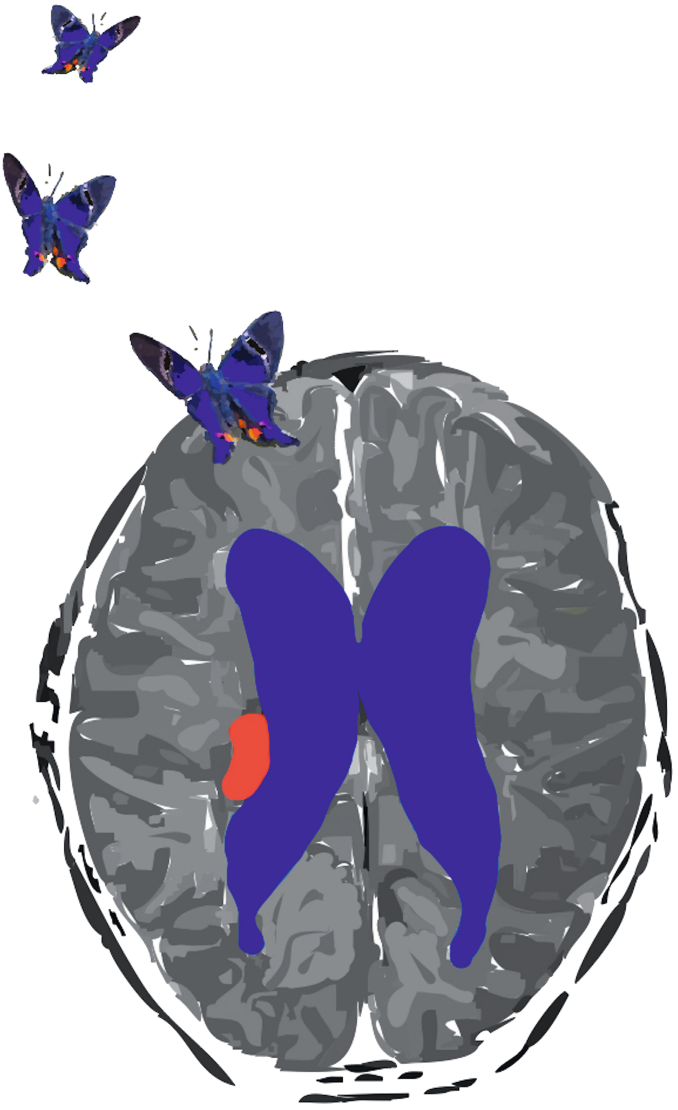
Neonatal Hemorrhagic Brain Injury:
Optimizing Treatment and Outcome



Mehmet N. Çizmeci

Neonatal Hemorrhagic Brain Injury: Optimizing Treatment and Outcome

Mehmet Nevzat Çizmeci

Provided by thesis specialist Ridderprint, ridderprint.nl

Printing: Ridderprint
Author: Mehmet Nevzat Çizmeci
Cover Design: Elif Ayşe Çizmeci
Lay-out: Anke Muijsers, persoonlijkproefschrift.nl
ISBN: 978-90-393-7439-9

Publication of this thesis was sponsored by B. Braun Medical B.V

Neonatal Hemorrhagic Brain Injury:

Optimizing Treatment and Outcome

Neonatale haemorrhagische hersenschade: verbetering van behandeling en uitkomst

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de

Universiteit Utrecht

op gezag van de

rector magnificus, prof. dr. H.R.B.M. Kummeling,

ingevolge het besluit van het college voor promoties

in het openbaar te verdedigen op

donderdag 12 mei 2022 des middags te 4.15 uur

door

Mehmet Nevzat Çizmeci

geboren op 29 februari 1980

te Ankara, Turkije

Promotor:

Prof. dr. L.S. de Vries

Copromotoren:

Dr. F. Groenendaal

Dr. P. Woerdeman

"Our true mentor in life is science"

Mustafa Kemal Atatürk

Table of Contents

"The torch that we hold in our hands and in our minds while marching on the road of progress and civilization is positive science"

Mustafa Kemal Atatürk

1

General Introduction

Problem Statement

Germinal matrix hemorrhage and intraventricular hemorrhage (GMH-IVH) continue to be a common and clinically significant form of brain injury in very preterm infants.[1] Despite recent advances in perinatal and neonatal care, it remains associated with high rates of neurodevelopmental impairment (NDI), especially when accompanied by parenchymal involvement and progressive ventricular dilatation.[1,2] The incidence of GMH-IVH is closely associated with the degree of prematurity, and the improved survival of very preterm infants over the last three decades has resulted in a greater number of infants with this type of brain injury.[3,4] Recent data show that GMH-IVH continues to affect around one in five very preterm infants, while it is seen in almost one-half of the extremely preterm population below 26 weeks' gestation.[2,5-7] In term infants, the overall incidence of symptomatic intracranial hemorrhage (ICH) involving the extra-axial cerebrospinal fluid (CSF) spaces is reported in less than 1 per 1000 live births, and severe GMH-IVH is a rare occurrence in this population unless it is associated with bleeding diathesis, trauma, and other conditions causing increased venous pressure such as cerebral sinus venous thrombosis.[8-10]

Post-hemorrhagic ventricular dilatation (PHVD), also commonly referred to as post-hemorrhagic hydrocephalus (PHH), is the most common complication of GMH-IVH and is further associated with increased risk of NDI.[1,11] The risk of PHVD increases with the severity of hemorrhage, and it is seen in around a quarter of very preterm infants with severe GMH-IVH.[5] Although relatively uncommon, PHVD can also occur in term newborns following intraventricular hemorrhage.[12,13] A large number of recent studies reflect an increasing interest in infants born preterm with PHVD and the question of 'when best to treat' has been a matter of debate for many years.[11]

This thesis mainly focuses on neuroimaging characteristics and associated neurodevelopmental outcomes of GMH-IVH, with a specific emphasis on the timing of interventions for PHVD to address this ongoing debate. Some chapters also focus on complications related to neurosurgical interventions for PHVD that were not previously reported in the neonatal literature. In this thesis, the following hypotheses were addressed:

1) In preterm infants with periventricular hemorrhagic infarction (PVHI), neurosonographic characteristics have changed over the last decade and this resulted in more favorable neurodevelopmental outcomes (Chapter 2).
2) In preterm infants with PHVD, having a lower threshold to initiate interventions based on cranial ultrasound (cUS) measurements results in less brain injury and more preserved brain volumes, and result in more favorable neurodevelopmental outcomes (Chapter 3 and 4).

3) In extremely preterm infants, PHVD may impact the maturational processes and cause microstructural white matter abnormalities and adverse neurodevelopmental outcomes (Chapter 5).
4) In infants with PHVD, rapid reduction of ventricular volumes with serial reservoir taps may result in ICH and affect neurodevelopmental outcomes (Chapter 6).
5) In infants with PHVD, corpus callosum injury secondary to neurosurgical interventions for PHVD may result in adverse neurodevelopmental outcomes (Chapter 7).
6) Ultrasound-guided percutaneous needle aspiration may be used as an effective bedside technique in unstable newborn infants with ICH (Chapter 8).

Neuropathology: Basic Mechanisms of Hemorrhagic Brain Injury

How Does GMH-IVH Cause Injury To the Developing Brain?

The presence of blood components in the germinal matrix region and intraventricular compartment have been shown to have negative effects on the developing brain in several animal studies.[14-16] Hemoglobin release from the blood products and their uptake by neurons and microglial cells, and formation of reactive oxygen species due to iron accumulation result in injury to the neural cells as well as axons and pre-oligodendrocytes.[17] Consistent findings were also observed in human studies showing disruption of the ventricular zone and reactive astrogliosis, impairment of proliferation and maturation of oligodendroglial and neuronal precursor cells in the germinal matrix region, and axonal injury and microglial activation in the white matter tissues.[17-20]

How Does PHVD Augment Injury In the Developing Brain?

The mechanisms of the deleterious effects of PHVD on the developing brain are also multifactorial and mediated mainly by mechanical distortion and subsequent ischemia, neuroinflammation and neurotoxicity.[11,17] Several animal and human studies showed CSF levels of tumor necrosis factor-α, transforming growth factor-β, interleukin-1β, interferon-γ, interleukin-6, interleukin-8, interleukin-18, and soluble Fas, elevated cerebral lactate production due to compression of the white matter, and diminished cerebral blood flow and oxygenation to cause additional injury.[11,21-27] It has been hypothesized that removal of hemorrhagic CSF by serial lumbar punctures (LP) may improve the neurodevelopmental outcomes by removal of CSF that contains blood and the inflammatory mediators mentioned above, decrease deposition of extracellular matrix proteins, reduce intracranial pressure and brain edema, and re-establish normal CSF drainage.[28]

Neuroimaging

Neuroimaging for Detecting Hemorrhage and Monitoring Its Complications

Today, cUS is the most widely used neuroimaging modality to diagnose GMH-IVH at the bedside due to its high sensitivity for detecting hemorrhagic brain injury.[1,29] cUS allows physicians caring for the newborn to accurately grade the severity of GMH-IVH based on the location of the GMH-IVH, and presence of acute ventricular dilatation and associated parenchymal hemorrhage, the so-called "PVHI" as described by Volpe (previously referred to as grade-4 hemorrhage by Papile).[30-33] However, cUS is less sensitive than magnetic resonance imaging (MRI) in identifying subtle hemorrhages and white matter injury, which can be seen in up to a quarter of the cases with severe GMH-IVH.[34,35] MRI will also detect small GMH-IVHs in the temporal and occipital regions better than cUS. However, MRI will require the infant to be transferred for scanning in most units, thus it is not the initial diagnostic imaging tool.[29] Computerized tomography (CT) is now largely replaced by MRI due to the ionizing radiation required for imaging, but also for the poor spatial resolution and lower sensitivity to detect small ischemic lesions when compared with MRI. Except for emergencies, CT scans are now generally avoided for newborn imaging.[36]

Below, examples of each grade of GMH-IVH are presented based on a recent consensus approach published by a joint group of neonatal neurology experts from the Netherlands and Canada.[30]

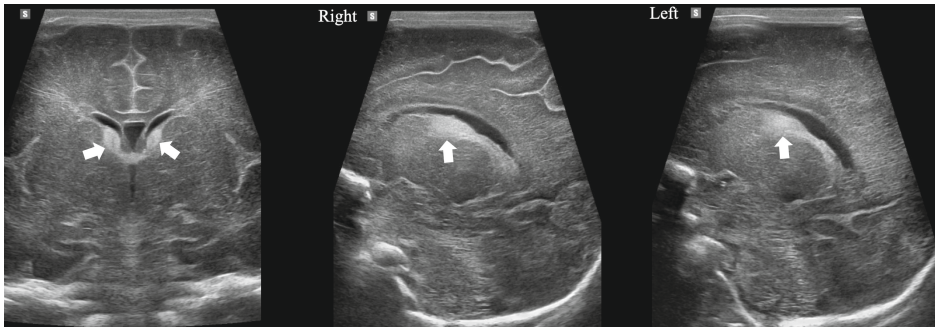


Figure 1: Coronal and sagittal cUS scans of a very preterm infant who was born at 27 weeks' gestation and scanned on postnatal day 4 presenting with bilateral grade-1 GMH-IVH. White arrows point to the round-shaped echogenicities that represent hemorrhages, which are confined to the caudo-thalamic notch that contain germinal matrix regions.

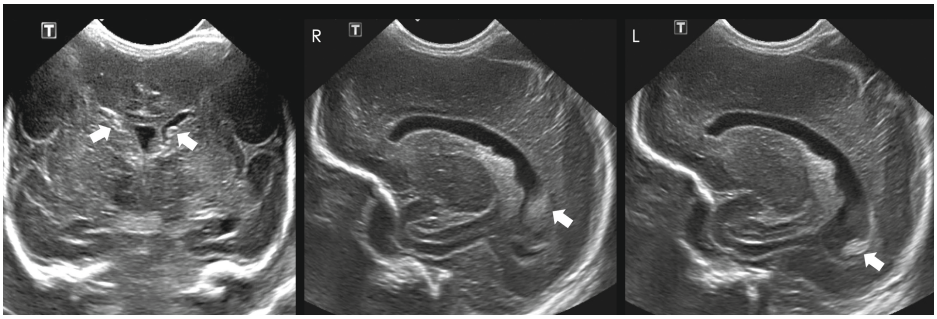


Figure 2: Coronal and sagittal cUS scans of a very preterm infant who was born at 28 weeks' gestation and scanned on postnatal day 3 presenting with bilateral grade-2 GMH-IVH. White arrows indicate hemorrhages that are in the posterior horn of the lateral ventricles, not causing acute distension of the ventricles.

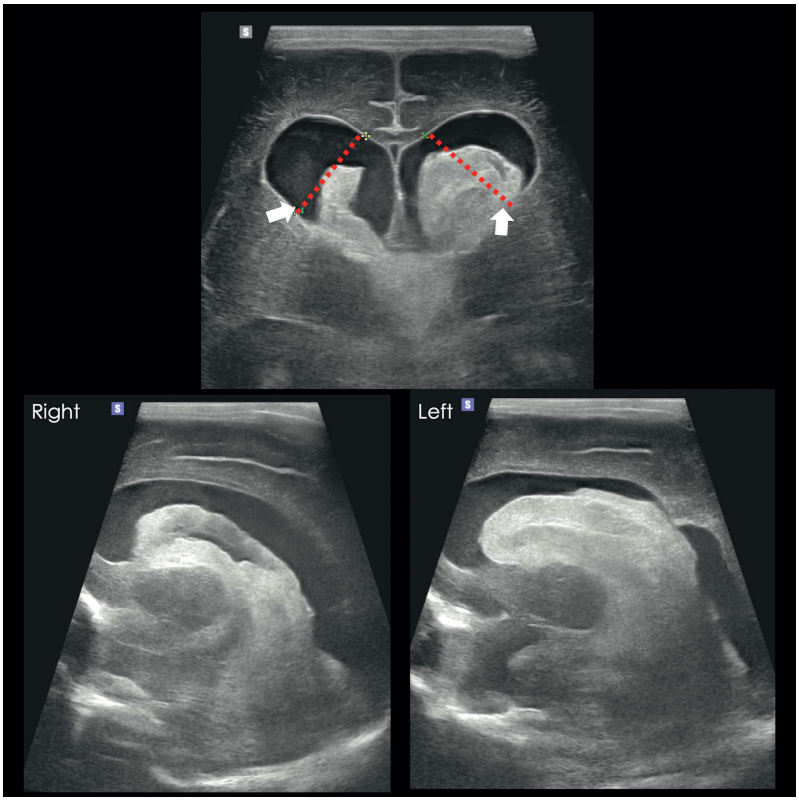


Figure 3: Coronal and sagittal cUS scans of a very preterm infant who was born at 30 weeks' gestation and scanned on postnatal day 14 presenting with bilateral grade-3 GMH-IVH. Blood clots in the intraventricular regions and foramen of Monro cause distension of the ventricles >6 mm (anterior horn width measurements shown by red dashed lines). The acute distension persisting >1 week is now referred to as "PHVD" at this stage.

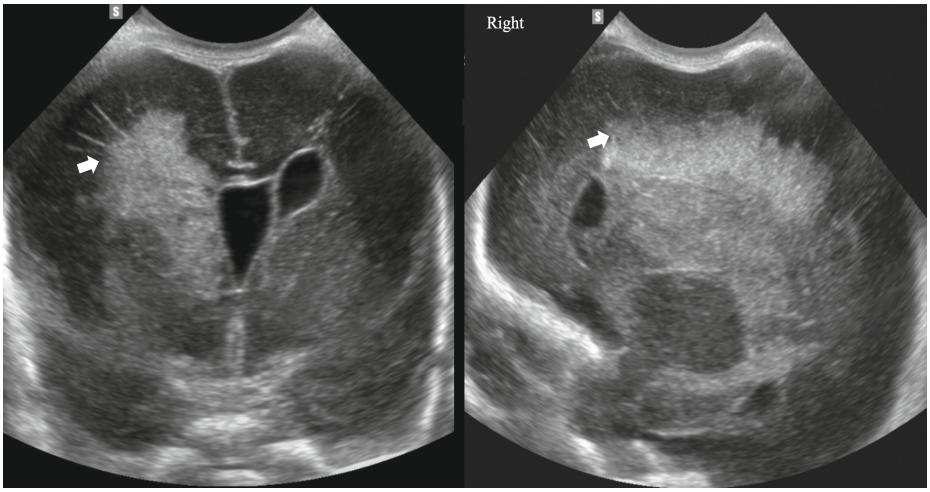
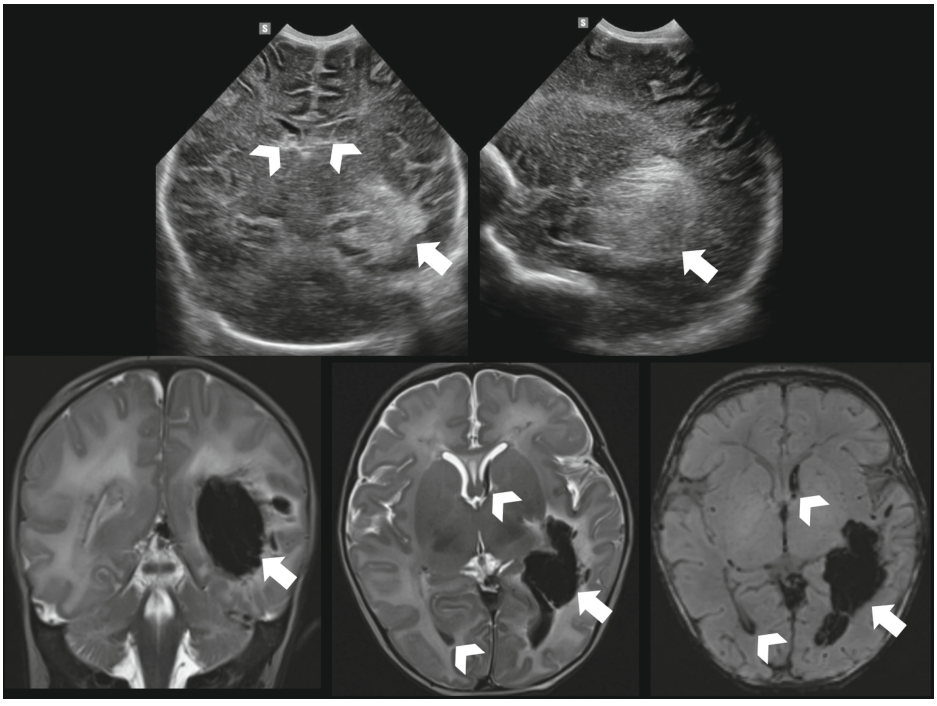


Figure 4: Coronal and sagittal cUS scans of a very preterm infant who was born at 25 weeks' gestation and scanned on postnatal day 7 presenting with a right-sided grade-3 GMH-IVH and accompanying PVHI that is extending to the frontal and parietal white matter in the right hemisphere and causing a midline shift. White arrows point to the hemorrhages that are in the periventricular white matter region. Of note, PVHI is a separate notation to the ipsilateral GMH-IVH and is no longer referred to as grade-4 hemorrhage.



< Figure 5: Coronal and sagittal cUS scans (top panel) and coronal and axial MR images (bottom panel) of a 39$^{3/7}$ week-old term infant presenting with ICH scanned on postnatal day 2. cUS scans show the left-sided temporo-parietal round-shaped echogenicity representing the hemorrhage (white arrows). Also of note, the infant has bilateral intraventricular hemorrhage (arrowheads). Coronal T2-weighted and axial T2-weighted MR images (bottom left and bottom middle, respectively) on postnatal day 2 demonstrate decreased signal intensities consistent with ICH. MR images in this infant also show increased signal intensities in the adjacent white matter regions. Susceptibility-weighted imaging (SWI) on the bottom right shows decreased signal intensity, also referred to as "blooming artefact", confirming the hemorrhage in the same region.

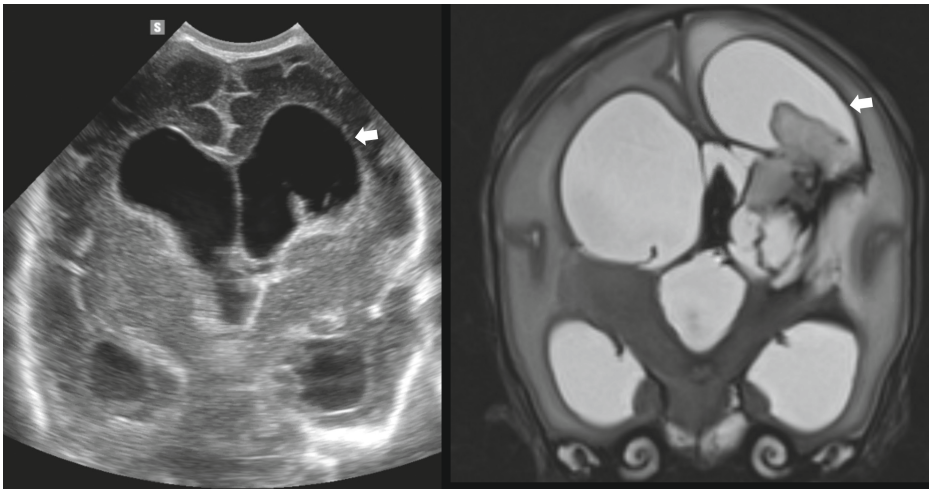


Figure 6: Coronal cUS scan (left) and T2-weighted MRI (right) of a preterm infant with a gestational age of 29 weeks scanned at 34 weeks' postmenstrual age presenting with bilateral grade-3 GMH-IVH. Acute distension of the ventricles persisted >1 week and is therefore referred to as "Post-hemorrhagic ventricular dilatation". PVHI on the left evolved into a large porencephalic cyst (white arrows).

In the Quest Of an Ideal Neuroimaging Protocol

In 2020, the American Academy of Pediatrics (AAP) published a statement on the routine neuroimaging of the preterm brain injury and recommended cUS screening of all preterm infants ≤30 weeks with an initial scan within the first 7 days, and repeat scans at 4-6 weeks of life and around term or discharge from the hospital.[37] These recommendations are similar to that of the Canadian Pediatric Society 2020 guidelines, which recommends an initial cUS scan within 7-14 days, and a repeat scan at 4-6 weeks of life.[36] However, literature on neuroimaging of the preterm brain shows that this infrequent screening protocol may limit the opportunities for the initiation of neurological interventions.[38] Moreover, complex patterns of preterm brain injury, such as PHVD as outlined in this thesis, are only briefly mentioned in these position papers. To

address these issues, a joint group of experts from North America and Europe published a comprehensive review in 2021 on the application of neuroimaging modalities in the preterm infant, emphasizing more frequent serial cUS to improve the timely recognition GMH-IVH and its complications.[38] The details of these recommendations are outlined in the table below.

Table 1: Recommended neuroimaging protocol of the preterm brain[38]

Timing	<28 weeks and/or <1000g	28-32 weeks
1st cUS scan	Day 1 (optional)	Day 1 (optional)
2nd cUS scan	3	4-7
3rd cUS scan	7	14
4th cUS scan	14	28
Repeat cUS scan	21	At term or discharge
Repeat cUS scan	28	
Repeat cUS scan	Every other week until 34 weeks PMA	
Repeat cUS scan	At term or discharge	
Brain MRI	**Routine MRI at term**	**Routine MRI at term if significant risk factors**

It is important to remember that cUS scans should be repeated more frequently than presented in the table above when GMH-IVH is detected. Generally, at least once weekly cUS scanning for low-grade hemorrhage (i.e grade-1 or grade-2) and twice weekly scanning for high-grade hemorrhage (i.e grade-3 with or without PVHI) is recommended as outlined in the aforementioned guideline.[38,39] The studies included in the present thesis used a neuroimaging approach that is similar to the one described above, as frequent cUS scanning has been a longstanding practice at the participating centers.

Finding an Objective Approach: Scoring Systems of Brain Injury

Several brain MRI scoring systems have been developed to address the extent and severity of brain abnormality at term-equivalent age and to predict long-term neurodevelopmental outcome in newborns. Majority of these scoring systems defined exclusively white matter and gray matter signal changes, which can be subjective in nature.[40-42] In 2013, Kidokoro et al.[43] developed a scoring system for brain MRI that more comprehensively and objectively defined brain injury as well as impaired brain growth. This scoring system was applied to brain MRI studies obtained from very preterm infants at term-equivalent age and was found to be a more comprehensive and objective approach to the nature and extent of brain injury in this population. In this thesis, we

used the scoring system described by Kidokoro et al[43] in the nested substudy of the ELVIS trial (Chapter 4).

Treatment of GMH-IVH and Related Complications

Treatment of GMH-IVH is supportive and the mainstay of treatment is reduction of intracranial pressure and thereby improvement of cerebral perfusion, timely detection of complications and avoidance of further brain injury.[1] Although LPs have not been shown to be effective in a recent meta-analysis to prevent PHVD, for the treatment of PHVD interventions typically start with LPs to decompress the ventricles as the initial step.[17,28] It has been hypothesized that the physical removal of CSF that contains blood components and protein might mitigate the inflammatory reaction, decrease deposition of extracellular matrix proteins, and re-establish normal CSF drainage.[28] However, the dilemma on when best to initiate LPs has been a hot topic of neonatal neurology for several decades.[11,44,45] The main question to be addressed is, whether to wait for onset of clinical findings such as an increasing head circumference >2 cm/week, bulging fontanel, split sutures, sunsetting phenomenon of the eyes, cardio-respiratory disturbances, or starting interventions based on cUS measurements well-before the onset of these clinical findings.[11,17] If the latter approach is adopted, then another dilemma is faced, that is determining the ideal cUS threshold for starting interventions.[11] Several studies have used practical sonographic markers such as the ventricular index (VI) described by Levene[46] in combination with anterior horn width (AHW) and thalamo-occipital distance.[47] Alternative markers are the frontal and occipital horn ratio (FOHR) and frontal and temporal horn ratio (FTHR) both of which have been shown to correlate well with ventricular volumes obtained from brain MRI and are used commonly by neurosurgeons to guide decisions.[48-50] Proper measurement techniques of these neuroimaging markers are described in detail below. In this thesis, we used a combination of these sonographic markers and used VI, AHW, TOD in all studies and included FOHR analysis in the nested substudy of the ELVIS trial.[51]

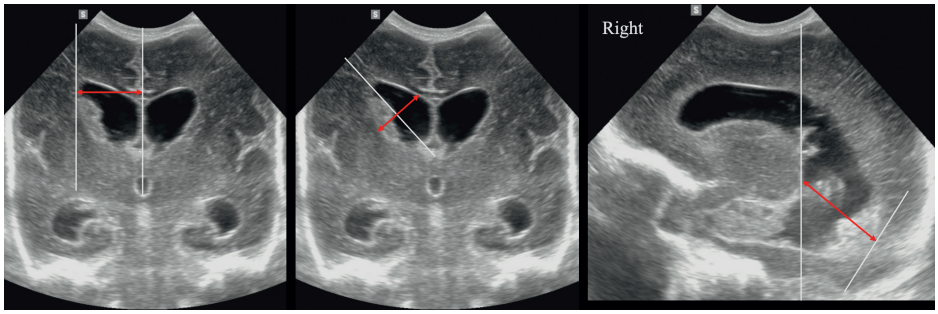
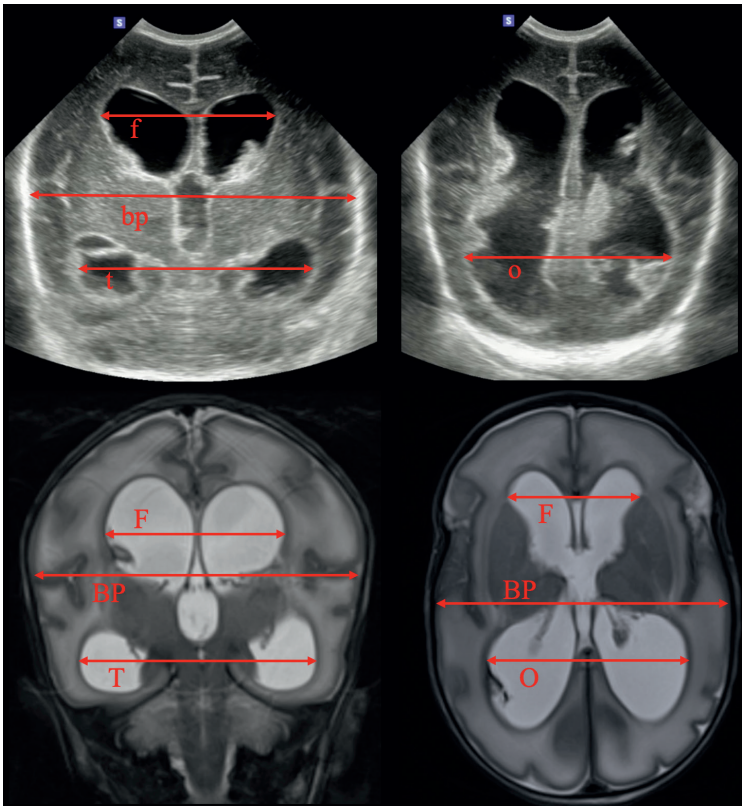


Figure 7: Sonographic markers to monitor distension of the ventricles and resultant PHVD. Coronal cUS scan on the left demonstrates the proper technique to obtain VI, which is the longest horizontal distance (red arrow) between the interhemispheric fissure and outermost portion of the lateral ventricle (white vertical lines) on the coronal plane where the 3rd ventricle and choroid plexus layering the bottom of the lateral ventricles can be visualized. The same image is also used to measure the AHW, which is the longest distance (red arrow) perpendicularly intersecting with the imaginary line (white arrow) that extends between the roof of the 3rd ventricle and outermost point of the lateral ventricle. Sagittal cUS scan on the right, shows the measurement technique of the TOD, which is the longest oblique distance between the most posterior points of the thalamus and posterior horn of the lateral ventricle. Note that these measurements should be done for both sides separately.



