unable to reproduce these findings, which might be explained by our infants being more mature and undergoing earlier intervention [32].

Near-infrared spectroscopy may also be of value in optimising timing of intervention. Observational studies [33, 34] have shown low regional cerebral oxygenation (rSO₂) values in infants with PHVD with recovery following intervention. Further research is needed to prove that near-infrared spectroscopy can be used as an aid for optimising timing of intervention.

Treatment

Diagnostic and therapeutic approaches for PHVD are known to vary among neonatal centres [25]. In about 25% of preterm infants with GMH-IVH and PHVD, insertion of a VP shunt is needed [24]. Neurosurgical intervention requires anaesthesia and daily punctures from the reservoir carry a risk of infection [35]. There may be complications, such as wound dehiscence or dysfunction requiring insertion of a second reservoir. Tapping a ventricular access device by a specially trained and dedicated team of

Table 2. Neurodevelopmental outcome: IVH grade III and IV

	n	Population	Grade	Outcome
<i>Grade III–IV</i>				
Adams-Chapman et al. [3], 2008	7,693	BW: <1,000 g	IVH III: n = 459 IVH IV: n = 311	MDI: 74.1; PDI: 77.4; CP: 23% MDI: 71.5; PDI: 73.2; CP: 37%
Brouwer et al. [48], 2008	214	GA: ≤34 weeks	IVH III: n = 94 IVH IV: n = 120	Grade III, CP 5/68 (7.4%); DQ >85: 61 (91%) Grade IV, CP 37/76 (48.7%); DQ >85: 58 (79%)
Maitre et al. [49], 2009	69	BW: <1,500 g	Unilateral PVHI: n = 52 Bilateral PVHI: n = 17	MDI: 82; PDI: 53; CP (mild-severe): 67% MDI: 49; PDI: 49; CP (mild-severe): 88%
Vassilyadi et al. [50], 2009	284	Mean GA: 29 weeks Mean BW: 1,320 g	IVH III: n = 43 IVH IV: n = 54	Good outcome/mild impairment: 44% Good outcome/mild impairment: 16%
Klebermass-Schrehof et al. [19], 2012	438	GA: <32 weeks	30	CP: normal cUS: 14.3% CP grade III: 63.6%; CP grade IV: 90.9% PDI/MDI <70: normal: 17.3/17.5% Grade III: 70/60%; grade IV: 85.7/62.5% Visual impairment: grade III/IV: 45.5/90.9%
Srinivasakumar [51] et al., 2013	39	GA: ≤34 weeks	11	CCa: 95; MCB: 86; LCC: 94
Bolisetty et al. [9], 2014	1,472	GA: 23–28 weeks	93	CP: 30%; neurodevelopmental delay: 17.5%; deafness: 8.6%; blind: 2.2%
<i>Grade III–IV + PHVD</i>				
Adams-Chapman et al. [3], 2008	76 93	BW: <1,000 g	n = 103: grade III + shunt n = 125: grade IV + shunt	MDI: 66.2; PDI: 64.1; CP: 57% MDI: 60.3; PDI: 55.2; CP: 80%
Bassan et al. [26], 2012	32	GA: <30 weeks	Early EVD (≤25 days of life): n = 6, grade III; n = 4, grade IV Late EVD (>25 days of life): n = 9, grade III; n = 13, grade IV	CP: 70%; Battelle total: 93.2 CP: 81.8%; Battelle total: 63.1
Brouwer et al [52], 2012	34	GA: <32 weeks	n = 17: grade III + VD n = 17: grade IV + VD	Normal neurodevelopmental outcome: 59.4%; CP: 25%; Mov-ABC <p5: 39%; IQ mean: 93
Srinivasakumar et al. [51], 2013	39	GA: ≤34 weeks	n = 16: +TNP n = 12: no TNP	CCa: 77; MCB: 67; LCC: 70 CCa: 90; MCB: 84; LCC: 82

CP: Bayley Scale of Infant Development III (18–24 months). BW = Body weight; CCa = cognitive composite score; DQ = development quotient; EVD = external ventricular drainage; LCC = language composite score; MCB = motor composite score; MDI = mental developmental index; Mov-ABC = movement ABC test; PDI = physical developmental index; VD = ventricular device.

neonatal staff, including doctors, physician assistants and nurses, may produce the lowest infection rate as well as a reliable schedule of tapping [36]. A wide range of ventricular access device- or VP shunt-related infections has been reported by different groups [37–39]. The use of a ventriculosubgaleal shunt also has been shown to be effective in the treatment of PHVD [40–42]. Neurodevelopmental outcome is influenced by infection and revision rate of a VP shunt [43].

To reduce the risk of infection, antibiotics are administered prior to and 2–3 days following reservoir and shunt insertion. Promising results have been shown using antibiotic-impregnated shunts. Their introduction reduced the incidence of shunt infection [44–46]. Impregnation of ventricular access devices with antibiotics may

become a reasonable option to minimise the risk of infection in these high-risk patients.

Neurodevelopmental Outcome

Outcome studies tend to be based on the severity of the haemorrhage (table 1). Some studies also take the development of PHVD and the need for neurosurgical intervention into account. The more immature the infant, the greater the risk of a severe haemorrhage. Klebermass-Schrehof et al. [19] have shown that outcome was worse in preterm infants with GA below 28 weeks compared to those with GA between 28 and 32 weeks. Long-term functional outcome of preterm infants with severe GMH-IVH has been reported by several groups (table 2) [48–52].

Bassan et al. [53] developed a PVHI severity score related to risk factors and outcome. The severity of the score depended on different ultrasonographic characteristics; unilateral or bilateral PVHI (localised in 1 territory or extensive, involving 2–5 territories) and occurrence of a midline shift. A higher severity score predicted a worse outcome.

Neurodevelopmental outcome mainly depends on the presence of associated parenchymal involvement. This was supported by the data of Maitre et al. [49] showing that the majority of preterm infants with a bilateral PVHI have a very poor cognitive and motor outcome. Subsequent development of a unilateral spastic CP following parenchymal involvement can be reliably predicted when an MRI is performed at term-equivalent age. Infants with an asymmetry in myelination almost invariably developed unilateral spastic CP [54].

Progressive PHVD following severe GMH-IVH was shown to be associated with a three- to four-fold increase in neurodevelopmental delay [55]. The need for neurosurgical intervention was shown to be associated with a poorer neurodevelopmental outcome [51]. Infants with progressive PHVD who received a temporising neurosurgical procedure (TNP) had worse outcomes compared with infants whose PHVD stabilised and needed no TNP. Srinivasakumar et al. [51] also suggest that increasing ventricular dimensions; anterior horn width, thalamo-occipital distance and VI may inversely affect neurodevelopmental outcome.

In the small population of Bassan et al. [26], the impact of external ventricular drainage timing on long-term neurodevelopmental outcome revealed that infants who received this drainage early (before day 25 after birth) had a better score on the Battelle Developmental Inventory at 6 years (median age). Preterm infants with PHVD and no initial parenchymal injury less often had reduced rates of cognitive, communication and social disabilities and also had a better motor outcome.

Conclusion

Despite improvements in neonatal care for preterm infants, there has not been a clear decline in the number of infants who develop a severe GMH-IVH. The neurodevelopmental outcome, especially in infants with a severe GMH-IVH, remains a cause for concern. There is still no consensus with regard to timing of intervention and treatment of infants with GMH-IVH who develop PHVD. The discrepancies between the studies underline the need for international collaboration to define the optimal strategy for these infants.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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