< Figure 8: More complex sonographic markers, both of which correlate with the ventricular volumes are represented in this figure. Frontal and temporal horn ratio (FTHR) = (F+T/2)/BP by coronal MRI or (f+t/2)/bp by coronal cUS scan. Frontal and occipital horn ratio (FOHR) = (F+O/ 2)/ BP by axial MRI or (f+o/2)/bp by coronal cUS scan.

These measurements should be plotted on the updated charts by El-Dib et al.[17], which is adapted from the longitudinal data derived from the large cohort of Brouwer et al.[52] Interventions for PHVD start with LPs to decompress the ventricular size and a previous study from our group has shown that LPs initiated before the onset of clinical findings may prevent the need for further neurosurgical interventions in a quarter of infants.[44,53] In a benchmark study by Leijser et al.[54], outcome was evaluated at 18-24 months and it has been shown that preterm infants undergoing intervention at an early stage, even when eventually requiring a VPS had normal developmental test scores that were similar to infants without intervention. In contrast, interventions following onset of clinical symptoms were associated with an increased risk of adverse outcome.

LPs are followed by more invasive temporizing neurosurgical measures if regression of ventricular size does not take place and for this purpose ventricular access device is the most commonly used technique.[17] A recent meta-analysis by Lai et al.[55] showed that later timing of the temporizing interventions predicted higher rates of conversion to ventriculo-peritoneal shunt (VPS) rate and moderate to severe NDI.

Removal of the hemorrhagic CSF by flushing the ventricles with artificial CSF, as used in the drainage, irrigation and fibrinolytic therapy (DRIFT) study[56], and the more recently introduced neuroendoscopic lavage[57] also seem to be promising; however, both techniques are complex and invasive.[11] Also of note, secondary GMH-IVH was reported in one-third of the DRIFT cases.[56] However, intermittent administration of urokinase was also recently studied in a preliminary clinical trial and early removal of hemorrhagic CSF with subsequent urokinase administration was shown to be associated with less VPS requirement and more favorable neurodevelopmental outcomes, with no reported secondary hemorrhages following the procedure.[58]

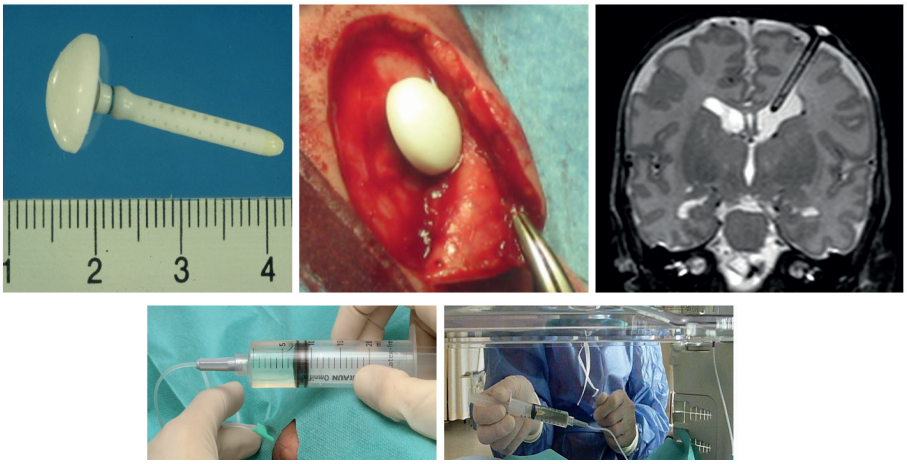


Figure 9: A reservoir is a commonly used VAD. The silicone tubing extends to the lateral ventricle and the dome-shaped reservoir remains under the skin, which enables ventricular taps as guided by radiologic assessments (Figures courtesy of Prof. Linda S. de Vries).

Currently, there is no consensus as to which method of temporizing neurosurgical intervention is best to prevent VPS requirement and NDI, and a meta-analysis by Badhiwala et al.[59] did not report difference in rates of intervention-related complications, death, or neurodevelopmental outcome between different intervention strategies. Some chapters of this thesis (Chapters 6 and 7) will focus on neurosurgical intervention related complications.

Permanent shunt placement is the final resort; however, this usually cannot be performed in the acute phase when the CSF contains excessive amounts of blood components and protein, due to the concern for shunt blockage and dysfunction. Although VPS is considered to be the definitive treatment for PHVD, it can be associated with significant complications, such as infection and shunt malfunction.[1,60] Therefore, novel neurosurgical techniques, such as endoscopic third ventriculostomy and neuroendoscopic lavage are also becoming popular in this population with an aim to prevent from VPS insertion.[61,62]

In contrast to preterm infants who present with GMH-IVH as the most common form of ICH, term newborns generally present with an extra-axial hemorrhage involving the subdural, subarachnoid, subpial, or subgaleal compartments and more rarely with an intra-parenchymal hemorrhage with or without an extra-axial component.[63] The combination of duration of compression of the adjacent brain tissue, the extent of bleeding, and often accompanying seizures can result in adverse neurodevelopmental outcomes; therefore, timely management of this condition in term newborns, which usually includes neurosurgical intervention, is of paramount importance.[64] While a decision for conventional neurosurgical decompression is most often made in the

neonatal population, this may not be possible for all newborns with a significantly compromised cardio-respiratory status.[63-65] cUS-guided bedside percutaneous needle aspiration has emerged as an alternative for these infants and Chapter 8 of the present thesis investigates the efficacy of this minimally invasive bedside treatment modality.[65,66]

Neurodevelopmental Outcomes

Mortality

Mortality in very preterm infants with low-grade GMH-IVH (grade-1 and grade-2) is not significantly higher than that of the general population born at similar gestational age (5-10%) and is usually due to the degree of prematurity and other systemic conditions rather than the GMH-IVH.[5] However, with severe GMH-IVH (grade-3 and PVHI), the mortality was reported to be around one-third of infants with grade-3 GMH-IVH and up to 40% for those with PVHI.[67]

Neurodevelopmental Impairment

NDI is a heterogeneous term and there is no single definition of NDI used in long-term follow-up studies, which makes it challenging to draw conclusions and compare results of different studies. However, a composite of one or more of the following is generally accepted as NDI in most studies: cerebral palsy (CP) requiring assistive device for ambulation or being non-ambulatory, a neurodevelopmental score <-2 SD in a standardized neurodevelopmental test, visual impairment with bilateral acuity <20/200, and hearing impairment requiring bilateral amplification or cochlear implant.[68-70] Two previous large cohort studies showed that NDI affects around 10-20% of very preterm infants with low-grade GMH-IVH (grade-1 and grade-2) and 20-40% of those with high-grade GMH-IVH (grade-3 and PVHI).[69,70] In a large cohort study of more than 1800 infants from France, CP was diagnosed at 5 years of age in 8, 11, 19, and 50% of surviving infants with GMH-IVH grades 1, 2, 3, and PVHI, respectively.[68] A recent study by Hollebrandse et al. showed higher rates of impairment in motor function, intellectual ability and academic skills at school-age in extremely preterm infants with high grade GMH-IVH; and higher rate of CP, but not intellectual ability, executive function, academic skills or overall motor function in infants with low-grade GMH-IVH. However, it is important to note that in infants with low-grade GMH-IVH, the major determinants of long-term NDI are the degree of prematurity and accompanying white matter injury, rather than the GMH-IVH.[38,71,72]

In this thesis, we presented NDIs with a holistic approach and provided all sub-optimal scores (neurodevelopmental test score in any domain between -1 and -2 SD) alongside abnormal scores (neurodevelopmental test score in any domain < -2 SD),

while also including all infants with CP, rather than focusing on the moderate/severe grades of this most common childhood disability.

Outline of this Thesis

Intracranial hemorrhage is an important cause of NDI in multiple developmental domains in both preterm and term infants as outlined in the general introduction. Proper evaluation of the neuroimaging modalities is critical in order to guide timely intervention strategies, and thoroughly inform parents and caregivers.

In Part-I, we addressed the association between neuroimaging findings of high-grade GMH-IVH (grade-3 and PVHI) and outcomes.

Part-I:
Neuroimaging Characteristics of High-Grade GMH-IVH and Association with Neurodevelopmental Outcomes

Chapter 2: Describes the neurosonographic characteristics and their association with neurodevelopmental outcomes at 2 years of age in preterm infants with PVHI.

Chapter 3: Describes the brain injury using an objective scoring system and brain volumes obtained with automatic volumetric analysis at term-equivalent age in preterm infants who underwent low-threshold versus high-threshold interventions for PHVD.

Chapter 4: Describes the neurodevelopmental outcomes at 2 years of age in preterm infants who underwent low-threshold versus high-threshold interventions for PHVD.

Chapter 5: Describes microstructural white matter abnormalities in preterm infants with PHVD with or without PVHI.

In Part-II, we addressed neurosurgical interventions used for the treatment of PHVD and possible adverse events due to these interventions and their association with neurodevelopmental outcomes.

Part-II:
Neurosurgical Interventions for Hemorrhagic Brain Injury and Related Complications

Chapter 6: Describes intra-parenchymal hemorrhages that may occur secondary to reservoir taps, while also investigating possible pathophysiologic mechanisms and association with neurodevelopmental outcomes at 2 years of age.

Chapter 7: Describes corpus callosum injury that may occur secondary to neurosurgical interventions for PHVD and investigates its association with neurodevelopmental outcomes at 2 years of age.

Chapter 8: Illustrates the use of ultrasound-guided percutaneous needle aspiration in newborn infants with ICH and provides a review of the literature.

Chapter 9: Summarizes the findings of this thesis and discusses the implications and future directions for research in this field.

Chapter 10: Summarize the results of this thesis in Dutch.

References

1. Leijser LM, de Vries LS. Preterm brain injury: Germinal matrix-intraventricular hemorrhage and post-hemorrhagic ventricular dilatation. Handb Clin Neurol 2019;162:173-99.
2. Yeo KT, Thomas R, Chow SS, et al. Improving incidence trends of severe intraventricular haemorrhages in preterm infants <32 weeks gestation: a cohort study. Arch Dis Child Fetal Neonatal Ed 2020;105:145-50.
3. Stoll BJ, Hansen NI, Bell EF, et al. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. JAMA 2015;314:1039-51.
4. Kenet G, Kuperman AA, Strauss T, Brenner B. Neonatal IVH--mechanisms and management. Thromb Res 2011;127 Suppl 3:S120-2.
5. Christian EA, Jin DL, Attenello F, et al. Trends in hospitalization of preterm infants with intraventricular hemorrhage and hydrocephalus in the United States, 2000-2010. J Neurosurg Pediatr 2016;17:260-9.
6. Bajwa NM, Berner M, Worley S, Pfister RE, Swiss Neonatal N. Population based age stratified morbidities of premature infants in Switzerland. Swiss Med Wkly 2011;141:w13212.
7. Group E, Fellman V, Hellstrom-Westas L, et al. One-year survival of extremely preterm infants after active perinatal care in Sweden. JAMA 2009;301:2225-33.
8. Hayden CK, Jr., Shattuck KE, Richardson CJ, Ahrendt DK, House R, Swischuk LE. Subependymal germinal matrix hemorrhage in full-term neonates. Pediatrics 1985;75:714-8.
9. Hanigan WC, Powell FC, Miller TC, Wright RM. Symptomatic intracranial hemorrhage in full-term infants. Childs Nerv Syst 1995;11:698-707.
10. Kersbergen KJ, Groenendaal F, Benders MJ, et al. The spectrum of associated brain lesions in cerebral sinovenous thrombosis: relation to gestational age and outcome. Arch Dis Child Fetal Neonatal Ed 2011;96:F404-9.
11. Cizmeci MN, Groenendaal F, de Vries LS. Timing of Intervention for Posthemorrhagic Ventricular Dilatation: An Ongoing Debate. J Pediatr 2021;234:14-6.
12. Schaumann A, Buhrer C, Schulz M, Thomale UW. Neuroendoscopic surgery in neonates - indication and results over a 10-year practice. Childs Nerv Syst 2021.
13. Bhattacharya D, Sharawat IK, Saini L. Intraventricular haemorrhage and obstructive hydrocephalus in a term neonate: an uncommon presentation of haemophilia B. BMJ Case Rep 2018;2018.
14. Juliet PA, Frost EE, Balasubramaniam J, Del Bigio MR. Toxic effect of blood components on perinatal rat subventricular zone cells and oligodendrocyte precursor cell proliferation, differentiation and migration in culture. J Neurochem 2009;109:1285-99.
15. Garton TP, He Y, Garton HJ, Keep RF, Xi G, Strahle JM. Hemoglobin-induced neuronal degeneration in the hippocampus after neonatal intraventricular hemorrhage. Brain Res 2016;1635:86-94.
16. Garton T, Hua Y, Xiang J, Xi G, Keep RF. Challenges for intraventricular hemorrhage research and emerging therapeutic targets. Expert Opin Ther Targets 2017;21:1111-22.
17. El-Dib M, Limbrick DD, Jr., Inder T, et al. Management of Post-hemorrhagic Ventricular Dilatation in the Infant Born Preterm. J Pediatr 2020.
18. Del Bigio MR. Cell proliferation in human ganglionic eminence and suppression after prematurity-associated haemorrhage. Brain 2011;134:1344-61.
19. Supramaniam V, Vontell R, Srinivasan L, Wyatt-Ashmead J, Hagberg H, Rutherford M. Microglia activation in the extremely preterm human brain. Pediatr Res 2013;73:301-9.
20. McAllister JP, Guerra MM, Ruiz LC, et al. Ventricular Zone Disruption in Human Neonates With Intraventricular Hemorrhage. J Neuropathol Exp Neurol 2017;76:358-75.
21. Cherian S, Whitelaw A, Thoresen M, Love S. The pathogenesis of neonatal post-hemorrhagic hydrocephalus. Brain Pathol 2004;14:305-11.

22. Vannucci RC, Hellmann J, Dubynsky O, Page RB, Maisels MJ. Cerebral oxidative metabolism in perinatal post-hemorrhagic hydrocephalus. Dev Med Child Neurol 1980;22:308-16.
23. Kochan M, McPadden J, Bass WT, et al. Changes in Cerebral Oxygenation in Preterm Infants With Progressive Posthemorrhagic Ventricular Dilatation. Pediatr Neurol 2017;73:57-63.
24. Van Bel F, Van de Bor M, Baan J, Stijnen T, Ruys JH. Blood flow velocity pattern of the anterior cerebral arteries. Before and after drainage of posthemorrhagic hydrocephalus in the newborn. J Ultrasound Med 1988;7:553-9.
25. Schmitz T, Heep A, Groenendaal F, et al. Interleukin-1beta, interleukin-18, and interferon-gamma expression in the cerebrospinal fluid of premature infants with posthemorrhagic hydrocephalus--markers of white matter damage? Pediatr Res 2007;61:722-6.
26. Schmitz T, Felderhoff-Mueser U, Sifringer M, Groenendaal F, Kampmann S, Heep A. Expression of soluble Fas in the cerebrospinal fluid of preterm infants with posthemorrhagic hydrocephalus and cystic white matter damage. J Perinat Med 2011;39:83-8.
27. Cherian S, Thoresen M, Silver IA, Whitelaw A, Love S. Transforming growth factor-betas in a rat model of neonatal posthaemorrhagic hydrocephalus. Neuropathol Appl Neurobiol 2004;30:585-600.
28. Whitelaw A, Lee-Kelland R. Repeated lumbar or ventricular punctures in newborns with intraventricular haemorrhage. Cochrane Database Syst Rev 2017;4:CD000216.
29. Plaisier A, Raets MM, Ecury-Goossen GM, et al. Serial cranial ultrasonography or early MRI for detecting preterm brain injury? Arch Dis Child Fetal Neonatal Ed 2015;100:F293-300.
30. Mohammad K, Scott JN, Leijser LM, et al. Consensus Approach for Standardizing the Screening and Classification of Preterm Brain Injury Diagnosed With Cranial Ultrasound: A Canadian Perspective. Front Pediatr 2021;9:618236.
31. Volpe JJ. Intraventricular hemorrhage in the premature infant--current concepts. Part I. Ann Neurol 1989;25:3-11.
32. Volpe JJ. Intraventricular hemorrhage in the premature infant--current concepts. Part II. Ann Neurol 1989;25:109-16.
33. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529-34.
34. Parodi A, Morana G, Severino MS, et al. Low-grade intraventricular hemorrhage: is ultrasound good enough? J Matern Fetal Neonatal Med 2015;28 Suppl 1:2261-4.
35. Ballabh P, de Vries LS. White matter injury in infants with intraventricular haemorrhage: mechanisms and therapies. Nat Rev Neurol 2021;17:199-214.
36. Guillot M, Chau V, Lemyre B. Routine imaging of the preterm neonatal brain. Paediatr Child Health 2020;25:249-62.
37. Hand IL, Shellhaas RA, Milla SS, Committee On F, Newborn SONSOR. Routine Neuroimaging of the Preterm Brain. Pediatrics 2020;146.
38. Inder TE, de Vries LS, Ferriero DM, et al. Neuroimaging of the Preterm Brain: Review and Recommendations. J Pediatr 2021;237:276-87 e4.
39. Ibrahim J, Mir I, Chalak L. Brain imaging in preterm infants <32 weeks gestation: a clinical review and algorithm for the use of cranial ultrasound and qualitative brain MRI. Pediatr Res 2018;84:799-806.
40. Valkama AM, Paakko EL, Vainionpaa LK, Lanning FP, Ilkko EA, Koivisto ME. Magnetic resonance imaging at term and neuromotor outcome in preterm infants. Acta Paediatr 2000;89:348-55.
41. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. N Engl J Med 2006;355:685-94.
42. Miller SP, Ferriero DM, Leonard C, et al. Early brain injury in premature newborns detected with magnetic resonance imaging is associated with adverse early neurodevelopmental outcome. J Pediatr 2005;147:609-16.

43. Kidokoro H, Neil JJ, Inder TE. New MR imaging assessment tool to define brain abnormalities in very preterm infants at term. AJNR Am J Neuroradiol 2013;34:2208-14.
44. Brouwer AJ, Groenendaal F, Han KS, de Vries LS. Treatment of neonatal progressive ventricular dilatation: a single-centre experience. J Matern Fetal Neonatal Med 2015;28 Suppl 1:2273-9.
45. Brouwer AJ, Brouwer MJ, Groenendaal F, Benders MJ, Whitelaw A, de Vries LS. European perspective on the diagnosis and treatment of posthaemorrhagic ventricular dilatation. Arch Dis Child Fetal Neonatal Ed 2012;97:F50-5.
46. Levene MI. Measurement of the growth of the lateral ventricles in preterm infants with real-time ultrasound. Arch Dis Child 1981;56:900-4.
47. Davies MW, Swaminathan M, Chuang SL, Betheras FR. Reference ranges for the linear dimensions of the intracranial ventricles in preterm neonates. Arch Dis Child Fetal Neonatal Ed 2000;82:F218-23.
48. Kulkarni AV, Drake JM, Armstrong DC, Dirks PB. Measurement of ventricular size: reliability of the frontal and occipital horn ratio compared to subjective assessment. Pediatr Neurosurg 1999;31:65-70.
49. Antes S, Kiefer M, Schmitt M, Lechtenfeld M, Geipel M, Eymann R. Frontal and temporal horn ratio: a valid and reliable index to determine ventricular size in paediatric hydrocephalus patients? Acta Neurochir Suppl 2012;114:227-30.
50. Radhakrishnan R, Brown BP, Kralik SF, et al. Frontal Occipital and Frontal Temporal Horn Ratios: Comparison and Validation of Head Ultrasound-Derived Indexes With MRI and Ventricular Volumes in Infantile Ventriculomegaly. AJR Am J Roentgenol 2019;213:925-31.
51. Cizmeci MN, Khalili N, Claessens NHP, et al. Assessment of Brain Injury and Brain Volumes after Posthemorrhagic Ventricular Dilatation: A Nested Substudy of the Randomized Controlled ELVIS Trial. J Pediatr 2019;208:191-7 e2.
52. Brouwer MJ, de Vries LS, Groenendaal F, et al. New reference values for the neonatal cerebral ventricles. Radiology 2012;262:224-33.
53. de Vries LS, Groenendaal F, Liem KD, et al. Treatment thresholds for intervention in posthaemorrhagic ventricular dilation: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2019;104:F70-F5.
54. Leijser LM, Miller SP, van Wezel-Meijler G, et al. Posthemorrhagic ventricular dilatation in preterm infants: When best to intervene? Neurology 2018;90:e698-e706.
55. Lai GY, Chu-Kwan W, Westcott AB, Kulkarni AV, Drake JM, Lam SK. Timing of Temporizing Neurosurgical Treatment in Relation to Shunting and Neurodevelopmental Outcomes in Posthemorrhagic Ventricular Dilatation of Prematurity: A Meta-analysis. J Pediatr 2021;234:54-64 e20.
56. Whitelaw A, Evans D, Carter M, et al. Randomized clinical trial of prevention of hydrocephalus after intraventricular hemorrhage in preterm infants: brain-washing versus tapping fluid. Pediatrics 2007;119:e1071-8.
57. Schulz M, Buhrer C, Pohl-Schickinger A, Haberl H, Thomale UW. Neuroendoscopic lavage for the treatment of intraventricular hemorrhage and hydrocephalus in neonates. J Neurosurg Pediatr 2014;13:626-35.
58. Park YS, Kotani Y, Kim TK, et al. Efficacy and safety of intraventricular fibrinolytic therapy for post-intraventricular hemorrhagic hydrocephalus in extreme low birth weight infants: a preliminary clinical study. Childs Nerv Syst 2021;37:69-79.
59. Badhiwala JH, Hong CJ, Nassiri F, Hong BY, Riva-Cambrin J, Kulkarni AV. Treatment of posthemorrhagic ventricular dilation in preterm infants: a systematic review and meta-analysis of outcomes and complications. J Neurosurg Pediatr 2015;16:545-55.
60. Arrington CN, Ware AL, Ahmed Y, Kulesz PA, Dennis M, Fletcher JM. Are Shunt Revisions Associated with IQ in Congenital Hydrocephalus? A Meta -Analysis. Neuropsychol Rev 2016;26:329-39.

61. Kulkarni AV, Sgouros S, Leitner Y, Constantini S, International Infant Hydrocephalus Study I. International Infant Hydrocephalus Study (IIHS): 5-year health outcome results of a prospective, multicenter comparison of endoscopic third ventriculostomy (ETV) and shunt for infant hydrocephalus. Childs Nerv Syst 2018;34:2391-7.
62. d'Arcangues C, Schulz M, Buhrer C, Thome U, Krause M, Thomale UW. Extended Experience with Neuroendoscopic Lavage for Posthemorrhagic Hydrocephalus in Neonates. World Neurosurg 2018;116:e217-e24.
63. Gupta SN, Kechli AM, Kanamalla US. Intracranial hemorrhage in term newborns: management and outcomes. Pediatr Neurol 2009;40:1-12.
64. Vinchon M, Pierrat V, Tchofo PJ, Soto-Ares G, Dhellemmes P. Traumatic intracranial hemorrhage in newborns. Childs Nerv Syst 2005;21:1042-8.
65. Vachharajani A, Mathur A. Ultrasound-guided needle aspiration of cranial epidural hematoma in a neonate: treating a rare complication of vacuum extraction. Am J Perinatol 2002;19:401-4.
66. Noguchi M, Inamasu J, Kawai F, et al. Ultrasound-guided needle aspiration of epidural hematoma in a neonate after vacuum-assisted delivery. Childs Nerv Syst 2010;26:713-6.
67. Brouwer A, Groenendaal F, van Haastert IL, Rademaker K, Hanlo P, de Vries L. Neurodevelopmental outcome of preterm infants with severe intraventricular hemorrhage and therapy for post-hemorrhagic ventricular dilatation. J Pediatr 2008;152:648-54.
68. Beaino G, Khoshnood B, Kaminski M, et al. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. Dev Med Child Neurol 2010;52:e119-25.
69. Bolisetty S, Dhawan A, Abdel-Latif M, et al. Intraventricular hemorrhage and neurodevelopmental outcomes in extreme preterm infants. Pediatrics 2014;133:55-62.
70. Payne AH, Hintz SR, Hibbs AM, et al. Neurodevelopmental outcomes of extremely low-gestational-age neonates with low-grade periventricular-intraventricular hemorrhage. JAMA Pediatr 2013;167:451-9.
71. Gomaa N, Miller SP. Intraventricular haemorrhage in preterm children: viewing longer term with a wider lens. Arch Dis Child Fetal Neonatal Ed 2021;106:2-3.
72. Hollebrandse NL, Spittle AJ, Burnett AC, et al. School-age outcomes following intraventricular haemorrhage in infants born extremely preterm. Arch Dis Child Fetal Neonatal Ed 2021;106:4-8.

Part I

Neuroimaging Characteristics of High-Grade GMH-IVH and Association with Neurodevelopmental Outcomes

"If one day my words contradict with what science says,
choose science"

Mustafa Kemal Atatürk

2

Periventricular Hemorrhagic Infarction in Very Preterm Infants: Characteristic Sonographic Findings and Association with Neurodevelopmental Outcome at Age 2 Years

Mehmet N. Cizmeci, Linda S. de Vries, Linh G. Ly, Ingrid C. van Haastert, Floris Groenendaal, Edmond N. Kelly, Jeffrey Traubici, Hilary E. Whyte, Lara M. Leijser

J Pediatr 2020; 217: 79-85 DOI: 10.1016/j.jpeds.2019.09.081

Abstract

Objective: To describe the sonographic characteristics of periventricular hemorrhagic infarction (PVHI) and their association with mortality and neurodevelopmental disability in very preterm infants born in 2008-2013.

Study design: Retrospective multicenter observational cohort study. Diagonal PVHI size was measured and severity score assessed. PVHI characteristics were scored and temporal trends were assessed. Neurodevelopmental outcome at 2 years of corrected age was assessed using either the Bayley Scales of Infant and Toddler Development, Third Edition or the Griffiths Mental Development Scales. Multigroup analyses were applied as appropriate.

Results: We enrolled 160 infants with median gestational age of 26.6 weeks. PVHI was mostly unilateral (90%), associated with an ipsilateral grade III intraventricular hemorrhage (84%), and located in the parietal lobe (51%). Sixty-four (40%) infants with PVHI died in the neonatal period. Of the survivors assessed at 2 years of corrected age, 65% had normal cognitive and 69% had normal motor outcomes. The cerebral palsy rate was 42%. The composite outcome of death or severe neurodevelopmental disability was observed in 58%, with no trends over the study period (P = .6). Increasing PVHI severity score was associated with death (P < .001). Increasing PVHI size and severity score were negatively associated with gross motor scores (P = .01 and .03, respectively). Trigone involvement was associated with cerebral palsy (41% vs 14%; P = .004). Associated post-hemorrhagic ventricular dilation (36%) was an independent risk factor for poorer cognitive and motor outcomes (P < .001 for both).

Conclusions: Increasing PVHI size and severity score were predictive of less optimal gross motor outcome and death in very preterm infants.

Introduction

Germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH) remains a common form of brain injury in very preterm infants with an overall incidence of around 25%.[1] Approximately 10%-15% of infants with GMHIVH exhibit a hemorrhagic lesion in the periventricular white matter, a so-called periventricular hemorrhagic infarction (PVHI), previously referred to as a grade IV Intraventricular hemorrhage (IVH).[1] Neuropathologic studies have shown that, rather than representing an extension of the IVH, PVHI is due to impaired venous drainage of the medullary veins in the periventricular white matter.[2-4] PVHI can be globular or triangular in shape and often evolves into a porencephalic cyst.[1,3,5-7] The destructive impact of PVHI on the developing preterm brain architecture has been demonstrated with advanced magnetic resonance imaging techniques.[8] However, cranial ultrasonography (US) remains the key diagnostic tool for the detection and monitoring of PVHI.[6,9-11] Previous cranial US studies have described the characteristics of PVHI, with the majority of cases being unilateral, extensive and predominantly affecting the frontal and parietal lobes.[1,6,11,12]

Several large cohort studies showed a decrease in the incidence of severe IVH, defined as grade III and IV according to Papile et al, over the past decades.[13-15] A recent large cohort study showed a decline in severe IVH to as low as 5.9% using the same classification.[16] The high mortality rate in infants with PVHI of up to 60% in the 1980s has also decreased to around 40%. Furthermore, recent studies have suggested a more favorable neurodevelopmental outcome related to PVHI.[6,12,17,18] The characteristics of PVHI, incidence, and implications for outcome, in the current era require reassessment. In this study, we sought to describe the sonographic characteristics of PVHI and investigate their trends from 2008-2013, while also studying their relation to mortality and/or neurodevelopmental disability.

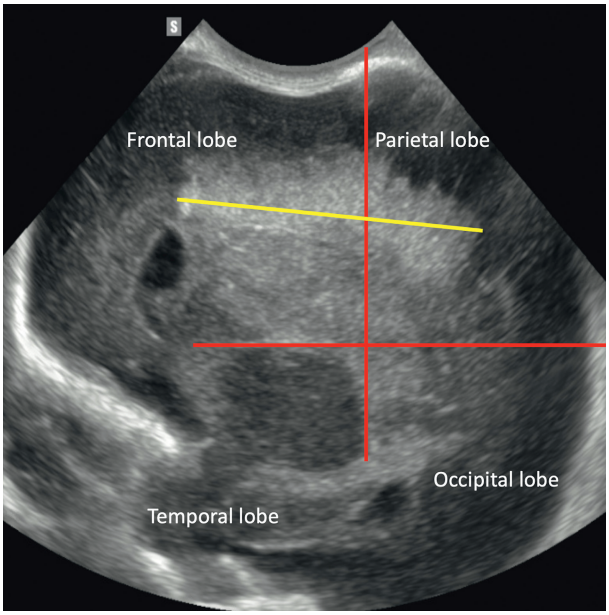
Methods

For this retrospective, multicenter, observational cohort study, preterm infants were eligible if they had a gestational age of <32 weeks and were admitted to 1 of 3 tertiary neonatal intensive care units (Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands; The Hospital for Sick Children and Mount Sinai Hospital, University of Toronto, Canada) between January 2008 and December 2013, and were diagnosed with PVHI. A database search of all available neonatal cranial US scans of eligible infants was conducted. Exclusion criteria included <3 cranial US scans within the first 10 postnatal days (to decrease the likelihood of underestimating the full extent of the hemorrhage), dysmorphic features or congenital anomalies suggesting a genetic syndrome, metabolic disorder, and congenital brain malformation. Approval from the

research ethics boards at each center was obtained; requirement for informed consent with anonymized data was waived.

Ultrasound Protocol and Image Assessment

Cranial US images were obtained through the anterior fontanel and at least 6 coronal and 5 sagittal planes were recorded. The mastoid window was used to obtain closer images of the posterior fossa if a cerebellar hemorrhage was suspected after imaging through the anterior fontanel. Imaging was done according to the local cranial US protocols, which remained constant throughout the study period. Detailed description of the cranial US procedures and protocols is presented in the Appendix-1. All digitally stored cranial US scans of included infants were assessed separately by 2 neonatologists with substantial experience in neonatal neuroimaging, who were blinded to the infants' clinical history and imaging findings. In equivocal cases, a third investigator with >30 years of experience in cranial US was consulted. Assessment included PVHI size, characteristics, accompanying IVH grade, severity, and associated lesions. PVHI was defined as an echogenic lesion in the brain parenchyma associated with an ipsilateral GMH-IVH, identified in both coronal and parasagittal views.[1] The side, shape, location, number of lobes involved, and grade of the ipsilateral IVH were noted. PVHI size was measured as the longest diagonal diameter of the echogenic lesion in the parasagittal view at the time of its maximum extent (Figure 1). Timing of first appearance of PVHI and evolution to its maximum extent in days were noted. Trends in PVHI characteristics during the study period were assessed.



< Figure 1: Right parasagittal cranial US image of a preterm infant with PVHI illustrating the measurement of the diagonal size of the lesion (yellow oblique line). To determine the lobes involved, 2 imaginary lines (long vertical and horizontal lines in red) bordering the posterior and superior margins of the thalamus on the involved side were drawn in the parasagittal plane.

For scoring PVHI severity, the scoring scheme as described by Bassan et al was used.[6] This scoring system is based on laterality, midline shift, and PVHI extent. Scores range from a minimum of 0 to a maximum of 3. To determine the lobes involved, 2 imaginary lines bordering the posterior and superior margins of the thalamus on the involved side were drawn in the parasagittal plane (Figure 1).[6] A special note was made regarding involvement of the central sulcus and/or trigone area in a parasagittal view, and development of a porencephalic cyst. The presence of IVH (as described by Volpe[19]) on the contralateral side and of cystic white matter injury, post-hemorrhagic

ventricular dilation, and cerebellar hemorrhage were recorded. Post-hemorrhagic ventricular dilation was defined as ventricular enlargement with the ventricular index being above the 97th percentile for postmenstrual age.[20]

Neurodevelopmental Outcome

Neurologic status was assessed by the attending neonatologist. Developmental assessments were performed by experienced developmental specialists (pediatric physiotherapist, special educator, child behavior specialist, or neonatologist), using the SD scores from the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III, cognitive and motor composite scores) or Griffiths Mental Development Scales (GMDS) 24 months of corrected age. Presence of cerebral palsy and, if applicable, severity and type were retrieved from the infants' files. The gross motor function classification system (GMFCS level I-V) was used to grade the severity of cerebral palsy.[21] The composite outcome of death or severe neurodevelopmental disability was defined as death or a cognitive or motor score more than 2 SD below the standardized mean for the test. A detailed description of the neurodevelopmental assessments and the scoring is available in the Appendix-2.

Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics v 25 (SPSS Inc, Chicago, Illinois). Continuous variables were presented as the mean (SD) and median (IQR) depending on their distribution. Categorical values were presented as number and percentages. The c2 test was used to compare categorical variables among groups. Mann-Whitney U test was used to compare nonparametric variables and Student t-test for comparison between sonographic variables with normal distribution. Trends in PVHI characteristics during the study period were assessed using the Kruskal-Wallis test to

compare nonparametric variables and ANOVA for normally distributed variables. The Pearson correlation coefficient was used to assess the correlation between continuous variables. Hierarchical multiple linear regression and logistic regression analyses were applied for the significant variables detected with the univariate analysis. Receiver operating characteristic analysis was used to evaluate the performance of the severity score to predict mortality. To evaluate intra and inter-observer agreement (interclass correlation coefficient [ICC]) for PVHI size measurements, cranial US from 10 infants were randomly assessed. ICC was classified as good for 0.8 <ICC<0.9 and excellent for ICC >0.9. With the present population of 160 infants (approximately 25 per year), we were able to detect a yearly difference in the size of 4 mm with an alpha of 0.05 and power of 0.80. Statistical significance was set at $P < .05$.

Results

PVHI was diagnosed in 163 out of 3764 (4.3%) of the preterm infants with a gestational age of <32 weeks who were admitted to the three participating centers during the study period. Three infants (2 from the Toronto and 1 from the Utrecht cohorts) were excluded due to insufficient number of cranial US. Clinical characteristics of 160 included infants are presented in Table 1.

Table 1: Clinical parameters of included very preterm infants (n=160) with PVHI.

Clinical parameters	
Gestational age, weeks	26.6 (25.1-28.0)
Birthweight, gram	900 (730-1132)
Male	97 (61)
Plurity	
Singleton	127 (79)
Twin/Triplet	33 (21)
†Apgar score at 1 min ≤5	66 (58)
†Apgar score at 5 min ≤5	27 (24)
‡Antenatal corticosteroid administration	73 (63)
†IPPV for initial respiratory stabilization	60 (53)
Inotrope requirement	24 (15)
Culture + EONS	17 (11)
hsPDA	
Pharmacological treatment	26 (16)
Surgical treatment	20 (12)

Table 1: *[Continued]*

Clinical parameters	
Death	64 (40)
Death, postnatal day	7 (4-17)

† Data available for 113 infants
‡ Data available for 116 infants
Numbers are depicted as n (%) or median (IQR)

PVHI Characteristics Intra- and interobserver reliability for the measurements of PVHI size showed an excellent correlation (ICC = 0.98 for both). Timing of the cranial US assessments and characteristics of PVHI are presented in Table II. Median (IQR) day of age at first detection of PVHI was 3 days and the largest PVHI size was reached by day 5 (3-8). PVHI was mostly unilateral, with an almost equal division between left and right hemisphere, and frequently associated with an ipsilateral grade III IVH. The parietal lobe, either isolated or in combination, was involved in the majority (51%) of infants, followed by the frontal and occipital lobes (30% and 18%, respectively). Bilateral PVHI (10%) more often involved >1 lobe at the side of the largest PVHI (82% vs 18%; P < .001) and showed a trend towards larger size (26 mm [14-31] vs 16 mm [12-25]; P = .06) compared with unilateral PVHI. Severity score was 0 in 63 (39%), 1 in 60 (38%), 2 in 35 (22%) and 3 in 2 (1%) infants.

Among the 96 infants who survived the neonatal period, PVHI evolved into a single large porencephalic cyst in 75 (78%), multiple small cysts in 18 (19%), and combination of both in 3 (3%) on later scans. Cystic white matter injury was present in 7 (7%) of survivors. Presence of trigone and central sulcus involvement and associated lesions are also presented in Table 2.

Table 2: Sonographic characteristics and outcome of included very preterm infants with PVHI.

Sonographic Characteristics	**n=160**
Day of life of first sonographic assessment	
1	87 (54)
2	34 (21)
3	26 (17)
4-6	13 (8)
Median (IQR)	1 (1-2)
Day of life of first sonographic detection of PVHI	

Table 2: *[Continued]*

Sonographic Characteristics	n=160
1	37 (22)
2-3	79 (50)
4-6	44 (28)
Median (IQR)	3 (2-4)
Side and location	
Right hemisphere	70 (44)
Frontal lobe	40 (29)
Parietal lobe	71 (52)
Temporal lobe	1 (1)
Occipital lobe	25 (18)
Left hemisphere	73 (46)
Frontal lobe	46 (32)
Parietal lobe	78 (53)
Temporal lobe	0 (0)
Occipital lobe	22 (15)
Both hemispheres	17 (10)
Frontal lobe	17 (32)
Parietal lobe	24 (44)
Temporal lobe	0 (0)
Occipital lobe	13 (24)
Number of lobes involved	
1	62 (39)
2	70 (44)
3	28 (18)
Grade of ipsilateral GMH-IVH	
I	5 (3)
II	23 (13)
III	147 (84)
Shape of lesion	88 (55)
Globular	66 (41)
Fan	6 (4)
Indeterminate	
Size, mm	18 (12-27)
Midline shift present	27 (17)
Trigone involvement	100 (62)

Table 2: *[Continued]*

Sonographic Characteristics	**n=160**
Central sulcus involvement	78 (49)
Associated cerebellar hemorrhage	15 (10)
Concomitant PHVD	57 (36)
Reservoir	24 (42)
VP-shunt	17 (30)
Cognitive outcome	
Normal (mean ± 1 SD)	48 (65)
Subclinical range (-1 and -2 SD)	17 (23)
Clinical range (< -2 SD)	9 (12)
Motor outcome	
Normal (mean ± 1 SD)	51 (69)
Subclinical range (-1 and -2 SD)	8 (11)
Clinical range (< -2 SD)	15 (20)
GMFCS scores	
Level I	18 (58)
Level II	7 (23)
Level III	3 (10)
Level IV	2 (6)
Level V	1 (3)

Numbers are depicted as n (%) or median (IQR)

PVHI size and sonographic characteristics did not change over the study period assessed per year of birth (P > .05 for all) (Figure 2). No correlation was found between gestational age or birth weight and diagonal PVHI size (r = 0.05, P = .5 for both), nor between any of the other clinical measures and PVHI size. Severity score was weakly correlated with gestational age and birth weight (r = 0.2, P = .01 and r = 0.2, P = .02, respectively). No further association was found between other clinical measures and severity score.

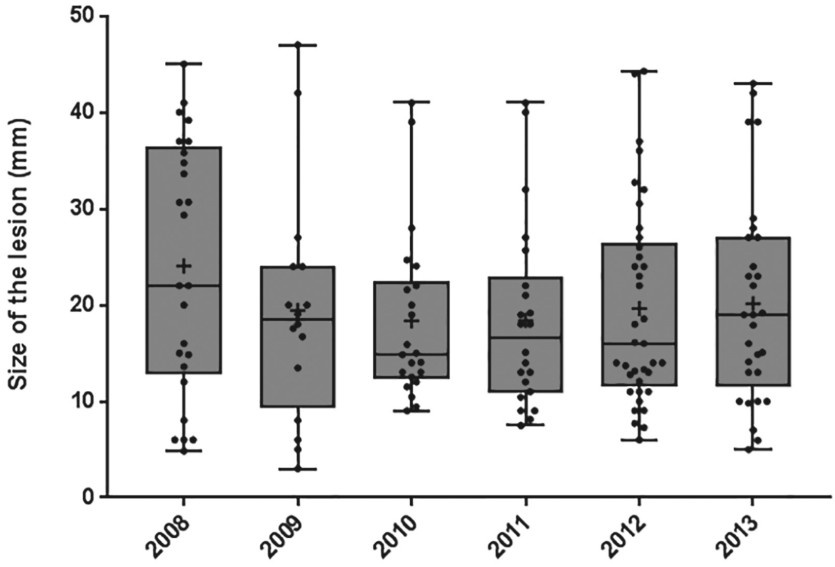


Figure 2: Box-plot graphics showing no trend in PVHI size during the study period.

Neurodevelopmental Outcome and Relation with PVHI Characteristics

Mortality

Sixty-four (40%) infants died at median postnatal day 7 (4-18); 50 (78%) died following a decision to redirect care. The rate of redirection of care over time remained unchanged (P = .4) and was similar in all 3 participating centers. In all infants who died following redirection of care, the decision was based on a combination of the degree of prematurity, the extent of IVHand PVHI, as well as the presence and severity of other morbidities. Characteristics of infants who died with and without redirection of care are shown in Table 3.

Table 3: Clinical characteristics of the study population who died with and without redirection of care.

	Mortality with Redirection of Care (n=50)	Mortality without Redirection of Care (n=14)	p
GA at birth, wk (mean ± SD)	25.8 ± 1.5	25.6 ± 1.7	0.9[a]
BW, g median (IQR)	805 (653-927)	715 (660-753)	0.3[b]
Sex			
Male	30 (60)	6 (43)	0.3[c]
Female	20 (40)	8 (57)	
Laterality			
Unilateral PVHI	37 (74)	13 (93)	0.1[c]
Bilateral PVHI	13 (26)	1 (7)	
Size of PVHI, mm	24 (13-35)	22 (12-39)	0.6[b]
Midline shift present, n (%)	19 (38)	4 (29)	0.3[c]
PHVD present, n (%)	15 (30)	3 (25)	0.7[c]
Severity score, median (IQR)	2 (1-2)	1 (0-2)	0.1[b]
[†]Mortality rate by center			
Wilhelmina Children's Hosp.	10 (71)	4 (29)	0.5[c]
The Hospital for Sick Children	18 (86)	3 (14)	
Mount Sinai Hosp.	22 (76)	7 (24)	
[‡]Mortality rate by years			
2008	12 (86)	2 (14)	
2009	8 (89)	1 (11)	
2010	7 (88)	1 (12)	0.4[c]
2011	7 (88)	1 (12)	
2012	9 (64)	5 (36)	
2013	7 (64)	4 (36)	

[a]t-test, [b]Mann-Whitney U test, [c]Chi Square test
[†]Numbers in parenthesis represent the percentage in each center
[‡]Numbers in parenthesis represent the percentage in each year

Univariate analysis revealed a significant association between increasing PVHI severity score (range 0-3) and mortality (22%, 32%, 83%, 100%, respectively; P < .001). Infants who died had larger PVHI compared with survivors (23 mm [13-35] vs 15 mm [11-22]; P = .002). There was also a significant difference in the size of PVHI among infants who died <7 days (25 mm [15-37]) compared with those who died >7 days (20 mm [11-27]) and survivors (15 mm [11-22], P = .001) (Figure 3).

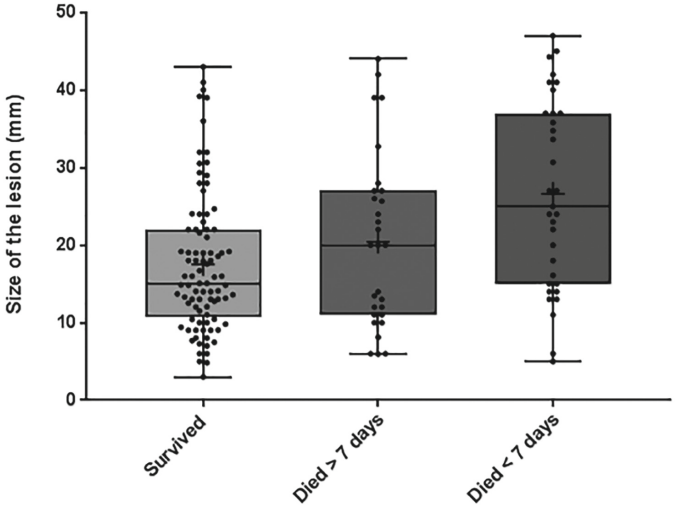


Figure 3: A significant difference in size of PVHI was seen among infants who died <7 days of birth compared with survivors.

Infants who died had lower median gestational age and birth weight (25.7 [24.7-27] vs 27.1 weeks [25.9-28.9] and 765 [658-911] vs 980 g [835-1250] g; P < .001 for both), and more often showed midline shift (85 vs 31%; P < .001) and bilaterality (82 vs 35%; P < .001) compared with survivors. Larger PVHI size was independently associated with increased likelihood of death after correcting for known risk factors for PVHI including gestational age, birth weight, center of birth, antenatal steroids, and low Apgar score at 5 minutes (OR 1.15, 95% CI 1.07-1.25; P < .001). Higher severity score was also associated with death after correcting for the same variables (OR 136 [10-1719]; P < .001 for a score of 2). The area under the receiver operating characteristic curve of the severity score for mortality was 0.74 (95% CI 0.65-0.83) with the cut-off value of 2.

Neurodevelopmental Outcomes

Among 96 survivors, 22 (23%) were lost to follow-up. Infants who were lost to follow-up were similar to those with follow-up with respect to demographic and clinical variables (P > .05 for all). Neurodevelopmental assessment was available for 74 (77%), of whom 63 (85%) underwent BSID-III and 11 (15%) GMDS assessment. The median age at follow-up was 23.8 months (19- 24.2). Mean BSID-III cognitive and motor composite scores were 95 (±19) and 96 (±16). Gross and fine motor scaled scores were 8 (±3) and 10 (±3), respectively. The mean GMDS developmental quotient was 95 (±9) (Table II). cerebral palsy was present in 31 survivors (42%), of whom 30 (97%) had unilateral spastic cerebral palsy and 1 (3%) spastic quadriplegia. Among the infants with cerebral palsy, 25 (81%) had a GMFCS level I-II, and 6 (19%) had III-V (Table 2). No change in outcome scores was

seen over the course of the study period. The composite outcome of death or severe neurodevelopmental disability was 58% (n = 80) in infants with known outcomes and did not change during the study period (P = .6) (Figure 4).

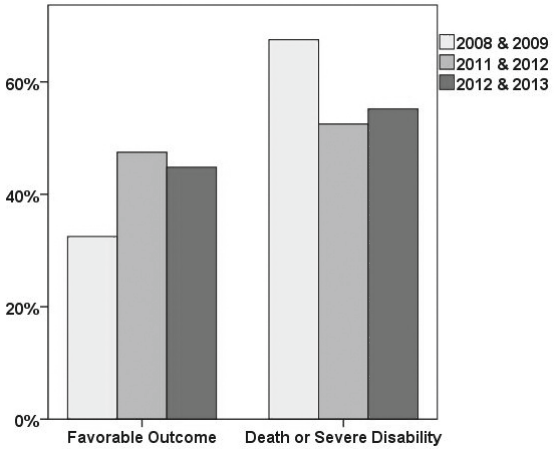


Figure 4: Bar charts showing the rate of favorable outcome versus the composite outcome of death or severe neurodevelopmental disability during the study period.

Both PVHI size and severity score were negatively associated with gross motor z scores (ß [95% CI] -0.04 [-0.07; -0.01]; P = .01; and (-0.5 [-0.9; -0.03]; P = .03) but not with fine motor and cognitive scores. Higher PVHI severity score was independently associated with increased likelihood of composite outcome of death or severe neurodevelopmental disability after correcting for gestational age, birth weight, year of birth, center of birth, antenatal steroids, and low Apgar score at 5 minutes (OR 10.8 [95% CI] 2.3-51.8; P = .003). Trigone involvement was associated with cerebral palsy (41% vs 14%; P = .004), even after correction for gestational age, birth weight, PVHI severity score, and post-hemorrhagic ventricular dilation (OR 4.0, 95% CI 1.3-12.5; P = .01), and a trend toward lower gross motor z scores (P = .05). No association was found between central sulcus involvement or any of the other PVHI characteristics and outcome scores and cerebral palsy (P > .05 for all). In the univariate analysis, infants with concomitant post-hemorrhagic ventricular dilation had lower median (IQR) z scores for cognitive (-1.4 [-2 to -0.08] vs 0.06 [-0.66 to 1], P < .001), gross motor (-1.16 [-2.7 to -0.7] vs -0.3 [-0.7 to -0.3], P = .001) and fine motor (-0.16 [-1.3 to -0.3] vs 0.7 [-0.03 to 1.1], P = .005) abilities than infants without post-hemorrhagic ventricular dilation. In the multivariable analysis, post-hemorrhagic ventricular dilation was an independent risk factor for less optimal cognitive and motor outcomes after controlling for gestational age, PVHI size, cystic white matter injury, and cerebellar hemorrhage (ß [95% CI] -1.3 [-0.7; -1.9]; P < .001, and -1.4 [-0.8; -2.0]; P < .001, respectively).

Discussion

Severe IVH continues to be a burden for very preterm infants despite ongoing improvements in perinatal care over recent years.[1,14,16] In this multicenter, observational study we described the sonographic characteristics of PVHI and their association with neurodevelopmental outcomes and mortality. Using a previously described severity score[6] and adding a novel quantitative measure of PVHI size, we found a more benign sonographic appearance of PVHI with respect to lesion severity, multiple lobe involvement, midline shift and bilaterality compared with studies from a decade ago.[5,6,12,22-26] Although mortality rate (40%) was similar, a composite outcome of death or severe neurodevelopmental disability (58%), and cognitive and motor outcomes at 2 years of corrected age were slightly better and cerebral palsy rate lower (42%) than previously reported.[5,12,17,25,27,28] Furthermore, the majority (81%) of infants with cerebral palsy were graded as GMFCS level I-II and could walk independently. These more favorable results should be interpreted with caution because of the relatively high rates of redirection of care. However, the mortality rate in the present study was not higher than that of previous cohorts, and the only previous study presenting the rates of redirection of care in infants with PVHI reported higher rates.[6] We also found that PVHI size and severity score were associated with less optimal gross motor score and trigone involvement with cerebral palsy. In contrast to our hypothesis, no changes were found over the course of our study period with respect to sonographic characteristics, absolute size of PVHI, or neurodevelopmental outcomes. Notably, post-hemorrhagic ventricular dilation had an independent adverse effect on cognitive and motor outcome.

Our incidence of PVHI (4.3%) in preterm infants was similar to that reported by Bassan et al. over a decade ago, which may partly be explained by the increased survival of extremely preterm infants at risk of PVHI.[1,7] Consistent with the literature, in our study most PVHIs involved the parietal lobe, were associated with an ipsilateral grade III IVH, globular in shape, reached maximum extent during the first postnatal week, and evolved into a porencephalic cyst.[1,5,6,12,17] Although left-sided predominance has been described in the past, consistent with Bassan et al, we found an almost equal distribution over left and right hemispheres in our cohort.[6,12,24] In 20% of infants, PVHI eventually showed evolution into multiple cysts in the white matter, which might easily be misclassified as cystic white matter injury.

Mortality related to PVHI of up to 60% reported in studies from over 2 decades ago, has decreased to 30%-40%.[12,17,28] We could not demonstrate any further improvement in survival rates in the current era, which may partly be due to a shift towards more and increasingly extremely preterm infants with a higher risk of death in the neonatal period.[1] We observed a relatively high rate of redirection of care in this cohort of very preterm infants with PVHI, with rates being similar for all three participating centers and

comparable with previous studies.[6] Redirection of care was discussed with the parents when the PVHI was bilateral, or unilateral but involving more than one lobe and usually causing a midline shift. These infants were born at <28 weeks of gestation, were

ventilator-dependent and showed signs of multiorgan failure. We also found a positive association between mortality and increasing PVHI severity score and size, midline shift, and bilaterality. These findings suggest that a more severe sonographic PVHI appearance is associated with a more severe clinical presentation that, in combination with other severe morbidities, could lead to death.

Although GMH-IVH grading was established by Papile et al[15] and adapted by Volpe[19] many years ago, there is no widely used method for grading the severity of PVHI. Bassan et al developed a severity score based on the number of involved cerebral lobes, laterality and midline shift, which is reproducible and strongly correlated with neurodevelopmental outcomes.[6] However, as the size and location of PVHI also may be major determinants of neurodevelopmental outcome and therewith of influence on prognosis, we also performed a quantitative measure of PVHI size along with the severity score.[6,7,17] Our rates of impairments (cognitive delays 35%; abnormal motor outcomes 31%; cerebral palsy rate 42%) were more favorable than reported in previous studies (cognitive delays in 1 out of 2, motor impairment in nearly 2 out of 3, and cerebral palsy rates up to 85%).[5,12,17,25,27,28] In addition, infants in our study showed lower PVHI severity scores (0: 39%; 1: 38%; 2: 22%; 3: 1%) compared with the cohort of Bassan et al (0: 29%; 1: 19%; 2: 34%; 3: 17%).[6] PVHI size and severity score were negatively related to gross motor scores, as was trigone involvement. Infants with trigone involvement were also more likely to develop cerebral palsy. As we did not find associations with any of the other outcome domains or between any of the other PVHI characteristics and outcomes, the more favorable severity scores may partly explain the relatively better neurodevelopmental outcomes in our study. Associated post-hemorrhagic ventricular dilation, was less frequent in our study than in previous studies and was negatively correlated with cognitive and motor impairment.[1,6,24] As post-hemorrhagic ventricular dilation has been shown to be a major determinant of the neurodevelopmental outcome, we speculate that lower rates of post-hemorrhagic ventricular dilation in combination with improved perinatal care may have contributed to better outcomes. However, PVHI remains a serious complication in very preterm infants, requiring improvements in prevention and rehabilitation.

The present study has several limitations. The study period of 6 years may have been too short to show changes in PVHI characteristics and outcome over time. We assessed PVHI size in 1 dimension and did not measure lesion area or volume, because volumetric measurements from cranial US are still challenging and examinations were not performed with a 3-dimensional probe during the study period. Including only infants with 3 or more cranial US scans within the first 10 days after birth led to the

exclusion of 3 infants, but it is unlikely that this had a significant impact on our findings. The follow-up rate of 77% is lower than the optimum rates noted for prospective studies and is a limitation. As magnetic resonance imaging was not available in all infants, we were not able to reliably comment on the occurrence of punctate and/or discrete white matter injuries in our study infants. Finally, the relatively high rates of redirection of care might have masked a higher rate of adverse neurodevelopmental outcomes than found in the present study. For that reason, we also included a composite outcome of death and/or adverse neurodevelopmental outcome. The main strengths of our study are the number of infants studied and the use of an objective measure of PVHI size in combination with a severity score. Furthermore, the participating centers have longstanding experience in neonatal neuroimaging and follow-up and used a strict cranial US protocol, which remained constant throughout the study period.

PVHI remains a severe complication of IVH in very preterm infants with important implications for neurodevelopmental outcome.[1,6,7,17] Our findings provide insight into the appearance, evolution, and neurodevelopmental outcome of PVHI in the era of modern-day perinatal care. We suggest that a detailed assessment of the sonographic characteristics of PVHI, using the severity score combined with lesion size and trigone involvement, can increase the potential of early prognostication of neurodevelopmental outcomes in very preterm infants, particularly gross motor outcome and cerebral palsy. Further studies are warranted to better understand the underlying mechanisms of PVHI, and increase the potential for early intervention strategies, prevention and family counselling.

Acknowledgment

We thank the developmental specialists and data managers for their dedicated help to obtain the pertinent data and records.

Appendix-1: Ultrasound Protocol

In Utrecht, sequential cranial ultrasonography (cUS) was performed by experienced attending neonatologists or physician assistants on admission, <24 hours of birth, on day 3 and 7, at least weekly thereafter until death, discharge or transfer to another hospital, and again around term-equivalent age. In Toronto, sequential cUS was performed by ultrasound technicians at <24 hours of birth, 1-3 times during the first week, and then weekly thereafter until death, discharge or term-equivalent age. At all sites, scanning was conducted with a multi-frequency convex probe using a Toshiba Aplio Ultrasound System (Canon Medical Systems Corporation, Tochigi, Japan).

Appendix-2: Neurodevelopmental Outcome

For each included infant, the outcome was evaluated by using a combination of neurological examination records and results from standardized developmental assessments around 24 months' corrected age, including cognition and motor performance. Bayley Scales of Infant and Toddler Development Third Edition (BSID-III) assessment provides a global evaluation to identify developmental delay. Cognitive and motor composite scores, corrected for prematurity with mean [±SD] for the general population 100 [±15], were collected, as well as fine and gross motor scaled scores with mean [±SD] is 10 [±3]. Griffiths Mental Development Scales (GMDS) assessment provides an overall developmental quotient (DQ) with subscales evaluating 5 domains; locomotor, personal–social, hearing–language, eye–hand coordination and performance. The mean (±standard deviation [SD]) DQ score for the general population is 100 (±12). Infants with mild impairment with a score of <85 and <88, respectively, were classified as "subclinical" range, and those with a score of <70 and <76, respectively, as "clinical" range. Z-scores were calculated in order to collectively compare the GMDS and BSID-III scores. Data pertinent to mortality and survival, including the cause of death, were noted from the infants' files.

References

1. Inder TE, Perlman JM, Volpe JJ. Preterm intraventricular hemorrhage/ posthemorrhagic hydrocephalus. In: Volpe JJ, Inder TE, Darras BT, de Vries LS, du Plessis AJ, Neil JJ, Perlman JM, eds. Neurology of the Newborn. Elsevier; 2017. p. 637-98.
2. Takashima S, Tanaka K. Microangiography and vascular permeability of the subependymal matrix in the premature infant. Can J Neurol Sci 1978;5:45-50.
3. Takashima S, Mito T, Ando Y. Pathogenesis of periventricular white matter hemorrhages in preterm infants. Brain Dev 1986;8:25-30.
4. Gould SJ, Howard S, Hope PL, Reynolds EO. Periventricular intraparenchymal cerebral haemorrhage in preterm infants: the role of venous infarction. J Pathol 1987;151:197-202.
5. de Vries LS, Roelants-van Rijn AM, Rademaker KJ, Van Haastert IC, Beek FJ, Groenendaal F. Unilateral parenchymal haemorrhagic infarction in the preterm infant. Eur J Paediatr Neurol 2001;5:139-49.
6. Bassan H, Benson CB, Limperopoulos C, Feldman HA, Ringer SA, Veracruz E, et al. Ultrasonographic features and severity scoring of periventricular hemorrhagic infarction in relation to risk factors and outcome. Pediatrics 2006;117:2111-8.
7. Bassan H, Feldman HA, Limperopoulos C, Benson CB, Ringer SA, Veracruz E, et al. Periventricular hemorrhagic infarction: risk factors and neonatal outcome. Pediatr Neurol 2006;35:85-92.
8. Arichi T, Counsell SJ, Allievi AG, Chew AT, Martinez-Biarge M, Mondi V, et al. The effects of hemorrhagic parenchymal infarction on the establishment of sensori-motor structural and functional connectivity in early infancy. Neuroradiology 2014;56:985-94.
9. Pape KE, Blackwell RJ, Cusick G, Sherwood A, Houang MT, Thorburn RJ, et al. Ultrasound detection of brain damage in preterm infants. Lancet 1979;1:1261-4.
10. Intrapiromkul J, Northington F, Huisman TA, Izbudak I, Meoded A, Tekes A. Accuracy of head ultrasound for the detection of intracranial hemorrhage in preterm neonates: comparison with brain MRI and susceptibility-weighted imaging. J Neuroradiol 2013;40:81-8.
11. Davis AS, Hintz SR, Goldstein RF, Ambalavanan N, Bann CM, Stoll BJ, et al. Outcomes of extremely preterm infants following severe intracranial hemorrhage. J Perinatol 2014;34:203-8.
12. Guzzetta F, Shackelford GD, Volpe S, Perlman JM, Volpe JJ. Periventricular intraparenchymal echodensities in the premature newborn: critical determinant of neurologic outcome. Pediatrics 1986;78:995-1006.
13. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. JAMA 2015;314:1039-51.
14. Horbar JD, Edwards EM, Greenberg LT, Morrow KA, Soll RF, Buus-Frank ME, Buzas JS, et al. Variation in performance of neonatal intensive care units in the United States. JAMA Pediatr 2017;171:e164396.
15. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1500 gm. J Pediatr 1978;92:529-34.
16. Handley SC, Passarella M, Lee HC, Lorch SA. Incidence Trends and risk factor variation in severe intraventricular hemorrhage across a population based cohort. J Pediatr 2018;200:24-9.
17. Bassan H, Limperopoulos C, Visconti K, Mayer DL, Feldman HA, Avery L, et al. Neurodevelopmental outcome in survivors of periventricular hemorrhagic infarction. Pediatrics 2007;120:785-92.
18. Radic JA, Vincer M, McNeely PD. Outcomes of intraventricular hemorrhage and posthemorrhagic hydrocephalus in a population-based cohort of very preterm infants born to residents of Nova Scotia from 1993 to 2010. J Neurosurg Pediatr 2015;15:580-8.

19. Volpe JJ. Intraventricular hemorrhage in the premature infant – current concepts. Part II. Ann Neurol 1989;25:109-16.
20. Levene MI. Measurement of the growth of the lateral ventricles in preterm infants with real-time ultrasound. Arch Dis Child 1981;56:900-4.
21. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39: 214-23.
22. Gibson JY, Massingale TW, Graves GR, LeBlanc MH, Meydrech EF. Relationship of cranial midline shift to outcome of very-low-birthweight infants with periventricular hemorrhagic infarction. J Neuroimaging 1994;4:212-7.
23. McMenamin JB, Shackelford GD, Volpe JJ. Outcome of neonatal intraventricular hemorrhage with periventricular echodense lesions. Ann Neurol 1984;15:285-90.
24. Murphy BP, Inder TE, Rooks V, Taylor GA, Anderson NJ, Mogridge N, et al. Posthaemorrhagic ventricular dilatation in the premature infant: natural history and predictors of outcome. Arch Dis Child Fetal Neonatal Ed 2002;87:37-41.
25. Rademaker KJ, Groenendaal F, Jansen GH, Eken P, de Vries LS. Unilateral haemorrhagic parenchymal lesions in the preterm infant: shape, site and prognosis. Acta Paediatr 1994;83:602-8.
26. Perlman JM, Rollins N, Burns D, Risser R. Relationship between periventricular intraparenchymal echodensities and germinal matrixintraventricular hemorrhage in the very low birth weight neonate. Pediatrics 1993;91:474-80.
27. Papile LA, Munsick-Bruno G, Schaefer A. Relationship of cerebral intraventricular hemorrhage and early childhood neurologic handicaps. J Pediatr 1983;103:273-7.
28. Roze E, Kerstjens JM, Maathuis CG, ter Horst HJ, Bos AF. Risk factors for adverse outcome in preterm infants with periventricular hemorrhagic infarction. Pediatrics 2008;122:46-52.

“The biggest battle is the war against ignorance”

Mustafa Kemal Atatürk

3

Assessment of Brain Injury and Brain Volumes after Post-Hemorrhagic Ventricular Dilatation: A Nested Substudy of the Randomized Controlled ELVIS Trial

Mehmet N. Cizmeci, Nadieh Khalili, Nathalie H. P. Claessens, Floris Groenendaal, Kian D. Liem, Axel Heep, Isabel Benavente-Fernandez, Henrica L. M. van Straaten, Gerda van Wezel-Meijler, Sylke J. Steggerda, Jeroen Dudink, Ivana Isgum, Andrew Whitelaw, Manon J. N. L. Benders, Linda S. de Vries, and the ELVIS study group

J Pediatr 2019; 208: 191-7 DOI: 10.1016/j.jpeds.2018.12.062

Abstract

Objective: To compare the effect of early and late intervention for post-hemorrhagic ventricular dilatation on additional brain injury and ventricular volume using term-equivalent age-MRI.

Study design: In the Early vs Late Ventricular Intervention Study (ELVIS) trial, 126 preterm infants ≤34 weeks of gestation with post-hemorrhagic ventricular dilatation were randomized to low-threshold (ventricular index >p97 and anterior horn width >6 mm) or high-threshold (ventricular index >p97 + 4 mm and anterior horn width >10 mm) groups. In 88 of those (80%) with a term-equivalent age-MRI, the Kidokoro Global Brain Abnormality Score and the frontal and occipital horn ratio were measured. Automatic segmentation was used for volumetric analysis.

Results: The total Kidokoro score of the infants in the low-threshold group (n = 44) was lower than in the high-threshold group (n = 44; median, 8 [IQR, 5-12] vs median 12 [IQR, 9-17], respectively; P < .001). More infants in the low-threshold group had a normal or mildly increased score vs more infants in the high-threshold group with a moderately or severely increased score (46% vs 11% and 89% vs 54%, respectively; P = .002). The frontal and occipital horn ratio was lower in the low-threshold group (median, 0.42 [IQR, 0.34-0.63]) than the high-threshold group (median 0.48 [IQR, 0.37-0.68], respectively; P = .001). Ventricular cerebrospinal fluid volumes could be calculated in 47 infants and were smaller in the low-threshold group (P = .03).

Conclusions: More brain injury and larger ventricular volumes were demonstrated in the high vs the low-threshold group. These results support the positive effects of early intervention for post-hemorrhagic ventricular dilatation.

Introduction

Substantial developments in obstetric and neonatal care have led to a significant increase in the survival of premature infants. Along with mortality, a further aim has been to reduce the major morbidities and improve neurodevelopmental outcomes. However, germinal matrix-intraventricular hemorrhage continues to be a serious complication of preterm birth.[1,2] Post-hemorrhagic ventricular dilatation (PHVD) occurs in approximately 30%-50% of the preterm infants after a severe hemorrhage and increases the risk of neurocognitive and motor impairments.[3]

Adverse effects of PHVD on the developing newborn brain include white matter injury and decreased volumes of deep gray matter and cerebellum. It is important to decrease these complications as much as possible with timely intervention.[4] After the use of temporizing methods, overall conversion to a permanent shunt varies from 20% to 65%, depending on the time of onset of the intervention.[5] Given the high rates of infection, dysfunction, and life-long dependence after ventriculoperitoneal (VP) shunt insertion, it would be beneficial if a treatment could reduce the risk of shunt requirement.[6,7] Removing the hemorrhagic cerebrospinal fluid (CSF) by lumbar punctures or taps from a ventricular reservoir may decrease the need for VP shunt placement because the removal of CSF that contains blood components, protein, and cytokines might reestablish normal CSF circulation.[8] Although the optimum timing of intervention continues to be a matter of debate in the neonatal literature, there is accumulating evidence showing the beneficial effects of early intervention on ventricular dilatation and outcomes.[9,10]

In the Early vs Late Ventricular Intervention Study (ELVIS) randomized controlled trial, no significant difference was found for the need for VP shunt in those treated before or after crossing the 97th percentile +4 mm line of the graph of Levene.[11] However, only a small number of infants in both study arms had a VP shunt inserted, the lowest number reported in the literature so far (19%-23%).[5] The aim of the present nested substudy was to compare the extent of injury in different brain regions, and brain volumes on term-equivalent age (TEA) magnetic resonance imaging (MRI) in patients randomized to the early or late intervention group.

Methods

Patients

A total of 126 infants participated in the ELVIS trial, a randomized controlled trial (ISRCTN43171322) conducted between 2006 and 2016 to compare the effects of low vs high-threshold treatment in preterm infants of ≤34 weeks' gestational age with progressive PHVD. Infants were eligible for the trial when they had an IVH grade III, with

or without a periventricular hemorrhagic infarct (PVHI) according to Volpe.[12] They were randomly allocated to either low-threshold group (intervention when an increase in ventricular width according to Levene[11] above the p97 line showing an increase toward the p97 + 4 mm line, but without crossing the p97 + 4 mm line, and an increase in diagonal anterior horn width [AHW] according to Davies et al.[13] of >6 mm and toward 10 mm, but not >10 mm) or high-threshold group (intervention once the ventricular width crossed the p97 + 4 mm line and the AHW was >10 mm). Antenatal and perinatal factors including gestational age, birth weight, sex, the severity of hemorrhage, and timing and type of intervention, and postmenstrual age at MRI day were collected for each patient from the patient files and/or hospital database. Approval from the research ethics board at each center and informed written parental consent were obtained for all of the patients and for the control infants participating in the study before enrollment into the study.

MRI Acquisition

In all centers, MRIs were acquired around TEA. A 3.0 Tesla magnetic resonance (MR) system (Philips Healthcare, Best, The Netherlands) using a sense head coil was available at 3 centers (University Medical Center Utrecht, University Medical Center Leiden, and Isala Hospital, Zwolle) and from 2014 onward at Southmead Hospital, Bristol. Until April 2014, a 1.5-Tesla MR system (GE Signa Excite HD system, Boston, Massachusetts) was used in Bristol. UniversityMedical Center Groningen (SonataVision, Siemens, Germany), University Hospital Puerta del Mar, Cadiz (Magnetom Symphony, Siemens), Radboud University Nijmegen Medical Centre (Magnetom Symphony, Siemens), University of Rotterdam (GE Signa Excite HD system), and University of Lisbon (Philips Healthcare) used a 1.5 Tesla MR system. All participating centers used conventional axial 3-dimensional T1-weighted imaging and T2-weighted imaging and followed a predefined MRI protocol according to their institutional guidelines during the study period. Only the high-quality images that were suitable for scoring and volumetric measurements were included in the study.

Assessment of Brain Injury

An investigator with >20 years of experience in reading neonatal MRIs who was blinded to the infant's clinical information, and the allocated arm of the trial, assessed the images. Ventricular measurements (ventricular index [VI] and AHW) were performed as described by Levene[11] and Davies et al.[13] The frontal and occipital horn (FOH) ratio was obtained by measuring the widest distances across the frontal horns and the occipital horns, and the average of these measurements was then divided by the largest biparietal diameter as defined by Kulkarni et al.[14] To evaluate the intraobserver reliability of the measurements, 15 studies from 15 random patients were assessed and

the intraclass correlation coefficient (ICC) was calculated. For the assessment of brain injury, a validated scoring system for evaluating the cerebral white matter, cortical gray matter, basal ganglia and thalami (BGT), and cerebellum abnormalities was used. The measurements were corrected for postmenstrual age, and a global brain abnormality score was calculated as the sum of the regional total scores and classified as normal (total score of 0-3), mild (total score of 4-7), moderate (total score of 8-11), and severe (total score of ≥12) as defined by Kidokoro et al.[15]

Assessment of Brain Volumes

Automatic segmentation of cerebral MRIs was applied on axial or coronal T2-weighted images for computerized volume analysis. The images were segmented into 8 regions: cerebellum, myelinated white matter, BGT, ventricular CSF, unmyelinated white matter, brain stem, cortical gray matter, and extracerebral CSF, as described by Moeskops et al.[16] The quality of the automatic segmentations was established by visual evaluation. Images with low-quality segmentations were excluded from further analysis, and high-quality images were manually edited when deemed necessary before further analysis. Subsequently, volumetric measurements of the segmented tissues were obtained by multiplying the number of segmented voxels per tissue by the voxel size. Thereafter, contours were drawn around the structure of interest on consecutive slices through the brain. Both porencephalic cysts and cysts after PVHI but not communicating with the lateral ventricles were included in ventricular volume measurements. The relative volumes of the brain regions were calculated by dividing the volume of the area of interest by total intracranial volume, which includes brain tissues and ventricular and extraventricular CSF spaces (Figure 1).

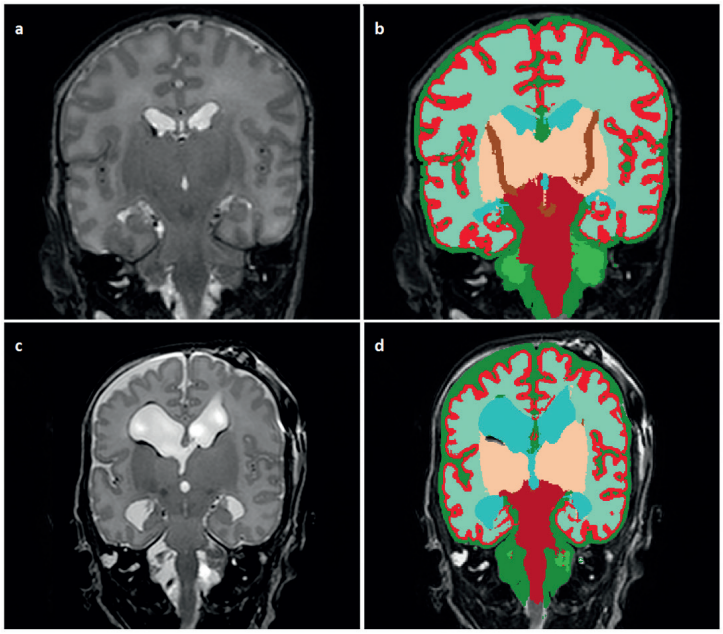


Figure 1: T2-weighted coronal MRIs obtained at TEA show A, mildly enlarged ventricular CSF volumes in a preterm infant in the low-threshold group, B, the same infant after automatic segmentation of the MRI into 8 regions for volumetric analysis, C, severely enlarged ventricular CSF volumes in a preterm infant in the high-threshold group, D, automatic segmentation of the Image in C.

Statistical Analyses

Statistical analyses of the data were performed using the Statistical Package for the Social Sciences v21.0 program (SPSS Inc, Chicago, Illinois). The continuous variables were presented as mean SD and median (IQR), depending on their distribution. The categorical values were presented as frequency and percentage. The Fisher exact and c2 tests were used to compare categorical variables among groups. The Mann-Whitney U test was used to compare nonparametric variables and the Student t-test was used for the comparison of variables that showed normal distribution. Logarithmic transformation was used to obtain a Gaussian distribution of the non-normally distributed volumetric measurements. Observed associations controlled for the grade of IVH by using multiple regression. To evaluate the reliability of measurements, ICC was calculated and classified as good for an ICC between 0.8 and 0.9 and excellent for an ICC of >0.9. Statistical significance was set at $P < .05$.

Results

Study Population

During the 10-year study period, 126 infants were enrolled into the ELVIS cohort, of whom 38 were not eligible for inclusion in the present study. Of these ineligible infants, MRI was not available owing to death in 16 or was not performed around TEA in 22 infants. The main reasons for not obtaining an MRI were transfer back to the referring hospital where no MR device was present, and not being able to transfer the infant again to the study site exclusively for imaging reasons at TEA (n = 17). Two had a very early MRI only and 2 had an MRI well beyond the neonatal period, and 1 had an MRI in a level 2 hospital with insufficient quality. The final sample consisted of 88 infants; 44 were in the low-threshold group and 44 were in the high-threshold group (Figure 2).

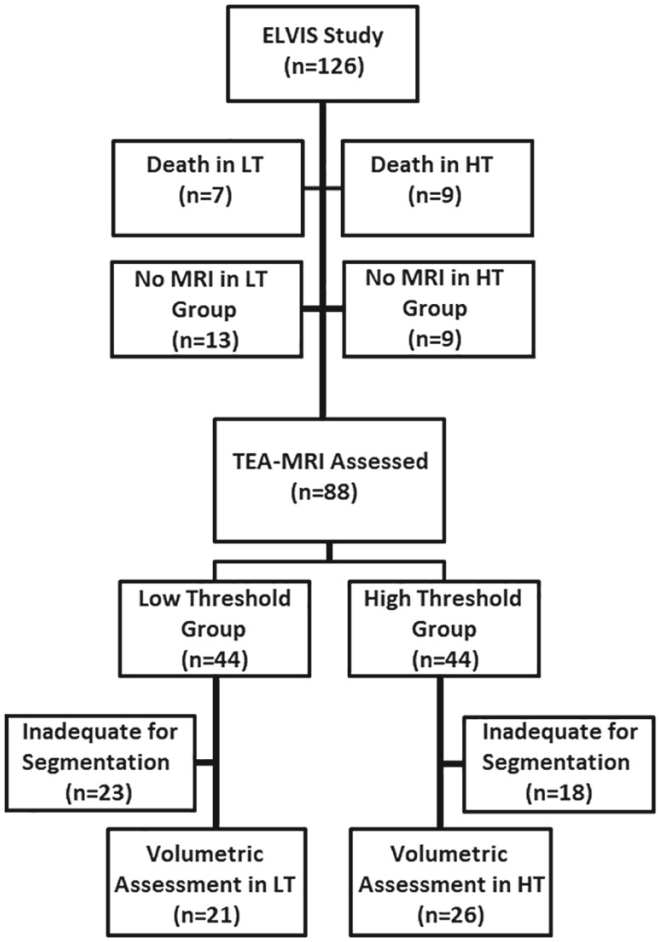


Figure 2: Flowchart of patient allocation and subsequent MRI assessments at TEA.

No statistically significant differences between the low-threshold and high-threshold groups were observed in terms of gestational age, sex, birth weight, and postmenstrual age at the time of MRI. Infants who were not included in the present study due to not having MRI were similar to those included with respect to demographic and clinical variables. Characteristics of the participants in whom MRI was completed are presented in Table 1.

Table 1: Clinical characteristics of the study population and MRI assessments.

	Low-Threshold Group (n=44)	**High-Threshold Group (n=44)**	**p**
GA at birth, wk (mean±SD)	28.1 ± 2.4	27.8 ± 2.7	0.6[a]
Birth weight, g (mean±SD)	1176 ± 361	1175 ± 404	0.9[a]
Sex			
Male	23 (52)	26 (59)	0.5[b]
Female	21 (48)	18 (41)	
Day of enrollment median (IQR)	9 (6-10)	9 (6-12)	0.9[c]
Postmenstrual age at MRI, (wk) median (IQR)	41.0 (40.4-42.7)	40.9 (40-41.7)	0.3[c]
GMH-IVH grade, n (%)			
Grade III	30 (68)	25 (57)	0.3[b]
Grade III + PVHI	14 (32)	19 (43)	
Reservoir inserted, n (%)	28 (64)	23 (52)	0.3[b]
VP-shunt inserted, n (%)	9 (20)	12 (27)	0.4[b]
Duration between VP-shunt and TEA-MRI, days, median (IQR)	4 (-1-28)	10 (-10-29)	0.8[c]
Ventricular measurements on MRI, mm, median (IQR)			
Ventricular width in mm	13.4 (12.6-15.1)	15.9 (14.5-18.8)	**<0.001**[c]
Anterior horn width in mm	6.6 (5.3-10.3)	10.6 (8.4-13.5)	**<0.001**[c]
FOH ratio, median (IQR)	0.42 (0.4-0.46)	0.48 (0.43-0.51)	**0.001**[c]
Total Kidokoro score, median	8 (5-12)	12 (9-17)	**<0.001**[c]
Infants with Grade III	7 (5-9)	10 (8-12)	**<0.001**[c]
Infants with Grade III + PVHI	13 (7-19)	16 (15-19)	**<0.001**[c]

Table 1: *[Continued]*

	Low-Threshold Group (n=44)	High-Threshold Group (n=44)	p
Kidokoro score severity, (%)			
Normal	3 (7)	0 (0)	
Mild	17 (39)	5 (11)	**0.002**[c]
Moderate	12 (27)	13 (30)	
Severe	12 (27)	26 (59)	

[a]t-test, [b]Chi Square test, [c]Mann-Whitney U test

FOH Ratio and Kidokoro Score

The intra-observer reliability showed an excellent correlation for the measurements (ICC = 0.94). Median ventricular measurements, including VI and AHW (P < .001 for both), and the FOH ratio were lower in the low-threshold group (P = .001). The total Kidokoro score for the infants in the low-threshold group was also lower than that of the high-threshold group (P < .001). The subgroup analyses were performed after excluding infants with PVHI. Data regarding these measurements and comparisons are presented in Table 1. When the groups were compared in terms of severity of the Kidokoro score, there were more infants in the low-threshold group with a normal or mildly increased score and more infants in the high-threshold group with a moderately or severely increased score (P = .002). The observed associations persisted after controlling for the grade of IVH. A linear correlation between the Kidokoro score and FOH ratio was found (r = 0.62; P < .001) and the average FOH ratio increased by 0.06 for every point increase in the Kidokoro score (95% CI, 0.05-0.08).

Kidokoro Subscores

In the cerebral white matter evaluation, statistically significant differences were observed between the groups in myelination delay, thinning of the corpus callosum, and dilatation of the lateral ventricles subscores. Furthermore, a trend toward biparietal volume reduction in the high-threshold group was seen (P = .07). The groups differed in cerebral white matter subscores (P = .001). In the cortical gray matter evaluation, infants in the high-threshold arm showed increased extracerebral spaces (P < .001) and a trend toward delayed gyral maturation (P = .07). The cortical and deep gray matter subscores were lower in the low-threshold group (P < .001). The groups were similar in terms of cerebellum signal abnormalities and volume reduction (P = .8 and P = .4, respectively). The subscore analysis of the infants is tabulated in Table 2.

Table 2: Kidokoro subscore analysis of the study population.

	Low-Threshold Group (n=44)	High-Threshold Group (n=44)	p
Cystic lesions			0.2[a]
None	27 (61)	18 (41)	
Focal unilateral	3 (7)	1 (2)	
Focal bilateral	2 (5)	3 (7)	
Extensive unilateral	11 (25)	20 (45)	
Extensive bilateral	1 (2)	2 (5)	
Focal signal abnormality			0.6[a]
None	33 (75)	28 (63)	
Focal punctate	6 (14)	7 (16)	
Extensive punctate	3 (7)	6 (14)	
Linear	2 (4)	3 (7)	
Myelination delay			**0.01**[a]
PLIC & corona radiata	0 (0)	0 (0)	
Only PLIC	32 (73)	21 (48)	
Minimal - no PLIC	12 (27)	23 (52)	
Thinning of the corpus callosum			**0.02**[a]
None	39 (89)	27 (62)	
Partial	2 (4)	5 (12)	
Global	3 (7)	11 (26)	
Dilated lateral ventricles			**0.01**[a]
Both sides <7.5 mm	12 (27)	3 (7)	
7.5mm ≤ one side <10 mm	9 (20)	5 (11)	
7.5mm ≤ both sides <10 mm/ one side ≥ 10 mm	13 (30)	13 (30)	
Both sides ≥ 10 mm	10 (23)	23 (52)	
Volume reduction			0.07[a]
cBPW ≥77 mm	26 (59)	18 (41)	
77 mm > cBPW ≥72 mm	13 (29)	13 (29)	
72 mm > cBPW ≥67 mm	2 (5)	10 (23)	
67 mm > cBPW	3 (7)	3 (7)	
Cerebral WM Subscore			
median (min-max)	4 (1-13)	7 (1-14)	**0.001**[b]

Table 2: *[Continued]*

	Low-Threshold Group (n=44)	High-Threshold Group (n=44)	p
Cortical GM signal abnormality			0.5[a]
None	44 (100)	43 (98)	
Focal unilateral	0 (0)	0 (0)	
Focal bilateral	0 (0)	1 (2)	
Extensive unilateral	0 (0)	0 (0)	
Extensive bilateral	0 (0)	0 (0)	
Gyral maturation			0.07[a]
Delay <2 weeks	4 (9)	1 (2)	
2 ≤ delay < 4 weeks	18 (41)	11 (25)	
Delay ≥ 4 weeks	22 (50)	32 (73)	
Increased extracerebral space			**<0.001[a]**
IHD < 4 mm	24 (55)	1 (2)	
4 mm ≤ IHD < 5 mm	8 (18)	8 (18)	
5 mm ≤ IHD < 6 mm	5 (11)	14 (32)	
IHD ≥ 6 mm	7 (16)	21 (48)	
Deep GM signal abnormality			0.2[a]
None	40 (91)	38 (87)	
Focal unilateral	0 (0)	4 (9)	
Focal bilateral	1 (2)	1 (2)	
Extensive unilateral	3 (7)	1 (2)	
Extensive bilateral	0 (0)	0 (0)	
Deep GM volume reduction			0.06[a]
cDGMA ≥ 9.5 mm^3	36 (82)	38 (86)	
9.5 mm^3 > cDGMA ≥ 8.5 mm^3	6 (14)	2 (5)	
8.5 mm^3 > cDGMA ≥ 7.5 mm^3	0 (0)	4 (9)	
7.5 mm^3 > cDGMA	2 (4)	0 (0)	
Cerebellum signal abnormality			0.8[a]
None	26 (59)	24 (55)	
Punctate unilateral	7 (16)	9 (21)	
Punctate bilateral	6 (14)	8 (18)	
Extensive unilateral	2 (4)	2 (4)	
Extensive bilateral	3 (7)	1 (2)	
Cerebellum volume reduction			0.4[a]

Table 2: *[Continued]*

	Low-Threshold Group (n=44)	High-Threshold Group (n=44)	p
cTCD ≥ 50 mm	30 (68)	23 (52)	
50 mm > cTCD ≥ 47 mm	7 (16)	11 (25)	
47 mm > cTCD ≥ 44 mm	3 (7)	5 (11)	
44 mm> cTCD	4 (9)	5 (11)	
Cortical GM and Deep GM Subscore			**<0.001[b]**
median (min-max)	4 (0-14)	6 (2-14)	

[a]Fisher's exact test; [b]Mann-Whitney U test

Brain and CSF Volumes on TEA-MRI

Brain and CSF volumes could be calculated in a total of 47 infants, of which 21 were in the low-threshold and 26 in the high-threshold group (Figure 2). No statistically significant differences in unadjusted brain and CSF volumes were observed in relation to PHVD (Table 3).

Table 3: Distribution of absolute and relative brain and CSF volumes between the groups.

Volumes	Low-Threshold Group (n=21)	High-Threshold Group (n=26)	P*
Ventricles			
Absolute	18 (11-30)	24 (17-37)	0.07
Relative	0.05 (0.02-0.07)	0.06 (0.04-0.09)	**0.03**
Absolute†	16 (12-27)	23 (15-31)	0.4
Relative†	0.04 (0.03-0.06)	0.06 (0.04-0.07)	0.1
Unmyelinated white matter			
Absolute	165 (136-186)	154 (128-184)	0.5
Relative	0.3 (0.2-0.4)	0.3 (0.2-0.4)	0.3
Absolute†	165 (140-186)	171 (129-185)	0.7
Relative†	0.3 (0.2-0.4)	0.3 (0.2-0.4)	0.6
Cortical gray matter			
Absolute	128 (119-166)	131 (117-155)	0.8
Relative	0.3 (0.2-0.4)	0.3 (0.1-0.4)	0.5
Absolute†	129 (119-173)	126 (114-152)	0.3
Relative†	0.3 (0.2-0.3)	0.2 (0.2-0.3)	0.06

Table 3: *[Continued]*

Volumes	Low-Threshold Group (n=21)	High-Threshold Group (n=26)	P*
Combined white&gray matter			
Absolute	304 (238-378)	302 (239-316)	0.3
Relative	0.6 (0.5-0.7)	0.5 (0.5-0.6)	0.06
Absolute†	307 (295-349)	302 (244-315)	0.1
Relative†	0.6 (0.5-0.7)	0.5 (0.5-0.6)	**0.03**
Basal ganglia & thalami			
Absolute	25 (21-27)	23 (19-25)	0.4
Relative	0.04 (0.03-0.05)	0.04 (0.04-0.05)	0.9
Absolute†	25 (22-27)	24 (22-25)	0.5
Relative†	0.05 (0.04-0.06)	0.05 (0.04-0.06)	0.8
Cerebellum			
Absolute	31 (25-41)	31 (23-41)	0.8
Relative	0.06 (0.05-0.07)	0.06 (0.03-0.18)	0.6
Absolute†	31 (25-41)	32 (25-47)	0.5
Relative†	0.06 (0.05-0.07)	0.05 (0.04-0.07)	0.5
Extracerebral CSF			
Absolute	127 (98-140)	116 (102-137)	0.9
Relative	0.2 (0.2-0.3)	0.2 (0.2-0.3)	0.5
Absolute†	113 (98-145)	119 (105-158)	0.4
Relative†	0.2 (0.2-0.3)	0.2 (0.2-0.3)	0.3

Data are presented as median (interquartile range)
Absolute volumes are presented in millilitres.
*p-values are presented after logarithmic transformation of relative volumes
†volumes after excluding infants with periventricular hemorrhagic infarct (n=17 in Low-Threshold group and 15 in High-Threshold group)

When the relative volumes of the brain regions were compared after normalization of the variables with logarithmic transformation, ventricular CSF volumes of the low-threshold group were lower than that of the high-threshold group (P = .03). Unmyelinated white matter volumes of the low-threshold and high-threshold groups were not significantly different (P = .3). The combination of the white matter and gray matter volumes showed a trend toward higher values in the low-threshold group when compared with the high-threshold group (P = .06). The analyses were performed after excluding infants with PVHI (n = 4 in the low-threshold and n = 11 in the high-threshold group), which resulted in a final sample of 17 infants in the low-threshold and 15 in the high-threshold

group. Gray matter volume showed a trend toward a higher value (P = .06), and the combination of the white matter and gray matter volumes was significantly higher in the low-threshold group (P = .03). There were no differences between groups in other regions of interest. The FOH ratio was positively associated with ventricular CSF volumes (ß, +145; 95% CI, 72-218; P < .001).

Discussion

In this nested substudy of our randomized, controlled ELVIS trial[5] of preterm infants with PHVD, infants who were in the low-threshold group had lower global brain abnormality scores and had lower regional total subscores of the cerebral white matter, cortical gray matter, and BGT on TEA-MRI. When the total Kidokoro scores were stratified according to the severity, there were significantly more infants with normal or mildly increased scores in the low-threshold group, and significantly more infants with moderately or severely increased scores in the high-threshold group, even though at the time of randomization the number of infants with a grade III hemorrhage or PVHI was similar in the study arms. Infants in the high-threshold group also demonstrated more delay in myelination and more often partial or global thinning of the corpus callosum. Moreover, lower FOH ratios, VI, and AHW at TEA and smaller ventricular CSF volumes were found in infants in the low-threshold group. In the subgroup analysis, after excluding infants with PVHI, the combination of the white matter and gray matter volumes was significantly higher in the low-threshold group (P = .03). Using a structured scale assessment together with the quantification of the ventricular dilatation acquired at TEA, we were able to identify injury in specific regions of the brain, demonstrating the possible beneficial effects of early intervention after the onset of PHVD.

The pathogenesis of PHVD is a complex process determined by both direct injury and secondary inflammatory interactions.[17-21] To address the net effects of PHVD on brain lesions in different regions, an objective structured scale assessment was used in combination with volumetric analysis in the present study. This approach enabled us to determine the correlation between ventricular size and the extent of brain injury. The smaller ventricular CSF volumes together with the lower global brain abnormality scores as well as lower regional total subscores of the major regions of the brain in the low-threshold group indicate the possible beneficial effects of early intervention as we found that almost one-half (46%) of the infants in the low-threshold group had normal or mildly increased Kidokoro scores compared with only 11% in the high-threshold group. In infants with PHVD, expanding ventricles might cause atrophy of the adjacent brain tissue as a result of compression by CSF under pressure.[22,23] By using a manual segmentation technique, Jary et al calculated cerebral, thalamic and cerebellar volumes, and demonstrated that brain growth is significantly impaired in PHVD.[22] Ventricles were

larger with a median volume of 48 mL (IQR, 27-145) than the ventricular volumes of both groups in our study (median volume, 18 mL and 24 mL in the low-threshold group and the high-threshold group, respectively). Brouwer et al reported data in a small group of infants and showed that PHVD was independently associated with decreased volumes of deep gray matter, cerebellum, and extracerebral CSF, despite early intervention.[4] They found a median ventricular volume of 18.3 mL (range, 8.6-64.5 mL) in infants with PHVD, which is lower than we report in the high-threshold group and overlaps considerably with values we found in the low-threshold group. It has been shown that in infants with severe IVH who developed PHVD, ventricular size may be an important determinant of long-term neurodevelopmental outcome and infants with severe IVH who developed PHVD had worse neurodevelopmental scores compared with those who did not develop PHVD.[12,24,25] Recently, Leijser et al reported in their large cohort of preterm infants with PHVD that those who underwent intervention based on ventricular measurements, before the development of symptoms, even when eventually requiring a VP shunt, had outcomes indistinguishable from those without intervention, all being within the normal range.[10] Infants who first received the intervention once clinical symptoms had occurred had worse outcomes. The volumes of the ventricles, and the combined volume of the unmyelinated white matter and gray matter regions were in favor of the low-threshold therapy in the present study. We also measured the VI and AHW on TEA-MRI, which revealed smaller lateral ventricles in the low-threshold group. Whether the smaller ventricular volumes and preserved unmyelinated white matter and gray matter volumes of infants who underwent low-threshold therapy will be associated with improved neurodevelopmental outcomes in the ELVIS trial is currently being assessed.

The higher Kidokoro scores in infants in the high-threshold group are in line with the accumulating literature, suggesting that progressive ventricular dilatation and prolonged pressure might be deleterious to the immature brain. A rapidly enlarging ventricular system could result in compression of adjacent brain parenchyma, and this has been used as an explanation for the MRI signal abnormalities in various regions of the brain.[26,27] Because infants in the high-threshold group had greater ventricular volumes than those in the low-threshold group, the Kidokoro scores of these infants, which increase directly with the presence of signal abnormalities could have increased. PHVD-induced microstructural white matter injury, as stated previously by Brouwer et al, might serve as another explanation for the signal abnormalities on TEA-MRI in our cohort.[4] It is also worth noting that FOH ratios showed a good correlation with ventricular volumetric measurements, which can be used as a practical assessment tool for calculating the ventricular volumes in patients with PHVD.

The present study has several limitations. First, because this was a multicenter study, MRI protocols were not the same across centers, which could have led to varying image qualities. Second, a relatively large number of segmented MRIs could not be

used for the volumetric analysis. This was due to the use of a convolutional neural network technique, which was trained on segmented images of preterm neonates without any pathology. As a consequence, the automatic segmentation had limitations in segmenting scans with PHVD. Furthermore, because the automatic segmentation method was trained with scans acquired in the main study site, it was not always able to provide optimal segmentation for images obtained with a different protocol. This technique also did not allow differentiation between the basal ganglia and thalamic volumes and could not demonstrate precise segmentation of myelinated white matter due to technical reasons. Third, because the present study was a nested substudy, it is possible that the lack of statistically significant differences in volumetric measurements was due to limited sample size. Finally, there is the potential for selection bias arising from the excluded MRIs. However, we found that the excluded infants were similar with respect to demographic and clinical characteristics. The main strength of our study was the use of an objective scoring system enabling assessment of the extent of brain injury and reliable quantification of the ventricular and brain volumes in 80% of the surviving infants.

PHVD remains a serious complication of IVH, and control of PHVD using lumbar punctures as studied in the ELVIS trial before or just after the VI crossed the p97 + 4 mm line was associated with the lowest need for VP shunt reported in the literature.[5] This nested substudy of the ELVIS trial, designed to address parenchymal injury in different regions of the brain together with the quantification of the CSF and brain volumes, demonstrates beneficial effects of early intervention on the extent of brain injury and ventricular CSF volumes. Whether these findings translate into improved neurological development is being assessed and will be the subject of a later report.

Acknowledgment

We thank the MR technicians for their dedicated help to obtain the MRIs.

References

1. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. JAMA 2015;314:1039-51.
2. Ellenbogen JR, Waqar M, Pettorini B. Management of posthaemorrhagic hydrocephalus in premature infants. J Clin Neurosci 2016;31:30-4.
3. Adams-Chapman I, Hansen NI, Stoll BJ, Higgins R, Network NR. Neurodevelopmental outcome of extremely low birth weight infants with posthemorrhagic hydrocephalus requiring shunt insertion. Pediatrics 2008;121:1167-77.
4. Brouwer MJ, de Vries LS, Kersbergen KJ, van der Aa NE, Brouwer AJ, Viergever MA, et al. Effects of posthemorrhagic ventricular dilatation in the preterm infant on brain volumes and white matter diffusion variables at term-equivalent age. J Pediatr 2016;168:41-9.
5. de Vries LS, Groenendaal F, Liem KD, Heep A, Brouwer AJ, van 't Verlaat E, et al. Treatment thresholds for intervention in posthaemorrhagic ventricular dilation: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2019;104:F70-5.
6. Wellons JC 3rd, Shannon CN, Holubkov R, Riva-Cambrin J, Kulkarni AV, Limbrick DD Jr, et al. Shunting outcomes in posthemorrhagic hydrocephalus: results of a Hydrocephalus Clinical Research Network prospective cohort study. J Neurosurg Pediatr 2017;2:19-29.
7. Hislop JE, Dubowitz LM, Kaiser AM, Singh MP, Whitelaw AG. Outcome of infants shunted for post-haemorrhagic ventricular dilatation. Dev Med Child Neurol 1988;30:451-6.
8. Cherian S, Whitelaw A, Thoresen M, Love S. The pathogenesis of neonatal post-hemorrhagic hydrocephalus. Brain Pathol 2004;14:305-11.
9. Bassan H, Eshel R, Golan I, Kohelet D, Ben Sira L, Mandel D, et al. Timing of external ventricular drainage and neurodevelopmental outcome in preterm infants with posthemorrhagic hydrocephalus. Eur J Paediatr Neurol 2012;16:662-70.
10. Leijser LM, Miller SP, van Wezel-Meijler G, Brouwer AJ, Traubici J, van Haastert IC, et al. Posthemorrhagic ventricular dilatation in preterm infants: when best to intervene? Neurology 2018;90:698-706.
11. Levene MI. Measurement of the growth of the lateral ventricles in preterm infants with real-time ultrasound. Arch Dis Child 1981;56: 900-4.
12. Inder TE, Perlman JM, Volpe JJ. Preterm Intraventricular Hemorrhage/Posthemorrhagic Hydrocephalus. In: Inder TE, Darras BT, de Vries LS, et al., eds. Volpe's neurology of the newborn. 6th ed. Philadelphia: Elsevier; 2018. p. 637-98.
13. Davies MW, Swaminathan M, Chuang SL, Betheras FR. Reference ranges for the linear dimensions of the intracranial ventricles in preterm neonates. Arch Dis Child Fetal Neonatal Ed 2000;82:218-23.
14. Kulkarni AV, Drake JM, Armstrong DC, Dirks PB. Measurement of ventricular size: reliability of the frontal and occipital horn ratio compared to subjective assessment. Pediatr Neurosurg 1999;31:65-70.
15. Kidokoro H, Neil JJ, Inder TE. New MR imaging assessment tool to define brain abnormalities in very preterm infants at term. AJNR Am J Neuroradiol 2013;34:2208-14.
16. Moeskops P, Viergever MA, Mendrik AM, de Vries LS, Benders MJ, Isgum I. Automatic segmentation of MR brain images with a convolutional neural network. IEEE Trans Med Imaging 2016;35:1252-61.
17. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol 2009;8:110-24.
18. Savman K, Blennow M, Hagberg H, Tarkowski E, Thoresen M, Whitelaw A. Cytokine response in cerebrospinal fluid from preterm infants with posthaemorrhagic ventricular dilatation. Acta Paediatr 2002;91:1357-63.

19. Whitelaw A, Cherian S, Thoresen M, Pople I. Posthaemorrhagic ventricular dilatation: new mechanisms and new treatment. Acta Paediatr 2004;93:11-4.
20. Srinivasakumar P, Limbrick D, Munro R, Mercer D, Rao R, Inder T, et al. Posthemorrhagic ventricular dilatation-impact on early neurodevelopmental outcome. Am J Perinatol 2013;30:207-14.
21. Tam EW, Miller SP, Studholme C, Chau V, Glidden D, Poskitt KJ, et al. Differential effects of intraventricular hemorrhage and white matter injury on preterm cerebellar growth. J Pediatr 2011;158:366-71.
22. Jary S, De Carli A, Ramenghi LA, Whitelaw A. Impaired brain growth and neurodevelopment in preterm infants with posthaemorrhagic ventricular dilatation. Acta Paediatr 2012;101:743-8.
23. Soul JS, Taylor GA, Wypij D, Duplessis AJ, Volpe JJ. Noninvasive detection of changes in cerebral blood flow by near-infrared spectroscopy in a piglet model of hydrocephalus. Pediatr Res 2000;48:445-9.
24. Resch B, Gedermann A, Maurer U, Ritschl E, Muller W. Neurodevelopmental outcome of hydrocephalus following intra-/periventricular hemorrhage in preterm infants: short- and long-term results. Childs Nerv Syst 1996;12:27-33.
25. van Zanten SA, de Haan TR, Ursum J, van Sonderen L. Neurodevelopmental outcome of post-hemorrhagic ventricular dilatation at 12 and 24 months corrected age with high-threshold therapy. Eur J Paediatr Neurol 2011;15:487-92.
26. McClain CD. Principles of paediatric neurosurgery. In: Matta BF, Smith M, eds. Core Topics in neuroanaesthesia and neurointensive care. Cambridge: Cambridge University Press; 2011. p. 205-21.
27. Mokri B. The Monro-Kellie hypothesis: applications in CSF volume depletion. Neurology 2001;56:1746-8.

"Those who know that they will not be able to rest along the way will never get tired"

Mustafa Kemal Atatürk

4

Randomized Controlled Early versus Late Ventricular Intervention Study In Posthemorrhagic Ventricular Dilatation: Outcome at 2 Years

Mehmet N. Cizmeci, Floris Groenendaal, Kian D. Liem, Ingrid C. van Haastert, Isabel Benavente-Fernandez, Henrica L. M. van Straaten, Sylke Steggerda, Bert J. Smit, Andrew Whitelaw, Peter Woerdeman, Axel Heep*, Linda S. de Vries*, and the ELVIS study group
**Shared senior authorship*

J Pediatr 2020; 226: 28-35 DOI:10.1016/j.jpeds.2020.08.014

Abstract

Objective: To compare the effect of intervention at low vs high threshold of ventriculomegaly in preterm infants with post-hemorrhagic ventricular dilatation on death or severe neurodevelopmental disability.

Study design: This multicenter randomized controlled trial reviewed lumbar punctures initiated after either a low threshold (ventricular index of >p97 and anterior horn width of >6 mm) or high threshold (ventricular index of >p97 + 4mmand anterior horn width of >10 mm). The composite adverse outcome was defined as death or cerebral palsy or Bayley composite cognitive/motor scores <–2 SDs at 24 months corrected age.

Results: Outcomes were assessed in 113 of 126 infants. The composite adverse outcome was seen in 20 of 58 infants (35%) in the low threshold group and 28 of 55 (51%) in the high threshold (P = .07). The low threshold intervention was associated with a decreased risk of an adverse outcome after correcting for gestational age, severity of intraventricular hemorrhage, and cerebellar hemorrhage (aOR, 0.24; 95% CI, 0.07-0.87; P = .03). Infants with a favorable outcome had a smaller frontal and occipital horn ratio (crude mean difference, 0.06; 95% CI, 0.09 to 0.03; P < .001) at term-equivalent age. Infants in the low threshold group with a ventriculoperitoneal shunt, had cognitive and motor scores similar to those without (P = .3 for both), whereas in the high threshold group those with a ventriculoperitoneal shunt had significantly lower scores than those without a ventriculoperitoneal shunt (P = .01 and P = .004, respectively).

Conclusions: In a post hoc analysis, earlier intervention was associated with a lower odds of death or severe neurodevelopmental disability in preterm infants with progressive post-hemorrhagic ventricular dilatation.

Introduction

Although recent studies report a decrease in the incidence of severe intraventricular hemorrhage (IVH), it continues to be a common and significant problem in very preterm infants.[1,2] The risk of an adverse neurodevelopmental outcome increases significantly when severe IVH (grade III with or without a periventricular hemorrhagic infarction) is complicated by post-hemorrhagic ventricular dilatation.[3-6] Significant cognitive and motor impairment was found among infants with posthemorrhagic ventricular dilatation at 18-24 months corrected age (CA) in several retrospective studies and in a limited number of randomized controlled trials (RCT), including the DRIFT trial.[7-11] In these RCTs, randomization for interventions was performed once the ventricular index was >4 mm above the 97th percentile according to the graph of Levene.[12]

In the Early vs Late Ventricular Intervention Study (ELVIS) trial (ISRCTN43171322), infants were randomized prior to crossing this percentile, when the ventricular index was >97th percentile and progressing towards the 97th percentile + 4 mm line. We previously reported that there was no significant difference in the primary composite adverse outcome of ventriculoperitoneal shunt (VP shunt) placement or death in infants with post-hemorrhagic ventricular dilatation who were treated at a lower vs higher threshold for intervention.[13] However, the number of infants who required a VP shunt was 19% and 23%, respectively, the lowest number reported so far in the literature. In a nested substudy of the ELVIS trial, we subsequently reported that infants in the higher threshold group had a significantly higher global brain abnormality score, larger frontal and occipital horn ratio (FOHR), and larger ventricular volumes, using the Kidokoro score and automated volumetric analysis on the term-equivalent age MRI.[14,15] In the present study, we assessed neurodevelopmental outcomes of the ELVIS cohort at 24 months CA to test the hypothesis that earlier intervention would result in improved neurodevelopmental outcomes.

Methods

The ELVIS trial was a multicenter RCT enrolling 126 preterm infants from July 2006 to July 2016. Infants were eligible for inclusion if they had an IVH grade III, with or without a periventricular hemorrhagic infarction (PVHI).6 Infants were randomly assigned to low-threshold (ventricular index >97th percentile and anterior horn width >6 mm and/or thalamo-occipital distance >25 mm) or high threshold (ventricular index of >97th percentile + 4 mm and anterior horn width of >10 mm) groups. Interventions started with lumbar punctures with a maximum number of 3. If necessary, this was followed by insertion and tapping from a subcutaneous ventricular reservoir, aiming for ventricular index <97th percentile line in both groups. Once or twice daily, 10 mL/kg

were removed based on cranial ultrasound measurements. Taps were continued until stabilization occurred or until infant's weight reached 2000-2500 g, at which stage the infant became eligible for a VP-shunt, if still required.13 Antenatal and perinatal factors including gestational age, birth weight, sex, hemorrhage severity, and timing and type of intervention were retrieved from the patient files. Approval from the research ethics board at each center and informed written parental consent were obtained for patients participating in the study before enrollment.

Neuroimaging Protocol and Assessment

All participating centers used conventional axial T1-weighted and T2-weighted imaging and followed a predefined MRI protocol according to their institutional guidelines. MRIs were acquired around term-equivalent age with a 3.0 Tesla MR magnet (Tesla Engineering, West Sussex, United Kingdom) at 4 centers, and a 1.5 Tesla MR magnet in others.[14] For the assessment of brain injury, a global brain abnormality score was calculated as the sum of the regional total scores and classified as normal (total score of 0-3), mild (total score of 4-7), moderate (total score of 8-11), and severe (total score of ≥12) as defined by Kidokoro et al.[15] The FOHR was obtained by measuring the widest distances across the frontal horns and the occipital horns, and the average of these measurements was then divided by the largest biparietal diameter as defined by Kulkarni et al.[16] Cerebellar hemorrhage was categorized as no or punctate cerebellar hemorrhage (score of 0-2), and extensive (score of 3-4) based on their MRI findings according to Kidokoro et al.[15] Automatic segmentation of cerebral MRIs was applied on axial or coronal T2-weighted images for computerized volume analysis as described by Moeskops et al.[17] A detailed description of the neuroimaging protocol is presented elsewhere.[14]

Neurodevelopmental Assessment

Participants were followed longitudinally and neurodevelopmental outcomes were assessed as part of the standard follow-up programs of the participating centers. Examiners were blinded to treatment group assignment. Cognitive and motor outcome were assessed with either the Bayley Scales of Infant Development, second edition (BSID-II) or the Bayley Scales of Infant and Toddler Development, third edition (BSITD-III) at 24 months CA. Cognitive and motor index or composite scores were corrected for prematurity. The conversion from the BSID-II mental developmental index to the BSITD-III composite cognitive score was calculated by the formula (59% of the BSID-II mental developmental index score plus 52) suggested by Lowe et al.[18] To include children who had an index score of <50 on the BSID-II or a cognitive or motor composite score of <55 or <46, respectively, on the BSITD-III, developmental quotients were calculated (developmental age equivalent [in months, based on raw test scores] divided by the

corrected test age and multiplied by 100).[19] The non-English testers in Portugal, Spain, and Sweden used the administration manual of the Bayley tests in English and each examiner followed the instructions and performed the items as described.[20] In the Netherlands, the Dutch norms for the BSID-III were available from 2014 onward.[21] The scores from previously tested children were recalculated using the Dutch edition. The severity of cerebral palsy (CP) was classified according to the Gross Motor Function Classification System, with moderate to severe CP defined as levels III-V.[22,23] CP was classified as spastic, ataxic, or dyskinetic and categorized as unilateral or bilateral.[24] The primary composite outcome was death, any grade CP, or a Bayley cognitive or motor score of <-2 SD.

Statistical Analyses

Data analysis was performed by the coordinating center, the University Medical Center Utrecht. Statistical analyses were performed using IBM SPSS Statistics version 25 (SPSS Inc, Chicago, Illinois). Continuous variables were presented as mean SD and median (IQR), depending on their distribution. Categorical values were presented as number and percentage. The Chi-squared and Fisher exact tests were used to compare categorical variables among groups. Mann-Whitney U test was used to compare nonparametric variables and the Student t-test for comparison between variables with normal distribution. Logarithmic transformation was performed to the ventricular volumes to yield variance homogeneity and Gaussian distribution. Hierarchical multiple linear regression and logistic regression analyses were applied for the significant variables detected with the univariate analysis. Gestational age was dichotomized using 28 weeks as a cut-off. Adjustment for gestational age, severity of IVH, and severity of cerebellar hemorrhage was performed in the multivariable regression models. Statistical significance was set at $P < .05$.

Results

Among the 109 survivors, a total of 100 (92%) were assessed at a mean CA of 25.1 ± 2.0 months. Of these infants, 86 (86%) were assessed with BSID-III and 14 (14%) with BSID-II. Of the 14 infants who were assessed with BSID-II, 10 were in the low threshold group and 4 in the high threshold. Four infants were further removed from the analysis owing to a missing Bayley domain, either cognitive or motor. The flowchart of the ELVIS trial is presented in (Figure 1).

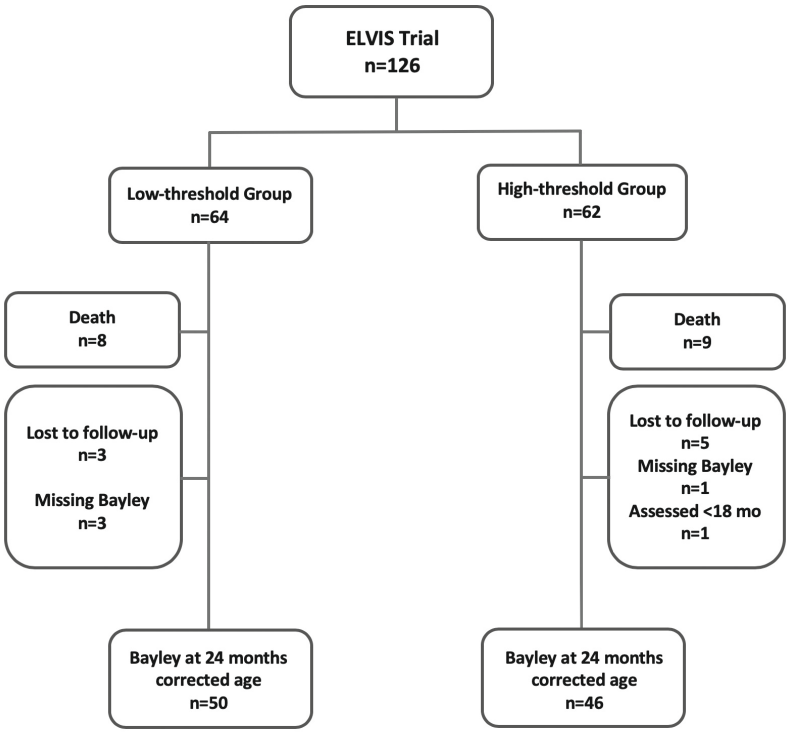


Figure 1: Flowchart of the ELVIS trial demonstrating follow-up of the study population.

The surviving infants of the two treatment arms were comparable with respect to clinical characteristics, except for the larger number of infants in the low threshold arm with prolonged mechanical ventilation (P = .05) (Table 1).

Table 1: Demographic and clinical characteristics of the surviving infants.

	Low-Threshold Group (n=56)	High-Threshold Group (n=51*)	p
Gestational age, week	28.1 ± 2.34	27.9 ± 2.56	0.9[a]
Birth weight, g	1198 ± 354	1180 ± 380	0.9[a]
Sex			0.8[b]
Male	32 (57)	32 (63)	
Female	24 (43)	19 (37)	
Antenatal steroids	27 (48)	19 (37)	0.3[b]
Early onset sepsis	10 (18)	8 (16)	0.8[b]
Late onset sepsis	18 (32)	21 (41)	0.4[b]
Mechanical ventilation >7 days	32 (57)	19 (37)	0.05[b]

Table 1: *[Continued]*

	Low-Threshold Group (n=56)	High-Threshold Group (n=51*)	p
Medical treatment for PDA	10 (34)	20 (39)	0.7[b]
Surgical treatment for PDA	4 (7)	5 (10)	0.7[b]
Medical treatment for NEC	2 (4)	3 (6)	0.7[b]
Surgical treatment for NEC	1 (2)	3 (6)	0.4[b]
Inotropes	23 (41)	17 (33)	0.4[b]
Postnatal corticosteroids	5 (9)	7 (14)	0.5[b]

[a]t-test, [b]Chi Square test. Data are presented as mean ± standard deviation (SD) or number (%)
* Incomplete demographic and clinical data in 2 infants

Outcomes

The composite outcome was assessed in 113 infants. Eight infants (13%) died in the low-threshold group and 9 (15%) in the high-threshold group.13 In the low-threshold group, 20 of 58 (35%) had an adverse composite outcome (death [n = 8], CP [n = 10], or a Bayley composite cognitive or motor score of < 2 SD [n = 6]), whereas in the high-threshold group, 28 of 55 (51%) had an adverse outcome (including death [n = 9], CP [n = 14], or a Bayley composite cognitive or motor score of <2 SD [n = 11]) (P = .07). In a post hoc multivariable analysis, low-threshold intervention was associated with a decreased risk of an adverse outcome after correcting for gestational age, severity of IVH, and cerebellar hemorrhage (aOR, 0.24; 95% CI, 0.07-0.87; P = .03). CP was seen in 5 of 66 infants (8%) with a grade-III IVH, and in 19 of 34 infants (56%) with a periventricular hemorrhagic infarction (P < .001). Topographic classification and severity of CP with respect to grade of IVH are presented in Table 2.

Table 2: Type and severity of cerebral palsy with respect to grade of intraventricular hemorrhage.

	Low-Threshold Group	High-Threshold Group
Grade-III	1/36 n=1, GMFCS Level III Bilat. spastic CP	4/30 n=1, GMFCS Level I-II Unilat. spastic CP n=1, GMFCS Level I-II Bilat. spastic CP n=2, GMFCS Level III ataxic/dyskinetic
PVHI	9/17 n=5, GMFCS Level I-II Unilat. spastic CP n=1, GMFCS Level II Bilat. spastic CP n=3, GMFCS Level III-V Bilat. spastic CP	10/17 n=8, GMFCS Level I-II Unilat. spastic CP n=1, GMFCS Level III-V Unilat. spastic CP n=1, GMFCS Level III-V Bilat. spastic CP

Data are presented as numbers.

Among the survivors, the median Bayley composite cognitive scores were 95 (IQR, 85-110) in the low-threshold and 91 (IQR, 80-101) in the high threshold group (P = .1). Categorical distribution of these infants is presented in detail in Table 3.

Table 3: Neurodevelopmental outcomes of the study population.

	Low-Threshold Group	High-Threshold Group	p*
Bayley cognitive score†			0.5
Normal range	39 (78)	32 (71)	
<-1 SD below the normative range	8 (16)	7 (16)	
<-2 SD below the normative range	3 (6)	6 (13)	
Bayley motor score††			0.1
Normal range	29 (61)	30 (64)	
<-1 SD below the normative range	14 (29)	7 (15)	
<-2 SD below the normative range	5 (10)	10 (21)	
Bayley cognitive score in CP			0.4
Normal range	4 (50)	9 (64)	
<-1 SD below the normative range	3 (38)	2 (14)	
<-2 SD below the normative range	1 (12)	3 (21)	
Bayley cognitive score in VP-shunt			0.1
Normal range	7 (64)	6 (46)	
<-1 SD below the normative range	3 (27)	2 (15)	
<-2 SD below the normative range	1 (9)	5 (39)	
Bayley motor score in CP			0.7
Normal range	1 (10)	2 (14)	
<-1 SD below the normative range	6 (60)	6 (43)	
<-2 SD below the normative range	3 (30)	6 (43)	
Bayley motor score in VP-shunt			0.2
Normal range	4 (40)	4 (31)	
<-1 SD below the normative range	5 (50)	3 (23)	
<-2 SD below the normative range	1 (10)	6 (46)	
Grade of intraventricular hemorrhage in CP			
Grade-III IVH	1/36 (3)	4/30 (13)	0.1
PVHI	9/17 (53)	10/17 (59)	0.7

*Fisher's exact test
Values are presented as number (%).
†Data available for 50 infants in the LT group and 45 in HT.
††Data available for 48 infants in the LT group and 47 in HT.

Survivors without CP had a higher composite cognitive score than those with CP (95 [IQR, 89-110] vs 85 [IQR, 74-96], respectively; P = .001). Infants without a VP shunt had higher composite cognitive score than those with a VP shunt (95 [IQR, 87-109] vs 85 [IQR, 70-99], respectively; P = .02). Infants in the low threshold group who required a VP shunt had a composite cognitive score similar to those without a VP shunt (median, 90 [IQR, 80-107] vs 96 [IQR, 87-110]; P = .3), however, those in the high threshold group with a VP shunt had a lower cognitive score than those without (80 [IQR, 62-96] vs 95 [IQR, 86-105]; P = .01) (Figure 2).

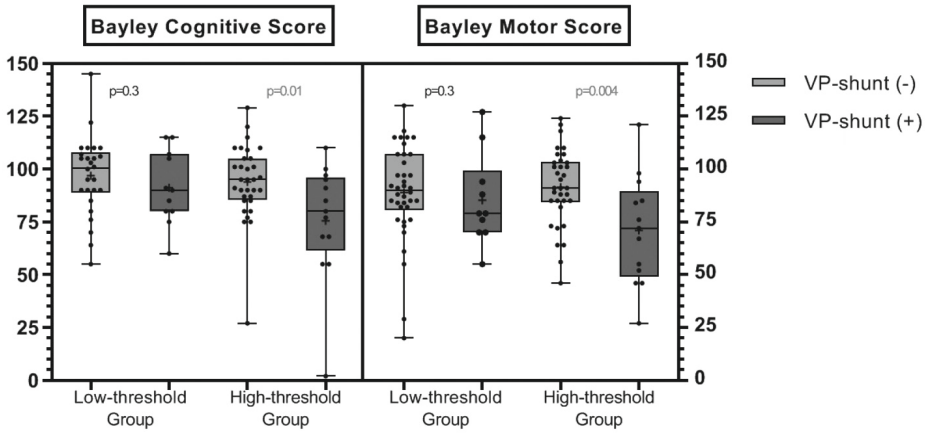


Figure 2: Box plot graphs showing the distribution of the Bayley cognitive and motor scores in relation to the timing of intervention and presence of ventriculo-peritoneal shunt.

Among the survivors, the median Bayley motor scores were 88 (IQR, 76-106) in the low-threshold and 88 (IQR, 72-101) in the high-threshold group, respectively (P = .6). Categorical distribution of these infants is presented in detail in Table 3. Survivors without CP had a higher composite motor score than those with CP (92 [IQR, 85-107] vs 73 [IQR, 55-82], respectively; P < .001). Infants without a VP-shunt had a higher composite motor score than those with VP-shunt (91 [IQR, 82-104] vs 76 [IQR, 55-94], respectively; P = .004). Infants in the low-threshold group who required a VP-shunt had a composite motor score not significantly different from those without a VP-shunt (median, 79 [IQR, 70-99] vs 90 [IQR, 81-107]; P = .3), but those in the high-threshold group with a VP-shunt had a lower composite motor score than those without (72 [IQR, 49-90] vs 91 [IQR, 84-103]; P = .004) (Figure 2).

Outcomes in Relation to Term-Equivalent Age MRI Variables

MRI was performed at term-equivalent age in 88 infants. Among the survivors, 0 of 3 (0%) infants with a normal, 1 of 21 (5%) with a mild, 5 of 21 (24%) with a moderate, and 25 of 37 (68%) with a severe Kidokoro score had an adverse composite outcome (P < .001) (Figure 3).

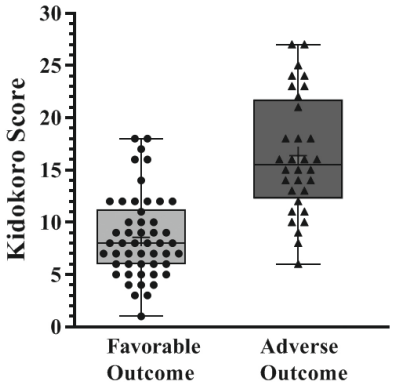


Figure 3: Box plot graphs showing the distribution of the Kidokoro scores in relation to the outcome.

Infants with a normal or mildly abnormal Kidokoro score had a higher Bayley composite cognitive and motor score when compared with the infants with a moderate or severe score (103 [IQR, 90-110] vs 91 [IQR, 79-104] and 95 [IQR, 88-111] vs 84 [IQR, 70-98]; P = .02 and P = .01, respectively). The mean ± SD FOHR was larger in infants with an adverse composite outcome than those without (0.49 ± 0.06 vs 0.43 ± 0.04; mean difference, 0.06 [95% CI, 0.09-0.03]; P < .001). A larger FOHR was negatively associated with a composite cognitive and motor score irrespective of group allocation (ß, -177 [95% CI, -247 to -109] and -162 [95% CI, -236 to -88], respectively; P < .001 for both) (Figure 4).

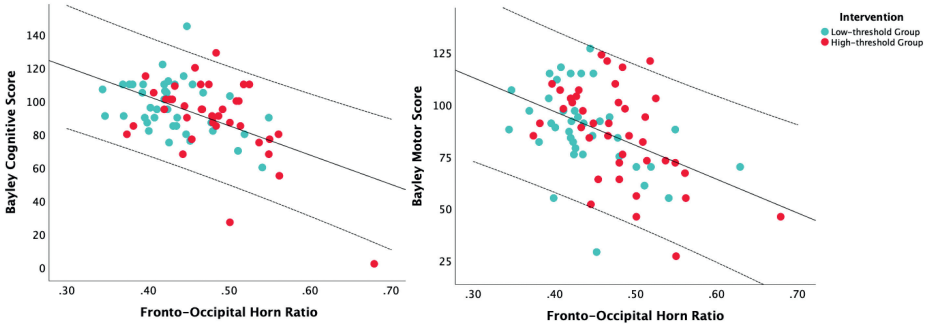


Figure 4: Scatter plot graphs with linear regression lines showing the relationship between the Bayley cognitive (left) and motor score (right), and frontal and occipital horn ratio. The solid line represents the mean and dashed lines represent 95% CIs.

In a subgroup of infants (n = 47) who had a volumetric analysis performed, infants with a favorable composite outcome had smaller ventricular volumes than those with an adverse outcome (mean, -1.26 ± 0.22 vs -1.10 ± 0.29; crude mean difference, -0.16; 95% CI, -0.32 to -0.001; P = .049). Infants with an extensive cerebellar hemorrhage (n = 8) had a lower Bayley composite cognitive and motor score than those with no or punctate cerebellar hemorrhage (75 [IQR, 42-86] vs 95 [IQR, 85-110]; P = .009 and 69 [IQR, 50-88] vs 91 [IQR, 76-103]; P = .01, respectively). Infants with an extensive cerebellar hemorrhage were also more likely to have an adverse composite outcome than those with no or punctate cerebellar hemorrhage (7 of 8 infants [88%] vs 24 of 74 infants [32%], respectively; P = .004). Extensive cerebellar hemorrhage was an independent risk factor for adverse outcome (OR, 19; 95% CI, 2-197; P = .01).

Discussion

In the ELVIS trial, we assessed outcome at 2 years of CA in very preterm infants and showed a trend toward an improved composite outcome in the low-threshold group compared with the high- threshold group. After adjusting for gestational age, severity of IVH, and cerebellar hemorrhage, earlier intervention reduced death or severe neurodevelopmental disability in infants with post-hemorrhagic ventricular dilatation. The interventions for both arms of the study were solely based on sonographic criteria and initiated while the infants were still asymptomatic.

In infants with post-hemorrhagic ventricular dilatation, CP was seen more often in infants with a periventricular hemorrhagic infarction, and the majority of these infants had unilateral CP, similar to what has been reported in the literature.[25] CP also occurred in infants with a grade III IVH, in which case bilateral CP was more common. As expected, the development of CP had a negative effect on especially motor, but also on

cognitive outcome. Although there was overlap between CP and low Bayley scores, the majority of the infants with CP in both groups had Gross Motor Function Classification System level I or II. This finding likely explains why some infants with CP had normal Bayley scores. Additionally, in a post hoc analysis, infants in the low-threshold group requiring a VP-shunt had cognitive and motor scores that were similar to infants without a VP shunt. In contrast, infants in the high threshold group who required a VP shunt had lower Bayley cognitive and motor scores compared with those without.

In a recent study by Leijser et al, neurodevelopmental outcome was evaluated at 18-24 months in infants with posthemorrhagic ventricular dilatation.[11] Investigators found that preterm infants undergoing intervention at an early stage, even when eventually requiring a VP-shunt, had developmental test scores that were similar to infants without intervention, all within the normal range. In contrast, intervention after the onset of clinical symptoms was associated with an increased risk of adverse outcomes. It is not straightforward, however, to compare our findings with previous RCTs, because randomization to one study arm, that is low-threshold, was significantly earlier in the ELVIS trial when compared with the timing of randomization in other studies. In the first RCT, the Ventriculomegaly Study, there was no upper limit for the ventricular index at enrollment and interventions were performed to prevent further dilatation, rather than bringing the ventricular size down to within the normal range.[26] Investigators found no difference in the primary outcome of VP shunt between the 2 groups.[4,26] In a subsequent RCT by the International Posthemorrhagic Ventricular Dilatation Drug Trial Group, there was again no upper limit on ventricular index and the composite outcome of death or VP-shunt placement was significantly higher in the treatment group. The use of acetazolamide and furosemide were also associated with higher rates of neurological morbidity.[7,27]

In an RCT using Drainage, Irrigation, and Fibrinolytic Therapy (DRIFT trial), rates of VP shunt placement were higher (38% and 39% in the treatment and standard therapy groups, respectively) than in the ELVIS trial (19% and 23% in the low-threshold and high-threshold groups, respectively).[8,28] Because the entry criteria for the two RCTs were different, no direct comparison can be made. In the DRIFT trial, infants were enrolled once the ventricular index exceeded the 97th percentile + 4mm line but there was no intention to bring the ventricular index down to within the normal range within 7-10 days. The ventricular index for infants in the DRIFT trial was significantly larger than for infants in the high-threshold arm of the ELVIS trial (Whitelaw A, personal communication, January 2020). Comparison could only be made for infants who exceeded the 97th percentile +4 mm line, because infants were referred to the study site once this line was crossed. This observation supports our hypothesis that draining cerebrospinal fluid earlier may prevent further brain injury. Cerebrospinal fluid containing blood components and inflammatory substances may have a negative effect

on the developing preterm brain, and earlier removal may have been beneficial; we were able to show that the majority of infants survived without a severe disability.[29,30]

Ventriculomegaly at term-equivalent age, even without evidence of increased intracranial pressure, has been shown to be an independent predictor of adverse cognitive and motor outcomes in preterm infants.[31-33] The pathogenesis of brain injury in infants with ventriculomegaly is a complex process and determined by both direct injury to adjacent brain tissues and secondary inflammatory interactions.[34-36] The relationship between ventricular volumes and outcome was demonstrated using 3-dimensional ultrasound imaging, and adverse outcome at 12 months was seen in preterm infants with larger ventricles.[37] However, the correlation between ultrasonographic and MRI measurements remains inconsistent and needs further investigation.[1,38] Jary et al performed manual brain segmentation on MRI and demonstrated that total cerebral volume, excluding the ventricles, correlated significantly with cognitive and motor outcomes.[39] In the ELVIS trial, automated segmentation methods to measure ventricular volumes could only be performed in around one-half of the infants with MRI owing to insufficient image quality. Infants with favorable outcomes had smaller relative ventricular volumes than those with adverse outcomes. The FOHR, which was shown to be a reliable and reproducible predictor of ventricular volumes in infants with ventriculomegaly, was assessed in a large number of infants.[14,40,41] Because we could not obtain volumetric measurements of all patients owing to technical challenges, we used FOHR instead in our previous nested substudy of the ELVIS trial.[14] In the present study, we found a larger FOHR in infants with an adverse composite outcome than those without, and greater ventricular volumes were negatively associated with Bayley cognitive and motor scores irrespective of group allocation. Preserved ventricular volumes with potentially better outcomes seem to justify the increase in additional interventions, that is, lumbar punctures and ventricular reservoirs, in the low threshold group.

An increasing Kidokoro score, which is a reliable tool to assess brain injury at term-equivalent age MRI, was also associated with an adverse composite outcome.[15] We previously hypothesized that the higher Kidokoro scores in infants in the high threshold group were caused by prolonged pressure on the periventricular white matter owing to progressive posthemorrhagic ventricular dilatation, which might be deleterious to the developing preterm brain.[14] Posthemorrhagic ventricular dilatation-induced microstructural brain injury, as stated previously by Brouwer et al, might serve as another explanation for increased Kidokoro scores.[42] In our previous study, we found more infants with a moderate or severe score in the high threshold group, and in the present study, we found that a moderate or severe Kidokoro score was associated with an increased odds of death and severe neurodevelopmental disability.[14] Also of note was that infants with an extensive cerebellar hemorrhage were more likely to have an

adverse composite outcome than those without, irrespective of the group allocation, which is in agreement with the literature.[43]

The present study has several limitations. The ELVIS trial was powered for the primary outcome of death or VP-shunt, and not for the secondary long-term outcomes, which may explain why our study found only a trend toward an improved outcome. In the post hoc analysis adjusting for gestational age, the severity of IVH, and the severity of cerebellar hemorrhage, we found a significant benefit for early intervention in reducing the composite adverse outcome. Because the infants were enrolled over a 10-year period, perinatal care may have changed in the participating centers. However, this would have similar effects on both study arms. Although the majority of infants were tested with the BSITD-III, a small group was tested with the BSID-II. To overcome this difference, we used the conversion formula from Lowe et al on BSID-II scores for calculating equivalent BSITD-III scores.[18] We were not able to collect data on socioeconomic status from the records of all infants and could not adjust the outcomes for this variable. Because the infants were born in different countries and the BSID-III has not been widely validated, we were not able to present data on language outcomes. Finally, not all survivors had a term-equivalent age MRI and in only around one-half of these was the MRI quality was sufficient to perform automated segmentation. The major strength of the present study is the high follow-up rate in centers with experience in neonatal neurology practices.

In conclusion, in this multicenter RCT, there was a beneficial effect of early intervention for posthemorrhagic ventricular dilatation on reducing mortality and severe neurodevelopmental disability, after adjusting for gestational age and severity of IVH and cerebellar hemorrhage.

Acknowledgment

We thank the neurosurgeons, neonatal intensive care nurses, developmental specialists, and data managers for their dedicated help to obtain the pertinent data and records.

References

1. Leijser LM, de Vries LS. Preterm brain injury: germinal matrix– intraventricular hemorrhage and post-hemorrhagic ventricular dilatation. In: de Vries LS, Glass HC, eds. Handbook of clinical neurology. New York (NY): Elsevier; 2019. p. 173-99.
2. Yeo KT, Thomas R, Chow SS, Bolisetty S, Haslam R, Tarnow-Mordi W, et al. Improving incidence trends of severe intraventricular haemorrhages in preterm infants <32 weeks gestation: a cohort study. Arch Dis Child Fetal Neonatal Ed 2020;105:145-50.
3. Fernell E, Hagberg G, Hagberg B. Infantile hydrocephalus in preterm, low-birth-weight infants-a nationwide Swedish cohort study 1979-1988. Acta Paediatr 1993;82:45-8.
4. Ventriculomegaly Trial Group. Randomised trial of early tapping in neonatal posthaemorrhagic ventricular dilatation: results at 30 months. Arch Dis Child Fetal Neonatal Ed 1994;70:129-36.
5. Persson EK, Hagberg G, Uvebrant P. Disabilities in children with hydrocephalus-a population-based study of children aged between four and twelve years. Neuropediatrics 2006;37:330-6.
6. Volpe JJ. Intraventricular hemorrhage in the premature infant–current concepts. Part II. Ann Neurol 1989;25:109-16.
7. Kennedy CR, Ayers S, Campbell MJ, Elbourne D, Hope P, Johnson A. Randomized, controlled trial of acetazolamide and furosemide in posthemorrhagic ventricular dilation in infancy: follow-up at 1 year. Pediatrics 2001;108:597-607.
8. Whitelaw A, Evans D, Carter M, Thoresen M, Wroblewska J, Mandera M, et al. Randomized clinical trial of prevention of hydrocephalus after intraventricular hemorrhage in preterm infants: brain-washing versus tapping fluid. Pediatrics 2007;119:1071-8.
9. Adams-Chapman I, Hansen NI, Stoll BJ, Higgins R , NICHD Research Network. Neurodevelopmental outcome of extremely low birth weight infants with posthemorrhagic hydrocephalus requiring shunt insertion. Pediatrics 2008;121:1167-77.
10. Bassan H, Eshel R, Golan I, Kohelet D, Ben Sira L, Mandel D, et al. Timing of external ventricular drainage and neurodevelopmental outcome in preterm infants with posthemorrhagic hydrocephalus. Eur J Paediatr Neurol 2012;16:662-70.
11. Leijser LM, Miller SP, van Wezel-Meijler G, Brouwer AJ, Traubici J, van Haastert IC, et al. Posthemorrhagic ventricular dilatation in preterm infants: when best to intervene? Neurology 2018;90:698-706.
12. Levene MI. Measurement of the growth of the lateral ventricles in preterm infants with real-time ultrasound. Arch Dis Child 1981;56:900-4.
13. de Vries LS, Groenendaal F, Liem KD, Heep A, Brouwer AJ, van 't Verlaat E, et al. Treatment thresholds for intervention in posthaemorrhagic ventricular dilation: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2019;104:70-5.
14. Cizmeci MN, Khalili N, Claessens NHP, Groenendaal F, Liem KD, Heep A, et al. Assessment of brain injury and brain volumes after posthemorrhagic ventricular dilatation: a nested substudy of the randomized controlled ELVIS trial. J Pediatr 2019;208:191-7.
15. Kidokoro H, Neil JJ, Inder TE. New MR imaging assessment tool to define brain abnormalities in very preterm infants at term. AJNR Am J Neuroradiol 2013;34:2208-14.
16. Kulkarni AV, Drake JM, Armstrong DC, Dirks PB. Measurement of ventricular size: reliability of the frontal and occipital horn ratio compared to subjective assessment. Pediatr Neurosurg 1999;31:65-70.
17. Moeskops P, Viergever MA, Mendrik AM, de Vries LS, Benders MJ, Isgum I. Automatic segmentation of MR brain images with a convolutional neural network. IEEE Trans Med Imaging 2016;35:1252-61.

18. Lowe JR, Erickson SJ, Schrader R, Duncan AF. Comparison of the Bayley II mental developmental index and the Bayley III cognitive scale: are we measuring the same thing? Acta Paediatr 2012;101:55-8.
19. Jary S, Kmita G, Whitelaw A. Differentiating developmental outcome between infants with severe disability in research studies: the role of Bayley developmental quotients. J Pediatr 2011;159:211-4.
20. Bayley N. Bayley Scales of Infant and Toddler Development. 3rd ed. San Antonio (TX): Harcourt Assessment; 2006.
21. Van Baar AL, Steenis LJP,Verhoeven M. Bayley Scales of Infant and Toddler Development - Derde Editie,Nederlandstalige Bewerking, Technische Handleiding. Amsterdam: Pearson Assessment and Information B.V; 2014.
22. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl 2007;109:8-14.
23. Palisano RJ, Hanna SE, Rosenbaum PL, Russell DJ, Walter SD, Wood EP, et al. Validation of a model of gross motor function for children with cerebral palsy. Phys Ther 2000;80:974-85.
24. Novak I, Morgan C, Adde L, Blackman J, Boyd RN, Brunstrom-Hernandez J, et al. Early, accurate diagnosis and early intervention in cerebral palsy: advances in diagnosis and treatment. JAMA Pediatr 2017;171:897-907.
25. Cizmeci MN, de Vries LS, Ly LG, vanHaastert IC, Groenendaal F, Kelly EN, et al. Periventricular hemorrhagic infarction inverypreterminfants: characteristic sonographic findings and association with neurodevelopmental outcomes at age 2 years. J Pediatr 2020;217:79-85.
26. Ventriculomegaly TrialGroup. Randomised trial of early tapping in neonatal posthaemorrhagic ventricular dilatation. Arch Dis Child 1990;65:3-10.
27. International PHVD Drug Trial Group. International randomised controlled trial of acetazolamide and furosemide in posthaemorrhagic ventricular dilatation in infancy. Lancet 1998;352:433-40.
28. Whitelaw A, Jary S, Kmita G, Wroblewska J, Musialik-Swietlinska E, Mandera M, et al. Randomized trial of drainage, irrigation and fibrinolytic therapy for premature infants with posthemorrhagic ventricular dilatation: developmental outcome at 2 years. Pediatrics 2010;125:852-8.
29. Habiyaremye G, Morales DM, Morgan CD, McAllister JP, CreveCoeur TS, Han RH, et al. Chemokine and cytokine levels in the lumbar cerebrospinal fluid of preterm infants with post-hemorrhagic hydrocephalus. Fluids Barriers CNS 2017;14:35.
30. Morales DM, Silver SA, Morgan CD, Mercer D, Inder TE, Holtzman DM, et al. Lumbar cerebrospinal fluid biomarkers of posthemorrhagic hydrocephalus of prematurity: amyloid precursor protein, soluble amyloid precursor protein alpha, and L1 cell adhesion molecule. Neurosurgery 2017;80:82-90.
31. Whitaker AH, Feldman JF, Van Rossem R, Schonfeld IS, Pinto-Martin JA, Torre C, et al. Neonatal cranial ultrasound abnormalities in low birth weight infants: relation to cognitive outcomes at six years of age. Pediatrics 1996;98:719-29.
32. Ment LR, Vohr B, Allan W, Westerveld M, Katz KH, Schneider KC, et al. The etiology and outcome of cerebral ventriculomegaly at term in very low birth weight preterm infants. Pediatrics 1999;104:243-8.
33. Fox LM, Choo P, Rogerson SR, Spittle AJ, Anderson PJ, Doyle L, et al. The relationship between ventricular size at 1 month and outcome at 2 years in infants less than 30 weeks' gestation. Arch Dis Child Fetal Neonatal Ed 2014;99:209-14.
34. Savman K, Blennow M, Hagberg H, Tarkowski E, Thoresen M, Whitelaw A. Cytokine response in cerebrospinal fluid from preterm infants with posthaemorrhagic ventricular dilatation. Acta Paediatr 2002;91:1357-63.

35. Whitelaw A, Cherian S, Thoresen M, Pople I. Posthaemorrhagic ventricular dilatation: new mechanisms and new treatment. Acta Paediatr Suppl 2004;93:11-4.
36. Srinivasakumar P, Limbrick D, Munro R, Mercer D, Rao R, Inder T, et al. Posthemorrhagic ventricular dilatation-impact on early neurodevelopmental outcome. Am J Perinatol 2013;30:207-14.
37. Lo M, Kishimoto J, Eagleson R, Bhattacharya S, de Ribaupierre S. Does ventricular volume affect the neurodevelopmental outcome in infants with intraventricular hemorrhage? Childs Nerv Syst 2020;36:569-75.
38. Beijst C, Dudink J, Wientjes R, Benavente-Fernandez I, Groenendaal F, Brouwer MJ, et al. Two-dimensional ultrasound measurements vs. magnetic resonance imaging-derived ventricular volume of preterm infants with germinal matrix intraventricular haemorrhage. Pediatr Radiol 2020;50:234-41.
39. Jary S, De Carli A, Ramenghi LA, Whitelaw A. Impaired brain growth and neurodevelopment in preterm infants with posthaemorrhagic ventricular dilatation. Acta Paediatr 2012;101:743-8.
40. O'Hayon BB, Drake JM, Ossip MG, Tuli S, Clarke M. Frontal and occipital horn ratio: a linear estimate of ventricular size for multiple imaging modalities in pediatric hydrocephalus. Pediatr Neurosurg 1998;29:245-9.
41. Radhakrishnan R, Brown BP, Kralik SF, Bain D, Persohn S, Territo PR, et al. Frontal occipital and frontal temporal horn ratios: comparison and validation of head ultrasound-derived indexes with MRI and ventricular volumes in infantile ventriculomegaly. AJR Am J Roentgenol 2019;213: 925-31.
42. Brouwer MJ, de Vries LS, Kersbergen KJ, van der Aa NE, Brouwer AJ, Viergever MA, et al. Effects of posthemorrhagic ventricular dilatation in the preterm infant on brain volumes and white matter diffusion variables at term-equivalent age. J Pediatr 2016;168:41-9.
43. Boswinkel V, Steggerda SJ, Fumagalli M, Parodi A, Ramenghi LA, Groenendaal F, et al. The CHOPIn Study: a multicenter study on cerebellar hemorrhage and outcome in preterm infants. Cerebellum 2019;18:989-98.

"Everything we see in the world is the creative work of women"

Mustafa Kemal Atatürk

5

Post-Hemorrhagic Ventricular Dilatation Affects White Matter Maturation in Extremely Preterm Infants

Astrid Nieuwets*, Mehmet N. Cizmeci*, Floris Groenendaal, Lara M. Leijser, Corine Koopman, Manon J. N. L. Benders, Jeroen Dudink, Linda S. de Vries, Niek E. van der Aa
**Shared first authorship*

Pediatr Res. 2021 Aug DOI: 10.1038/s41390-021-01704-2

Abstract

Background: Data on microstructural white matter integrity in preterm infants with post-hemorrhagic ventricular dilatation (PHVD) using diffusion tensor imaging (DTI) are limited. Also, to date, no study has focused on the DTI changes in extremely preterm (EP) infants with PHVD.

Methods: A case-control study of EP infants <28 weeks' gestation with PHVD was conducted. Diffusivity and fractional anisotropy (FA) values of corticospinal tracts (CST) and corpus callosum (CC) were measured using DTI at term-equivalent age. Outcomes were assessed at 2-years-corrected age.

Results: Twenty-one infants with PHVD and 21 matched-controls were assessed. FA values in the CC were lower in infants with PHVD compared with controls (mean difference, 0.05 [95% confidence interval (CI), 0.02–0.08], $p < 0.001$). In infants with periventricular hemorrhagic infarction, FA values in the CC were lower than in controls (mean difference, 0.05 [95% CI, 0.02–0.09], $p = 0.005$). The composite cognitive and motor scores were associated with the FA value of the CC (coefficient 114, $p = 0.01$ and coefficient 147, $p = 0.004$; respectively).

Conclusions: Extremely preterm infants with PHVD showed lower FA values in CC. A positive correlation was also shown between the composite cognitive and motor scores and FA value of the CC at 2-years-corrected age.

Introduction

Germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH) is the most common neurological disorder of the very preterm population and the risk of an adverse neurodevelopmental outcome increases significantly when GMH-IVH is complicated by post-hemorrhagic ventricular dilatation (PHVD).[1–3] Experimental models and human studies have consistently shown that the mechanisms of the detrimental effects of PHVD are multifactorial and mediated mainly by mechanical distortion, neuroinflammation, and neurotoxicity.[1,4–7] Prolonged distending pressure of the ventricles, along with inflammatory substances and blood products in the hemorrhagic cerebrospinal fluid (CSF), can lead to secondary white matter injury and disturbed myelination as seen in infants with progressive PHVD and subsequent neurodevelopmental sequelae.[3,8–10] The application of magnetic resonance imaging (MRI) combined with advanced analytical approaches is increasingly being used to enhance our understanding of the neurodevelopmental problems that preterm infants face.[11] Diffusion tensor imaging (DTI) is an advanced MRI technique, which allows the examination of fiber tracts in the neonatal brain by utilizing the three-dimensional anisotropy of water diffusion.[12,13] DTI is widely applied in studies of the developing brain, as measures obtained with this technique provide objective and predictable indices of white matter development and injury.[1,13,14] These indices include the molecular diffusion rate of water (mean diffusivity, MD), the directional preference of diffusion (fractional anisotropy, FA), the diffusion rate along the main axis of diffusion (axial diffusivity, AD), and the rate of diffusion in the transverse direction (radial diffusivity, RD).[14] Very preterm infants with brain injury show lower FA and AD, and higher RD and MD values compared with infants without brain injury using DTI across multiple white matter regions, especially in those anatomically close to the ventricles, such as corpus callosum (CC) and corticospinal tracts (CST).[15] While DTI has been used to assess white matter tracts in preterm infants with GMH-IVH, changes in white matter microstructure using DTI in infants with PHVD have not been studied extensively. Also, to date, no study has focused on the DTI changes in extremely preterm (EP) infants with PHVD.[14–16] In this study, we sought to assess the effects of PHVD on FA, AD, RD, and MD values in extremely preterm infants and hypothesized that PHVD may adversely impact the highly dynamic and vulnerable maturational processes in the white matter and neurodevelopmental outcomes at 2-years-corrected age.

Methods

Study population

In this single-center retrospective case-control study, extremely preterm infants <28 weeks' gestation with PHVD who were admitted to the level three neonatal

intensive care unit of the Wilhelmina Children's Hospital, University Medical Center Utrecht, between September 2007 and April 2016 were eligible. Sequential cranial ultrasonography (cUS) was performed by experienced attending neonatologists or physician assistants on admission, on days 3 and 7, and at least weekly thereafter until term-equivalent age (TEA). Scanning was conducted with a multifrequency microconvex probe using a Toshiba Aplio Ultrasound System (Canon Medical Systems Inc., Tochigi, Japan). During the study period, the cUS scanning protocol remained unchanged. Infants with PHVD were included if they had progressive measurements of the ventricular index (VI) > 97th percentile and anterior horn width (AHW) > 6mm on at least two cUS scans using reference charts described by Levene[17] and Davies et al.,[18] respectively. Ultrasonographic criteria and treatment thresholds for intervention are described in detail in a previous article.[19] Periventricular hemorrhagic infarction (PVHI) was defined as a unilateral parenchymal hemorrhage ipsilateral to the GMH-IVH, as defined by Volpe.[20] Infants were excluded if they had a chromosomal abnormality, genetic disorder, coexisting cerebellar hemorrhage, congenital or acquired central nervous system infection, and/or inborn errors of metabolism. For each infant with PHVD, a gestational age (GA) (within ±7 days) and sex-matched preterm infant without signs of hemorrhagic or ischemic preterm brain injury on cUS was included for the control group. Demographic data were extracted from the patients' files and/or electronic hospital database. Data on antenatal and perinatal factors including GA, birth weight, sex, the severity of GMH-IVH, and clinical data including the use of postnatal steroids, prolonged mechanical ventilation for >7 days, late-onset sepsis, necrotizing enterocolitis (NEC) requiring surgical treatment, hemodynamically significant patent ductus arteriosus and retinopathy of prematurity were collected. Due to the pseudonymization of clinically acquired data, written informed consent from the parents or legal guardians of the study infants was not deemed necessary by the Institutional Review Board (IRB), and a waiver of consent was provided for this study.

Neuroimaging protocol and DTI assessment

Term-equivalent age-MRI (TEA-MRI) was obtained using a 3-Tesla Philips Achieva MR scanner (Achieva, Philips Medical Systems, Best, the Netherlands). Prior to the MRI at TEA, infants were sedated, wrapped in a vacuum pillow, and positioned in an 8-channel SENSE head coil. Each neonate was given hearing protection consisting of Minimuffs (Natus Medical Incorporated, San Carlos, CA) and Earmuffs (EMs 4 Kids, Brisbane, QLD, Australia). DTI data were acquired in the axial plane with a slice thickness of 2 mm. The DTI sequences included a single non-diffusion-weighted image and additional diffusion-weighted images with a b-value of 800 s/mm2. Within the study period, the hospital scanning protocols changed; DTI scans with both 32 diffusion-weighted images (single-shot echo-planar imaging, repetition time 6817 ms, echo time 97 ms, 50x2 mm slices,

field of view 190x190 mm, matrix 128x128) and with 45 diffusion-weighted images (single-shot spin-echo echo-planar imaging sequence, repetition time 6500ms, echo-time 80 ms, 45x2 mm slices, field of view 160x160 mm, matrix 80x80) were performed and used for this study. In the final analysis, FA, AD, RD, and MD were used to compare the groups.

Using the ExploreDTI toolbox (http://www.exploredti.com/) for Matlab (The MathWorks Inc., Natick, MA), scans were converted, corrected, and analyzed. Each scan was corrected for signal drift and subject motion. The DTI data were registered to the Oishi template with a rigid registration to correct for the different scan angulations of the subjects.[21] The DTI tensor was estimated using the previously described REKINDLE (robust extraction of kurtosis indices with linear estimation) approach.[22] DTI scans were then checked for quality using data quality summary and diffusion-weighted data were corrected for motion-induced outliers. Diffusion-weighted images with more than 10% outliers were removed, and if more than 10% of diffusion-weighted images had to be removed the DTI scan was excluded. Whole-brain tractography was performed with a seed point resolution of 1.5, seed fractional anisotropy threshold of 0.1, fiber length range of 30–500 mm, and angle threshold of 40°. Three fiber tracts were isolated; the CC and the bilateral CST. To isolate the fibers in the CC, AND-gates were manually drawn in the sagittal plane starting from the midsagittal line with two gates on either side. These gates define which fibers are included during tractography. For the CST, two gates were drawn in the axial plane: one in the anterior part of the middle cerebral peduncle where descending corticospinal and ascending sensorimotor fibers are separated from other descending fibers by the pontine crossing fibers, and one at the level where the CST and anterior limb of the internal capsule form the most well-defined angle as described previously.[23] The left and right gates were placed on the same slide. Tracts that passed through both gates were selected for further analysis. In some cases, the selected tracts showed an abnormal course, e.g., crossing at the pontine level and returning to the contralateral motor cortex. We therefore only used the part of the tract between the two AND-gates for further analysis. This was done for both the CST and the CC. In a study of adult stroke patients, this approach was found to be more sensitive for differences between both CST and was found to have high inter-rater reliability (>90%).[24] We, therefore, did not study an inter or intra-rater reliability.

Neurodevelopmental assessment

Participants' neurodevelopmental outcomes were assessed longitudinally as part of the standard neurodevelopmental follow-up program. Developmental assessments were performed by experienced developmental specialists (pediatric physiotherapist or pediatric psychologist) using the Bayley Scales of Infant and Toddler Development, Third Edition (BSITD-III), or Griffiths Mental Development Scales (GMDS). The composite

cognitive and motor scores at 24-months-corrected age were categorized as the normal range (mean ± 1 standard deviation [SD]), subclinical range (<–1 SD), and clinical range (<–2 SD). Developmental Z-scores were calculated for cognitive and motor scores for each infant to compare different test types. Cerebral palsy (CP) and, if applicable, its type was defined based on the definition by Rosenbaum et al.[25] The gross motor function classification system (GMFCS levels I–V) was used to grade the severity of CP.[26] The presence of post-neonatal epilepsy requiring antiseizure medication was retrieved from the infants' files.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics, version 27 (IBM Corp., Armonk, N.Y.). Continuous variables were presented as mean (±SD) and median (interquartile range [IQR]) depending on their distribution. Categorical values were presented as number and percentage. The chi-squared and Fisher's exact tests were used to compare categorical variables among groups. Mann–Whitney U test was used to compare nonparametric variables and Student t-test for comparison between variables with normal distribution. In infants with PHVD, subgroup analysis was done for infants with and without PVHI. The Kruskal–Wallis test and one-way analysis of variance (ANOVA) test were used to determine the difference in subgroup analysis. A post-hoc analysis was performed to determine the statistical differences in multi-group comparisons. Univariable linear regression included the entire cohort of 42 infants and this was used to determine risk factors for an adverse neurodevelopmental outcome. The sample size precluded multivariable regression analysis. Statistical significance was set at $p < 0.05$.

Results

Twenty-one infants with PHVD and 21 matched-controls were included in the analysis. The mean (±SD) gestational age was 26.5 ± 0.9 weeks for both groups. Birth weight was similar across the groups (960 ± 154 g vs 892 ± 180 g in infants with and without PHVD, respectively; $p = 0.2$). More infants required invasive mechanical ventilation in the PHVD group (63% vs 30%; $p = 0.04$). In infants with PHVD, 10 (48%) also had a unilateral PVHI. Of the 21 infants with PHVD, 3 (14%) infants did not require intervention for PHVD; in these infants, PHVD resolved spontaneously under watchful monitoring. Eighteen (86%) infants required interventions, starting with lumbar punctures (LP). Out of these 18, fourteen (67%) underwent an early intervention and received LPs before the VI crossed the P97 + 4mm line on cUS scans. Fifteen infants (71%) received a reservoir insertion following the LPs and eight (38%) required a ventriculo-peritoneal shunt for

permanent CSF diversion. Clinical characteristics of included infants and distribution of the comorbidities are presented in Table 1.

Table 1: Demographic and clinical characteristics of the study population.

	Infants with PHVD (n=21)	Control Group (n=21)	p
Gestational age, weeks	26.5 ± 0.9	26.5 ± 0.9	0.9
Birth weight, g	960 ± 154	892 ± 180	0.2
Sex			
Male	12 (57)	12 (57)	1.0
Female	9 (43)	9 (43)	
Accompanying PVHI	10 (48)	-	
Lumbar punctures	18 (86)	-	
Reservoir placement	15 (71)	-	
Ventriculo-peritoneal shunt placement	8 (38)	-	
Early Intervention[†]	14 (78)	-	
Postnatal corticosteroids	4 (19)	5 (25)	0.6
Invasive mechanical ventilation	12 (63)	6 (30)	**0.04**
Culture positive late onset sepsis	4 (19)	4 (19)	1
Surgical treatment for NEC or PDA	4 (19)	4 (19)	1
LASER treatment for ROP	1 (5)	0 (0)	0.3

[†]Number in parenthesis reflects the percentage of infants who underwent interventions (n=18)
Data are presented as mean ± standard deviation (SD) or number (%)

DTI Characteristics

There was a narrow range for performing the TEA-MRI and the mean ± SD postmenstrual age at the time of TEA-MRI was similar across the groups (38.8 ± 0.56 weeks and 38.8 ± 0.57 weeks in infants with PHVD and control infants, respectively; p = 0.8). The number of infants scanned with the updated protocol was the same across the groups (n = 12/21, 57% for both). In the PHVD group, 4 infants had diffusion-weighted scans with more than >10% motion-induced outliers. In these infants, a total of 10 DWI scans were removed. In the control group, 3 infants had scans with more >10% motion-induced outliers, resulting in the removal of 7 scans. FA values in the CC were lower in infants with PHVD compared with controls (mean difference, 0.05 [95% confidence interval (CI), 0.02–0.08], p < 0.001). In infants with PHVD accompanied by PVHI, FA values in the CC were lower than in controls (mean difference, 0.05 [95% CI, 0.02–0.09], p = 0.005). FA values in the CC were similar between infants with PHVD and infants with

PHVD accompanied by PVHI (p = 0.9). RD values in CC were higher in infants with PHVD compared with controls (mean difference, 91 x 10^{-6} mm^2/s [95% CI, 3 x 10^{-6} to 179 x 10^{-6}], p = 0.04). RD values in CC were also greater in infants with PHVD accompanied by PVHI than in controls (mean difference, 73 x 10^{-6} mm^2/s [95% CI, 2 x 10^{-6} –145 x 10^{-6}], p = 0.004). No significant differences were found in diffusivity and FA values in the CST between PHVD and control infants. In infants with PVHI, FA values of the CST ipsilateral to the PVHI showed a trend toward lower values when compared to those of controls (p = 0.09). Details of the DTI analysis for the CST and CC are presented in Tables 2 and 3.

Table 2: Diffusion tensor imaging parameters of the corticospinal tract and corpus callosum of the study infants.

	Infants with PHVD (n=21)	**Control Infants (n=21)**	**p**
Postmenstrual age at MRI, wk	38.8 ± 0.56	38.8 ± 0.57	0.8
DTI scan protocol			1
32-diffusion weighted images	9 (43)	9 (43)	
45-diffusion weighted images	12 (57)	12 (57)	
		0.35 ± 0.04	
Mean FA in CST	0.36 ± 0.07		0.9
FA ipsilateral to PVHI	0.32 ± 0.06		0.09
FA contralateral to PVHI	0.35 ± 0.06		0.9
		1632 ± 50 x 10^{-6}	
Mean AD in CST	1600 ± 79 x 10^{-6}		0.07
AD ipsilateral to PVHI	1596 ± 105 x 10^{-6}		0.2
AD contralateral to PVHI	1581 ± 112 x 10^{-6}		0.4
		1154 ± 53 x 10^{-6}	
Mean MD in CST	1144 ± 99 x 10^{-6}		0.4
MD ipsilateral to PVHI	1169 ± 110 x 10^{-6}		0.7
MD contralateral to PVHI	1135 ± 130 x 10^{-6}		0.6
		916 ± 68 x 10^{-6}	
Mean RD in CST	917 ± 116 x 10^{-6}		0.6
RD ipsilateral to PVHI	956 ± 122 x 10^{-6}		0.3
RD contralateral to PVHI	912 ± 144 x 10^{-6}		0.8

Table 2: *[Continued]*

	Infants with PHVD (n=21)	Control Infants (n=21)	p
		0.32 ± 0.04	
FA in corpus callosum	0.27 ± 0.05		**<0.001**
FA in infants with PVHI	0.25 ± 0.05		**0.005**
		2037 ± 74 x 10^{-6}	
AD in corpus callosum	2012 ± 98 x 10^{-6}		**0.03**
AD in infants with PVHI	1984 ± 84 x 10^{-6}		0.2
		1495 ± 79 x 10^{-6}	
MD in corpus callosum	1535 ± 96 x 10^{-6}		0.3
MD in infants with PVHI	1571 ± 86 x 10^{-6}		0.2
		1224 ± 95 x 10^{-6}	
RD in corpus callosum	1311 ± 119 x 10^{-6}		**0.04**
RD in infants with PVHI	1350 ± 113 x 10^{-6}		**0.004**

Data are presented as mean ± standard deviation (SD) or number (%)
Infants with PHVD are compared with control infants
Units for AD, MD, and RD are presented as mm^2/sec

Table 3: Post-hoc analysis of the diffusion tensor imaging parameters of the corticospinal tract and corpus callosum.

	PHVD + PVHI (n=10)	PHVD Only (n=11)	Control Infants (n=21)	p
Mean FA in corticospinal tract	0.33 ± 0.05	0.36 ± 0.06	0.36 ± 0.04	
PHVD+PVHI vs PHVD only				0.3
PHVD only vs Controls				0.6
PHVD+PVHI vs Controls				0.6
Mean AD in corticospinal tract	1589 ± 102 x 10^{-6}	1609 ± 59 x 10^{-6}	1632 ± 51 x 10^{-6}	
PHVD+PVHI vs PHVD only				0.9
PHVD only vs Controls				0.2
PHVD+PVHI vs Controls				0.4
Mean MD in corticospinal tract	1152 ± 119 x 10^{-6}	1138 ± 88 x 10^{-6}	1154 ± 54 x 10^{-6}	
PHVD+PVHI vs PHVD only				0.6
PHVD only vs Controls				0.4
PHVD+PVHI vs Controls				0.9

Table 3: *[Continued]*

	PHVD + PVHI (n=10)	PHVD Only (n=11)	Control Infants (n=21)	p
Mean RD in corticospinal tract	934 ± 131 x 10^{-6}	903 ± 107 x 10^{-6}	916 ± 69 x 10^{-6}	
PHVD+PVHI vs PHVD only				0.4
PHVD only vs Controls				0.5
PHVD+PVHI vs Controls				0.9
Mean FA in corpus callosum	0.25 ± 0.05	0.27 ± 0.04	0.32 ± 0.04	
PHVD+PVHI vs PHVD only				0.9
PHVD only vs Controls				**0.03**
PHVD+PVHI vs Controls				**0.01**
Mean AD in corpus callosum	2012 ± 99 x 10^{-6}	1961 ± 67 x 10^{-6}	2037 ± 74 x 10^{-6}	
PHVD+PVHI vs PHVD only				0.7
PHVD only vs Controls				0.06
PHVD+PVHI vs Controls				0.3
Mean MD in corpus callosum	1571 ± 86 x 10^{-6}	1507 ± 99 x 10^{-6}	1495 ± 79 x 10^{-6}	
PHVD+PVHI vs PHVD only				0.7
PHVD only vs Controls				0.9
PHVD+PVHI vs Controls				0.4
Mean RD in corpus callosum	1350 ± 114 x 10^{-6}	1280 ± 120 x 10^{-6}	1224 ± 95 x 10^{-6}	
PHVD+PVHI vs PHVD only				0.7
PHVD only vs Controls				0.4
PHVD+PVHI vs Controls				0.1

Data are presented as mean ± standard deviation
Units for AD, MD, and RD are presented as mm^2/sec

Neurodevelopmental outcomes

All 42 infants were included in the outcome analysis. Of the infants with PHVD, 4 (19%) were assessed with GMDS and 17 (81%) with BSITD-III, while 5 infants (24%) were assessed with GMDS and 16 (76%) with BSITD-III in the control group (p = 0.7). The mean ± SD composite cognitive score was 92 ± 14 in infants with PHVD, and 102 ± 13 in the control group (p = 0.02); the composite motor score was 90 ± 13 and 105 ± 14, respectively (p < 0.001). Cognitive and motor Z-scores were greater in infants without PHVD (mean difference, 0.72 [95% CI, 0.12–1.3] and 1.1 [95% CI, 0.5–1.72]; p = 0.02 and <0.001, respectively) when compared with infants with PHVD. Details of the neurodevelopmental outcomes in the subgroup analyses are presented in Table 4.

In infants with PVHI, the mean ± SD FA values of the ipsilateral and contralateral CST were 0.32 ± 0.06 and 0.35 ± 0.06, respectively. Four (40%) infants with PVHI developed CP. In the univariate analysis, the FA value of the CC was associated with composite cognitive score (coefficient 114; 95% CI, 28–200; p = 0.01) and composite motor score (coefficient 147; 95% CI, 52–243; p = 0.004). The limited sample size (n = 42) precluded further multivariable regression analysis. The composite cognitive and motor outcome scores in relation to the FA values of the CC are presented in Fig. 1.

Table 4: Subgroup analysis of the neurodevelopmental outcomes of the study infants.

	PHVD + PVHI (n=10)	**PHVD Only (n=11)**	**Control Infants (n=21)**	**p**
Corrected age at assessment, months	24.3 (23.8-25.1)	24.1 (23.8-24.3)	24.3 (24.1-25.1)	0.3
Composite cognitive score	83 ± 12	102 ± 8	102 ± 13	
PHVD+PVHI vs PHVD only				**0.008**
PHVD only vs Controls				0.9
PHVD+PVHI vs Controls				**<0.001**
Composite motor score	81 ± 10	98 ± 11	105 ± 14	
PHVD+PVHI vs PHVD only				**0.009**
PHVD only vs Controls				0.3
PHVD+PVHI vs Controls				**<0.001**
Cognitive Z-score	-1.3 ± 0.9	0.1 ± 0.5	0.1 ± 0.9	
PHVD+PVHI vs PHVD only				**0.004**
PHVD only vs Controls				0.9
PHVD+PVHI vs Controls				**<0.001**
Motor Z-score	-1.4 ± 0.8	-0.1 ± 0.7	0.3 ± 0.9	
PHVD+PVHI vs PHVD only				**0.006**
PHVD only vs Controls				0.4
PHVD+PVHI vs Controls				**<0.001**
Cognitive score category				**0.04**
Normal range	5 (50%)	10 (91%)	19 (91%)	
Subclinical range	4 (40%)	1 (9%)	2 (9%)	
Clinical range	1 (10%)	0 (0%)	0 (0%)	

Table 4: *[Continued]*

	PHVD + PVHI (n=10)	PHVD Only (n=11)	Control Infants (n=21)	p
Motor score category[†]				**0.015**
Normal range	4 (40%)	8 (80%)	18 (90%)	
Subclinical range	5 (50%)	2 (20%)	2 (9%)	
Clinical range	1 (10%)	0 (0%)	0 (0%)	
Cerebral palsy	4 (40%)	2 (18%)	0 (0%)	**0.007**
Post-neonatal epilepsy	1 (10%)	2 (18%)	0 (0%)	0.12

Data are presented as median (interquartile range, IQR), mean ± standard deviation (SD) or number (%)

[†]Motor scores were available in 10/11 of infants with PHVD without PVHI and 20/21 of the control group

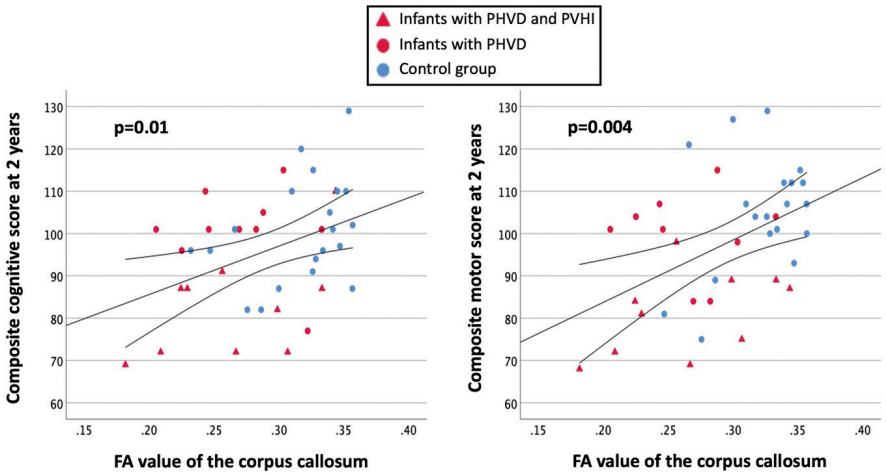


Figure 1: Association between the corpus callosum FA and cognitive scores. Scatter plots of fractional anisotropy values of the corpus callosum and composite cognitive and motor scores at 2-years-corrected age show the association between lower FA values in infants with PHVD and lower neurodevelopmental outcome scores at 2-years-corrected age.

Discussion

In this single-center retrospective case-control study, we assessed the effects of PHVD on microstructural white matter microstructure with a specific focus on CC and CST in a cohort of EP infants. In keeping with our hypothesis, we found lower FA and higher RD values in CC in infants with PHVD compared to that of controls, reflecting impaired microstructure of these commissural nerve fibers located near the dilated ventricles.

Infants with PHVD who also had PVHI, showed lower FA and higher RD values in CC compared to those of controls, although not different from those with PHVD only. Contrary to our hypothesis, we did not find altered diffusivity or FA values in CST in infants with PHVD; however, in infants with PVHI, ipsilateral FA values of CST showed a trend towards decrease reflecting the possible impact of parenchymal injury affecting the maturational processes in these white matter tracts. As expected, cognitive and motor scores were less favorable in infants with PHVD and FA values of the CC were associated with both cognitive and motor scores. To the best of our knowledge, this is the first report of impaired white matter microstructure demonstrated by DTI in an exclusive cohort of EP infants with PHVD.

DTI is the most widely used diffusion-weighted analysis approach in the developing brain, which has proven to be useful for assessing maturational characteristics.[13] Prior work has shown that DTI is sensitive to the underlying microstructural neuroanatomical abnormalities in white matter associated with common forms of preterm brain injury.[12,14,15,27] The developing preterm brain demonstrates a predictable pattern of DTI changes with decreasing MD and RD, and increasing FA values in the cerebral white matter.[12,27,28] The increase in FA starts while the white matter structures are still at the pre-myelinating stage due to the escalation in axonal membrane maturation and change in axon caliber.[13,29,30] At this early stage, the highest FA values are seen in the unmyelinated but well-organized commissural fibers of the CC.[13] We focused on this stage of white matter maturation in our EP cohort and the impaired FA values in CC in the present study likely reflect the impact of injury in the context of PHVD. This observation is in line with previous observations of Lean et al.[15] who showed altered DTI parameters in white matter regions anatomically close to the ventricles in very preterm infants.

The CST myelinates histologically between 32 and 35 weeks of gestation and this myelination is first seen on MRI of a very preterm infant in the posterior limb of the internal capsule from 36 to 38 weeks.[31] The late stage of the increase in FA values in the developing white matter is closely related to the emergence of myelin, thus the initial signs are observed in the projection fibers of the CST around term.[32] The lower FA in the CST in preterm infants with brain injury has been hypothesized to be indicative of fewer axons and less restricted water diffusion caused by impaired myelination alongside a propensity towards lower FA values due to immaturity.[33] Lower FA values in CST in infants with PHVD compared to control infants in these studies may be due to local compression and impaired reabsorption of CSF, negatively affecting the DTI values due to proximity of this particular ROI to the enlarged ventricles. The CST has also been shown to be susceptible to inflammation, axonal injury leading to disturbances in myelin sheath development, and deformation caused by ipsilateral PVHI.[15,23] The axonal injury following PVHI, so-called pre-Wallerian degeneration, begins within a week of

the injury and progresses through several pathophysiologically distinct stages over the next weeks to evolve into Wallerian degeneration.[34] Changes in water diffusion during the evolution of pre-Wallerian degeneration can be visualized early with DTI.[23] We were unable to show impaired DTI values in CST in infants with isolated PHVD, which might be reflecting the protective effect of early intervention for PHVD in the majority of the infants studied. In a previous randomized controlled study, we found that almost twice as many infants undergoing high-threshold intervention (52% vs 27%) showed significant myelination delay in CST assessed with the Kidokoro score at TEA.[35] This previous observation is in keeping with our current finding suggesting that timely interventions may prevent vulnerable regions of the developing brain from disturbances caused by PHVD. Avoidance of mechanical injury to the periventricular white matter with preservation of cerebral perfusion, and removal of inflammatory and neurotoxic substances from the CSF are among the several hypotheses why an earlier intervention may result in more favorable neurodevelopmental outcomes.[36] We also observed a trend toward a decrease in ipsilateral FA values of CST in infants with PVHI; however, the limited number of infants in the present study, might have prevented this trend from reaching statistical significance. It is important to note that the small sample size might have also masked the DTI changes in CST in infants with isolated PHVD.

Microstructural white matter changes may explain the increased risk of adverse neurodevelopmental outcomes seen in preterm infants with brain injury.[14] Roze et al.[23] demonstrated that early neonatal DTI obtained within 4 weeks after birth is predictive of abnormal motor outcome in preterm infants with PVHI. By using an atlas-based approach, they showed that all infants with unilateral spastic CP had an FA asymmetry index of >0.05, which is the optimal cut-off value on early DTI. They suggested that early DTI could be used to predict a motor outcome, but the assessment of myelination at TEA may still be required.[23] In another study using DTI, Lean et al.[15] focused on white matter microstructure following different types of brain injury in very preterm infants and suggested that lower FA and higher MD values in CC were associated with increased risk for motor impairments at 2 years. More recently, Obeid et al.[37] showed that in infants with high-grade GMH-IVH, increased frontal and temporal horn ratio correlated with lower FA in various white matter regions and higher GMFCS levels of CP. Similar impairments in cognitive and language development and executive functioning were also reported by others following microstructural changes in CC as reflected by altered diffusivity at TEA.[38,39] Our findings on cognitive and motor outcomes are in agreement with these previous observations, as we found a positive correlation between the FA value of the CC and composite cognitive and motor scores in the univariate analysis; however, the limited sample size precluded further multivariable regression in our model. Also in keeping with the recent literature, infants with PVHI had lower cognitive and motor scores compared to infants with isolated PHVD and controls.[40]

The present study has several limitations. First, the sample size was small, which limited the statistical analyses and precluded controlling for multiple factors in the regression model, including sex, age at MRI, and DTI sequence. However, infants were matched for gestational age and sex, and therefore it is unlikely that these factors have affected our results. Second, we were not able to take into account the different parts of the CC, but analyzed the DTI parameters of the CC as a single unit, thus we were unable to quantify the effect of injury on the genu, corpus, and splenium of the CC separately. Third, although the number of infants scanned with two different DTI protocols is the same across the groups, the study infants were not further matched for different DTI protocols. This may have caused variations in measured DTI parameters due to differences in image acquisition technique. Fourth, as reported by others, DTI fails to represent appropriately the tissue microstructure in the presence of crossing fibers, and in a restricted environment, diffusion of water molecules is no longer Gaussian and the tensor model deviates from the signal.[13] Fifth, infants with PHVD were included in the present study if they had progressive measurements of the VI and AHW; however, thalamo-occipital distance could not be taken into account as this measurement was not available for all infants. The strength of this study is the selective recruitment of EP infants with GMH-IVH who developed PHVD while excluding infants with cerebellar injury, as this type of brain injury may also cause neurodevelopmental impairments in multiple domains.

In conclusion, in this case-control study, focusing on EP infants with PHVD, we showed lower FA values in the CC, reflecting the impaired microstructure of these commissural nerve fibers that are close to the dilated ventricles. We also found a positive correlation between FA values of the CC and composite cognitive and motor scores at 2-years-corrected age. Innovations in diffusion-weighted image acquisition are likely to enable neonatal white matter microstructure to be assessed in detail in the future.[13] Further studies on a larger group of preterm infants with PHVD are needed to assess the effects of PHVD on white matter microstructure. These studies are warranted to further elucidate the effects of this common type of brain injury on fiber organization in different white matter tracts.

References

1. Ballabh, P. & de Vries, L. S. White matter injury in infants with intraventricular haemorrhage: mechanisms and therapies. Nat. Rev. Neurol. 17, 199–214 (2021).
2. Yeo, K. T. et al. Improving incidence trends of severe intraventricular haemorrhages in preterm infants <32 weeks gestation: a cohort study. Arch. Dis. Child. Fetal Neonatal Ed. 105, 145–150 (2020).
3. El-Dib, M. et al. Management of post-hemorrhagic ventricular dilatation in the infant born preterm. J. Pediatr. https://doi.org/10.1016/j.jpeds.2020.07.079 (2020).
4. Strahle, J. M. et al. Role of hemoglobin and iron in hydrocephalus after neonatal intraventricular hemorrhage. Neurosurgery 75, 696–705 (2014).
5. Guo, J. et al. Minocycline-induced attenuation of iron overload and brain injury after experimental germinal matrix hemorrhage. Brain. Res. 1594, 115–124 (2015).
6. Del Bigio, M. R. Cellular damage and prevention in childhood hydrocephalus. Brain. Pathol. 14, 317–324 (2004).
7. Ulfig, N., Bohl, J., Neudorfer, F. & Rezaie, P. Brain macrophages and microglia in human fetal hydrocephalus. Brain. Dev. 26, 307–315 (2004).
8. Brouwer, M. J. et al. Effects of posthemorrhagic ventricular dilatation in the preterm infant on brain volumes and white matter diffusion variables at term-equivalent age. J. Pediatr. 168, 41–49 (2016).
9. Lockwood Estrin, G. et al. Altered white matter and cortical structure in neonates with antenatally diagnosed isolated ventriculomegaly. Neuroimage. Clin. 11, 139–148 (2016).
10. Ou, X. et al. Impaired white matter development in extremely low-birth-weight infants with previous brain hemorrhage. Am. J. Neuroradiol. 35, 1983–1989 (2014).
11. Kanel, D., Counsell, S. J. & Nosarti, C. Advances in functional and diffusion neuroimaging research into the long-term consequences of very preterm birth. J. Perinatol. 41, 689–706 (2021).
12. Miller, S. P. et al. Serial quantitative diffusion tensor MRI of the premature brain: development in newborns with and without injury. J. Magn. Reson. Imaging 16, 621–632 (2002).
13. Pecheva, D. et al. Recent advances in diffusion neuroimaging: applications in the developing preterm brain. F1000Res 7, 1326 (2018).
14. Dibble, M., Ang, J. Z., Mariga, L., Molloy, E. J. & Bokde, A. L. W. Diffusion tensor imaging in very preterm, moderate-late preterm and term-born neonates: a systematic review. J. Pediatr. 232, 48–58 (2021).
15. Lean, R. E. et al. Altered neonatal white and gray matter microstructure is associated with neurodevelopmental impairments in very preterm infants with high grade brain injury. Pediatr. Res. 86, 365–374 (2019).
16. Morales, D. M. et al. Tract-specific relationships between cerebrospinal fluid biomarkers and periventricular white matter in posthemorrhagic hydrocephalus of prematurity. Neurosurgery 88, 698–706 (2021).
17. Levene, M. I. Measurement of the growth of the lateral ventricles in preterm infants with real-time ultrasound. Arch. Dis. Child. 56, 900–904 (1981).
18. Davies, M. W., Swaminathan, M., Chuang, S. L. & Betheras, F. R. Reference ranges for the linear dimensions of the intracranial ventricles in preterm neonates. Arch. Dis. Child. Fetal Neonatal Ed. 82, 218–223 (2000).
19. de Vries, L. S. et al. Treatment thresholds for intervention in posthaemorrhagic ventricular dilation: a randomised controlled trial. Arch. Dis. Child. Fetal Neonatal Ed. 104, 70–75 (2019).
20. Volpe, J. J. Intraventricular hemorrhage in the premature infant-current concepts. Part II. Ann. Neurol. 25, 109–116 (1989).

21. Deshpande, R., Chang, L. & Oishi, K. Construction and application of human neonatal DTI atlases. Front. Neuroanat. 9, 138 (2015).
22. Tax, C. M., Otte, W. M., Viergever, M. A., Dijkhuizen, R. M. & Leemans, A. REKINDLE: robust extraction of kurtosis INDices with linear estimation. Magn. Reson. Med. 73, 794–808 (2015).
23. Roze, E. et al. Neonatal DTI early after birth predicts motor outcome in preterm infants with periventricular hemorrhagic infarction. Pediatr. Res. 78, 298–303 (2015).
24. Feldman, S. J., Boyd, L. A., Neva, J. L., Peters, S. & Hayward, K. S. Extraction of corticospinal tract microstructural properties in chronic stroke. J. Neurosci. Methods 301, 34–42 (2018).
25. Rosenbaum, P. et al. A report: the definition and classification of cerebral palsy April 2006. Dev. Med. Child. Neurol. Suppl. 109, 8–14 (2007).
26. Palisano, R. J. et al. Validation of a model of gross motor function for children with cerebral palsy. Phys. Ther. 80, 974–985 (2000).
27. de Bruine, F. T. et al. Tractography of developing white matter of the internal capsule and corpus callosum in very preterm infants. Eur. Radiol. 21, 538–547 (2011).
28. Kersbergen, K. J. et al. Microstructural brain development between 30 and 40 weeks corrected age in a longitudinal cohort of extremely preterm infants. Neuroimage 103, 214–224 (2014).
29. Wimberger, D. M. et al. Identification of “premyelination” by diffusion-weighted MRI. J. Comput. Assist. Tomogr. 19, 28–33 (1995).
30. Huppi, P. S. et al. Quantitative magnetic resonance imaging of brain development in premature and mature newborns. Ann. Neurol. 43, 224–235 (1998).
31. Cowan, F. M. & de Vries, L. S. The internal capsule in neonatal imaging. Semin. Fetal Neonatal Med. 10, 461–474 (2005).
32. Brody, B. A., Kinney, H. C., Kloman, A. S. & Gilles, F. H. Sequence of central nervous system myelination in human infancy. I. An autopsy study of myelination. J. Neuropathol. Exp. Neurol. 46, 283–301 (1987).
33. Rose, S. E. et al. Altered white matter diffusion anisotropy in normal and preterm infants at term-equivalent age. Magn. Reson. Med. 60, 761–767 (2008).
34. Aldskogius, H. & Kozlova, E. N. Central neuron-glial and glial-glial interactions following axon injury. Prog. Neurobiol. 55, 1–26 (1998).
35. Cizmeci, M. N. et al. Assessment of brain injury and brain volumes after posthemorrhagic ventricular dilatation: a nested substudy of the randomized controlled ELVIS trial. J. Pediatr. 208, 191–197 (2019).
36. Cizmeci, M. N., Groenendaal, F. & de Vries, L. S. Timing of intervention for posthemorrhagic ventricular dilatation: an ongoing debate. J. Pediatr. 234, 14–16 (2021).
37. Obeid, R. et al. The utility of the fronto-temporal horn ratio on cranial ultrasound in premature newborns: a ventriculomegaly marker. Pediatr. Res. 89, 1715–1723 (2021).
38. Thompson, D. K. et al. Regional white matter microstructure in very preterm infants: predictors and 7 year outcomes. Cortex 52, 60–74 (2014).
39. Thompson, D. K. et al. Corpus callosum alterations in very preterm infants: perinatal correlates and 2 year neurodevelopmental outcomes. Neuroimage 59, 3571–3581 (2012).
40. Cizmeci, M. N. et al. Randomized controlled early versus late ventricular intervention study in posthemorrhagic ventricular dilatation: outcome at 2 years. J. Pediatr. 1, S0022–S3476 (2020).

Part II

Neurosurgical Interventions for Hemorrhagic Brain Injury and Related Complications

“My moral heritage is science and reason”

Mustafa Kemal Atatürk

6

Intraparenchymal hemorrhage after serial ventricular reservoir taps in neonates with hydrocephalus and association with neurodevelopmental outcome at 2 years of age

Mehmet N. Cizmeci, Linda S. de Vries, Maria Luisa Tataranno, Alexandra Zecic, Laura A. van de Pol, Ana Alarcon, Floris Groenendaal, Peter A. Woerdeman

J Neurosurg Pediatr. 2021 Sep 17:1-8 DOI: 10.3171/2021.6.PEDS21120

Abstract

Objective: Decompressing the ventricles with a temporary device is often the initial neurosurgical intervention for preterm infants with hydrocephalus. The authors observed a subgroup of infants who developed intraparenchymal hemorrhage (IPH) after serial ventricular reservoir taps and sought to describe the characteristics of IPH and its association with neurodevelopmental outcome.

Methods: In this multicenter, case-control study, for each neonate with periventricular and/or subcortical IPH, a gestational age-matched control with reservoir who did not develop IPH was selected. Digital cranial ultrasound (cUS) scans and term-equivalent age MRI (TEA-MRI) studies were assessed. Ventricular measurements were recorded prior to and 3 days and 7 days after reservoir insertion. Changes in ventricular volumes were calculated. Neurodevelopmental outcome was assessed at 2 years corrected age using standardized tests.

Results: Eighteen infants with IPH (mean gestational age 30.0 ± 4.3 weeks) and 18 matched controls were included. Reduction of the ventricular volumes relative to occipitofrontal head circumference after 7 days of reservoir taps was greater in infants with IPH (mean difference −0.19 [95% CI −0.37 to −0.004], p = 0.04). Cognitive and motor Z-scores were similar in infants with and those without IPH (mean difference 0.42 [95% CI −0.17 to 1.01] and 0.58 [95% CI −0.03 to 1.2]; p = 0.2 and 0.06, respectively). Multifocal IPH was negatively associated with cognitive score (coefficient −0.51 [95% CI −0.88 to −0.14], p = 0.009) and ventriculoperitoneal shunt with motor score (coefficient −0.50 [95% CI −1.6 to −0.14], p = 0.02) after adjusting for age at the time of assessment.

Conclusion: This study reports for the first time that IPH can occur after a rapid reduction of the ventricular volume during the first week after the initiation of serial reservoir taps in neonates with hydrocephalus. Further studies on the use of cUS to guide the amount of cerebrospinal fluid removal are warranted.

Introduction

Neonatal hydrocephalus is a common neurological condition and a major risk factor for neurodevelopmental disabilities in both preterm and term infants.[1,2] The most common cause of hydrocephalus in the neonatal population is germinal matrix hemorrhage–intraventricular hemorrhage (GMH-IVH) resulting in posthemorrhagic ventricular dilatation (PHVD), but it can also occur due to obstruction of CSF pathways by genetic, developmental, and acquired conditions.[1,3,4] When impairments in CSF circulation lead to ventricular dilatation, the developing brain may be negatively affected, especially due to ventricular distension that compresses periventricular brain parenchyma, but also due to the presence of blood products and cytokines.[5] Thus, the mainstay of management is alleviation of increased CSF volume with interventions.[1,6]

Due to the small size and clinical instability of preterm infants, high CSF concentrations of protein and blood products, and the unsuitability of the preterm abdomen for a shunt system, decompressing the ventricles with a temporary device is often the first neurosurgical intervention.[6] For this purpose, numerous temporary CSF diversion techniques are available for neonates, including external ventricular drainage, a ventricular access device, and a ventriculosubgaleal shunt.[6] Placement of a reservoir as a ventricular access device with an aim to serially aspirate CSF is a widely used technique.[1] However, complications related to this technique other than infection and mechanical obstruction are not well studied, and, to date, no observational study has been conducted to describe the characteristics of intraparenchymal hemorrhages (IPHs) after serial ventricular reservoir taps, which have been reported after insertion of a ventriculoperitoneal shunt (VPS).[7,8] We hypothesized that rapid reduction of ventricular volumes with serial reservoir taps might result in IPH and sought to assess the neuroimaging features of this condition, while also studying its relation to neurodevelopmental outcomes at 2 years.

Methods

In this multicenter, case-control study, preterm and term neonates were eligible if they had a unifocal or multifocal IPH after serial ventricular reservoir taps and were admitted to one of 4 tertiary neonatal intensive care units (Wilhelmina Children's Hospital, University Medical Center Utrecht [UMCU], Utrecht, the Netherlands; Ghent University Hospital, Ghent, Belgium; Emma Children's Hospital, Amsterdam University Medical Centers, Amsterdam, the Netherlands; and Hospital Sant Joan de Déu, Barcelona, Spain) between January 2000 and June 2020. In the participating centers, neurosurgical interventions were initiated with the placement of a ventricular reservoir regardless of the etiology of hydrocephalus as the standard approach with an aim to gradually reduce

the ventricular size and avoid VPS placement when the CSF still contained blood clots. A database search of neonatal cranial ultrasound (cUS) scans and brain MRI of eligible infants was conducted. For each neonate with IPH, a matched control with reservoir and a gestational age of ± 7 days who did not develop IPH was found for the control group.

Demographic data were obtained from the patients' files and/or electronic hospital database. Data on antenatal and perinatal factors, including gestational age, birth weight, sex, and hemorrhage severity; comorbidities, including the use of postnatal steroids, prolonged mechanical ventilation for > 7 days, sepsis, necrotizing enterocolitis, patent ductus arteriosus, and retinopathy of prematurity; and VPS status were collected. Approval from the research ethics board at each center and signed parental informed consent for inclusion in the study were obtained.

Neuroimaging Protocol and Assessment

Participating centers followed a predefined MRI protocol according to their institutional guidelines and obtained conventional axial T1-weighted and T2-weighted images. MR images were acquired for all infants around term-equivalent age (TEA) with a 3T MR magnet at two centers and a 1.5T MR magnet in the other two. Cranial US was performed in accordance with the local cUS protocols, which remained constant throughout the study period. Cranial US was performed through the anterior fontanel, and 6 coronal and 5 sagittal planes were assessed. All cUS and MR scans obtained in included infants were assessed by an investigator (M.N.C.) with formal training in neuroimaging, who was blinded to the infants' clinical history and neuroimaging findings. In equivocal cases, a senior investigator (L.S.d.V.) with >30 years of experience in neonatal neuroimaging was consulted. Assessments included grade of accompanying GMH-IVH as described by Volpe,[9] and timing, number, and location of the IPH. The distinction between periventricular hemorrhagic infarction (PVHI) and periventricular IPH was made based on the anatomical location and relation with GMH-IVH. IPH was categorized as periventricular, subcortical, or both based on its location on cUS and MRI. To assess the size of the lateral ventricles, objective measurements on both sides were used to include ventricular index (VI) as described by Levene[10] and anterior horn width (AHW) and thalamooccipital distance (TOD) as described by Davies et al.[11] The number of lumbar punctures and total amount of CSF removal after reservoir taps were recorded separately. Ventricular measurements were recorded prior to starting reservoir taps and 3 days and 7 days after reservoir taps in all infants. Ventricular volumes were calculated based on the VIs on cUS scans as described by Benavente-Fernandez et al.[12] Reduction in ventricular volumes was measured 3 and 7 days after taps from the reservoir. The reservoir tapping protocol was 10 ml/kg/day in 2 aliquots, aspirated at 1 ml/min. The tap was preceded by daily cUS measurement of the ventricular size in all centers. Change in the ventricular volumes was calculated and trended for the first 7 days of reservoir

taps. Relative ventricular volumes were calculated by dividing the ventricular volume by the occipitofrontal head circumference to the power of 3 that was obtained at the time of reservoir insertion.

Neurodevelopmental Assessment

Neurodevelopmental outcomes were assessed as part of the standard follow-up programs of the participating centers. Developmental assessments were performed by experienced developmental specialists (pediatric physiotherapist or pediatric psychologist) using the composite cognitive and motor scores from the Bayley Scales of Infant Development, Second Edition (BSID-II), Bayley Scales of Infant and Toddler Development, Third Edition (BSITD-III), or Griffiths Mental Development Scales (GMDS) based on the study year and routine practice of the center at 24 months corrected age. Cognitive and motor composite scores were corrected for prematurity. Developmental Z scores were calculated for cognitive and motor scores for each infant to compare different test types. Presence of cerebral palsy (CP) and, if applicable, topographical data were retrieved from the infants' files. The gross motor function classification system (GMFCS levels I–V) was used to grade the severity of CP.[13] Presence of postneonatal epilepsy requiring antiseizure medication was also retrieved from the patient charts.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 26 (IBM Corp.). Categorical variables are presented as number and percentage. The chi-square and Fisher's exact tests were used to compare categorical variables among groups. Continuous variables are presented as mean ± SD and median (IQR) depending on their distribution. The Mann-Whitney U-test was used to compare nonparametric variables and the Student t-test for comparison between variables with Gaussian distribution. Logarithmic transformation was performed for the ventricular volumes to yield variance homogeneity and normal distribution. Multiple linear regression was applied for the significant variables detected with the univariate analysis, and adjustment for gestational age and severity of GMH-IVH was performed in the multivariable regression models. Statistical significance was set at $p < 0.05$.

Results

Eighteen infants with IPH after serial taps from the ventricular reservoir and 18 matched controls without IPH were included in the final analysis. At UMCU where the majority (30/36, 83%) of the study infants were admitted, 13 infants were found to have IPH after reservoir taps of 174 infants with a reservoir who had a TEA-MRI, with an incidence of

7.4%. The mean ± SD gestational age (30 ± 4.3 vs 30.7 ± 3.5 weeks in infants with and those without IPH, respectively; p = 0.6) and birth weight (1541 ± 902 vs 1606 ± 593 g in infants with and those without IPH, respectively; p = 0.8) were similar between the groups. There was no difference in the number of infants who underwent lumbar punctures prior to reservoir insertion (n = 14 [78%] vs n = 17 [94%] in infants with and those without IPH, respectively; p = 0.2). The median age at ventricular reservoir insertion and corresponding postmenstrual ages were also similar between the groups (22 days [IQR 49 days] vs 17 days [IQR 19 days] and 34.9 weeks [IQR 4.4 weeks] vs 34.3 weeks [IQR 4.7 weeks], respectively; p = 0.4 for both). In 10 (56%) infants with IPH, the reservoir was placed when the VI was > 4 mm above the 97th percentile and the AHW was > 10 mm. In 7 (39%) infants without IPH, the reservoir was placed when the VI was > 4 mm above the 97th percentile and AHW was > 10 mm. Groups were similar with respect to the timing of interventions (p = 0.3). The percentages of VPS treatment of all infants with PHVD during the study period were 39% and 55% in infants with PHVD and congenital hydrocephalus, respectively (p = 0.2). There was no difference between the groups with respect to PVHI and coexisting comorbidities of prematurity. Clinical characteristics of included infants are presented in Table 1.

Table 1: Demographic and clinical characteristics of the study population.

	Infants with Intraparenchymal Hemorrhage (n=18)	**Infants without Intraparenchymal Hemorrhage (n=18)**	**p**
Gestational age, weeks	30 ± 4.3	30.7 ± 3.5	0.6[a]
Birth weight, g	1541 ± 902	1606 ± 593	0.8[a]
Postnatal age at reservoir insertion (days)	22 (12-61)	17 (12-31)	0.4[b]
Postmenstrual age at reservoir insertion (weeks)	34.9 (32.3 - 36.7)	34.3 (31.5 - 36.2)	0.4[b]
Sex			
Male	10 (56)	10 (56)	>0.99[c]
Female	8 (34)	8 (34)	
Etiology of hydrocephalus			
PHVD	15 (83)	17 (94)	0.3[c]
Congenital	3 (17)	1 (6)	
Accompanying PVHI	3 (17)	2 (11)	0.6[c]
Ventriculo-peritoneal shunt	15 (83)	11 (61)	0.1[c]
Postnatal steroids	7 (39)	9 (50)	0.5[c]
Mechanical ventilation >7 days	7 (39)	6 (33)	0.7[c]

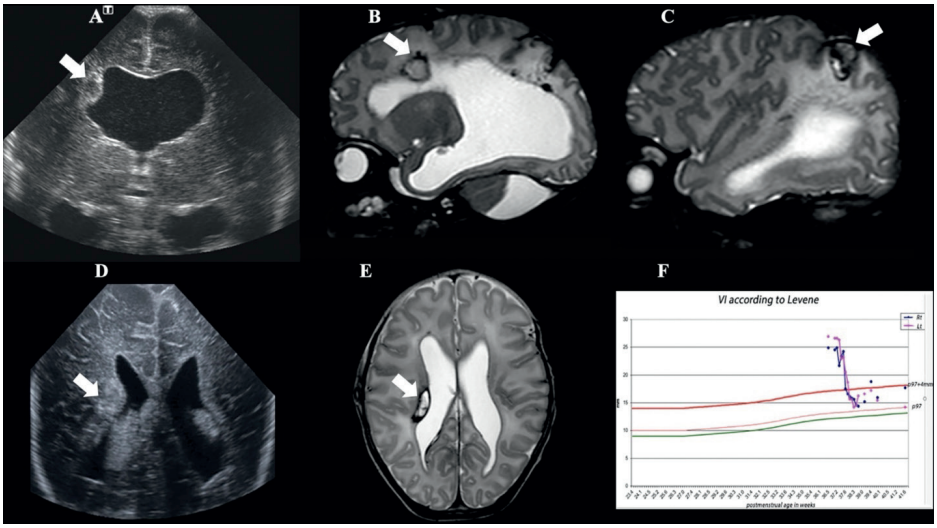
Table 1: *[Continued]*

	Infants with Intraparenchymal Hemorrhage (n=18)	Infants without Intraparenchymal Hemorrhage (n=18)	p
Late-onset neonatal sepsis	3 (17)	4 (22)	0.7[c]
Medically managed NEC	1 (6)	0 (0)	0.5[c]
Surgical treatment for NEC	0 (0)	2 (11)	0.1[c]
Surgical treatment for PDA	2 (11)	1 (6)	0.5[c]
Surgical treatment for ROP	3 (17)	0 (0)	0.07[c]

[a]t-test, [b]Mann-Whitney U test, [c]Chi Square test.
Data are presented as mean ± standard deviation (SD), median (interquartile range) or number (%)

Neuroimaging Characteristics of IPH

The median time to detection of IPH after initiating serial reservoir taps was 12 (IQR 21) days. In 13 (72%) infants, IPH was detected by cUS scans, and in the remaining 5 (28%) infants, IPH was not seen on cUS and but was detected by TEA-MRI. In 10 (56%) infants, IPH was multifocal, and in the other 8 (44%) infants, it was unifocal. Six (33%) infants had a periventricular IPH, 6 (33%) had subcortical, and 6 (33%) had both periventricular and subcortical hemorrhages (Fig. 1).



< Figure 1: Cranial ultrasound and MRI findings of two cases, with white arrows pointing to the lesions in each image. A–C: Images obtained in an infant with multifocal IPH after reservoir insertion. Coronal cUS scan demonstrating increased echogenicity consistent with IPH in the periventricular white matter of the right frontal lobe (A). Parasagittal T2-weighted image showing decreased signal intensity in the right frontal lobe adjacent to the frontal horn of the lateral ventricle (B) and in the subcortical brain parenchyma (C). D–F: Images obtained from an infant with periventricular IPH after reservoir insertion. Coronal cUS scan demonstrating increased echogenicity consistent with IPH in the periventricular white matter of the right parietal lobe (D). Axial T2-weighted image showing the same lesion as in panel D (E). Line graph demonstrating the rapid decrease in the VIs of the right and left lateral ventricles (F).

Ventricular measurement data were incomplete in 4 infants with IPH and could not be included in the analysis. Details of ventricular measurements and ventricular volumes are given in Table 2.

Table 2: Ventricular measurements and cerebrospinal fluid volumes of the study population.

	Infants with Intraparenchymal Hemorrhage (n=14)	**Infants without Intraparenchymal Hemorrhage (n=18)**	**p***
Prior to ventricular taps, mm			
Right VI	15 (14-20)	16 (15-18)	0.6
Left VI	17 (16-22)	16 (15-18)	0.1
Total VI	34 (30-41)	32 (30-36)	0.2
Right AHW	11 (9-16)	11 (9-13)	0.7
Left AHW	13 (9-21)	12 (10-14)	0.5
Total AHW	24 (19-36)	23 (21-27)	0.6
Right TOD	38 (28-42)	33 (27-35)	0.2
Left TOD	38 (30-40)	33 (29-39)	0.3
Total TOD	76 (58-81)	66 (58-72)	0.1
3 days after ventricular taps, mm			
Right VI	13 (11-16)	13 (12-16)	0.9
Left VI	14 (13-20)	14 (12-16)	0.5
Total VI	28 (24-37)	27 (24-33)	0.6
Right AHW	8 (6-13)	8 (7-9)	0.5
Left AHW	9 (8-17)	8 (6-10)	0.2
Total AHW	18 (13-30)	16 (14-19)	0.3
Right TOD	32 (30-41)	32 (23-35)	0.3

Table 2: *[Continued]*

	Infants with Intraparenchymal Hemorrhage (n=14)	Infants without Intraparenchymal Hemorrhage (n=18)	p*
Left TOD	34 (29-37)	33 (29-35)	0.6
Total TOD	65 (60-78)	63 (56-68)	0.3
7 days after ventricular taps, mm			
Right VI	12 (10-16)	13 (11-16)	0.9
Left VI	13 (11-20)	13 (12-16)	0.9
Total VI	23 (22-37)	26 (24-32)	0.9
Right AHW	8 (5-15)	7 (7-10)	0.9
Left AHW	7 (6-16)	8 (7-11)	0.8
Total AHW	14 (10-32)	16 (13-20)	0.9
Right TOD	29 (25-38)	31 (27-33)	0.8
Left TOD	31 (27-36)	33 (28-36)	0.5
Total TOD	60 (53-72)	65 (57-69)	0.9
Total CSF removal, ml/kg			
3 days after reservoir taps	36 (27-49)	28 (23-40)	0.1
7 days after reservoir taps	81 (70-121)	70 (64-87)	0.1
Maximum singe tap volume, ml/kg	17 (10-21)	18 (12-20)	0.8
Reduction in VI, mm			
3 days after reservoir taps	5 (4-7)	4 (1-6)	0.2
7 days after reservoir taps	9 (6-12)	6 (2-8)	**0.04**
Reduction in AHW, mm			
3 days after reservoir taps	7 (3-9)	7 (3-10)	0.9
7 days after reservoir taps	9 (5-19)	6 (2-11)	0.2
Reduction in TOD, mm			
3 days after reservoir taps	6 (1-14)	3 (-3-7)	0.3
7 days after reservoir taps	8 (4-22)	3 (-3-7)	**0.04**
Ventricular volumes, mm^3			
Prior to reservoir taps	50 (38-64)	47 (43-52)	0.4
3 days after reservoir taps	40 (32-56)	39 (32-44)	0.5
7 days after reservoir taps	32 (26-59)	35 (32-45)	0.8

*Mann-Whitney U test
Data are presented as median (interquartile range)

Reduction in the VI and TOD after 7 days of reservoir taps was significantly greater in infants with IPH (median 9 mm [IQR 6 mm] vs 6 mm [IQR 6 mm], p = 0.04 and 8 mm [IQR 18 mm] vs 3 mm [IQR 10 mm], p = 0.04, respectively). Reduction of the ventricular volumes relative to occipitofrontal head circumference after 7 days of reservoir taps was greater in infants with IPH (mean difference −0.19 [95% CI −0.37 to −0.004], p = 0.04).

Neurodevelopmental Outcomes

All infants survived the neonatal period. Two (11%) infants with IPH and 1 (6%) without IPH were < 2 years corrected age and could not be included in the outcome analysis. One (6%) infant without IPH due to missing outcome data and 2 (11%) with IPH due to very late reservoir insertion (postnatal days 74 and 77) were removed from the outcome analysis. Fifteen (50%) infants were assessed with GMDS and 15 (50%) with BSID-II/BSITD-III. The mean ± SD corrected age at the time of assessment was 21 ± 2.7 and 23 ± 4.8 months, in infants with and those without IPH, respectively (p = 0.2). The mean ± SD composite cognitive scores were 92 ± 13 in infants with IPH and 101 ± 12 in infants without IPH, and the composite motor scores were 92 ± 11 and 100 ± 11 (p = 0.1 and 0.06 for cognitive and motor scores, respectively). Cognitive and motor Z-scores were similar in infants with IPH and those without IPH (mean difference 0.42 [95% CI −0.17 to 1.01] and 0.58 [95% CI −0.03 to 1.2], p = 0.2 and 0.06, respectively). Infants with VPS had lower motor Z-scores (mean difference, 0.77 [95% CI 0.12–1.43], p = 0.02). In the multivariable model, multifocal IPH was negatively associated with cognitive score (coefficient −0.51 [95% CI −0.88 to −0.14], p = 0.009) and VPS with motor score (coefficient −0.50 [95% CI −1.6 to −0.14], p = 0.02) after adjusting for age at the time of neurodevelopmental assessment. Five (36%) infants with IPH, 2 of whom had a PVHI, developed CP. Of these infants, 4 (80%) had unilateral spastic CP (GMFCS level I) and 1 (20%) had bilateral spastic CP (GMFCS level IV). Two (13%) infants without IPH developed CP, and of these infants, 1 (50%) with a PVHI had unilateral spastic CP (GMFCS level I) and 1 (50%) bilateral spastic CP (GMFCS level III) (p = 0.2). In each group, 1 infant developed postneonatal epilepsy requiring antiseizure medication (p = 0.9).

Discussion

In this multicenter, case-control study, we report for the first time that IPH can occur after a rapid reduction in the ventricular volume during the 1st week after the initiation of serial reservoir taps. The majority (56%) of these hemorrhages were multifocal, but some were unifocal and showed an equal distribution in the periventricular and subcortical regions of the brain parenchyma. Early detection of the periventricular IPH was possible using cUS, but the majority of the subcortical IPHs were first noted with TEA-MRI, which underscores the importance of performing TEA-MRI. The presence of

multifocal IPH was negatively associated with cognitive outcomes and VPS with motor outcomes at 2 years corrected age. Although IPH after VPS surgery has been reported in the literature, to the best of our knowledge, this is the first study to describe IPH as a distinct entity following ventricular reservoir placement.[7,8]

In the present study, regardless of the IPH being unifocal or multifocal, none of the infants with IPH had bleeding around the reservoir track. It has been previously shown that bleeding can develop along the path of the catheter after VPS surgery.[14,15] Direct surgical injury during catheter placement has been regarded as the primary cause of the hemorrhage, and it was attributed to injury to the ependymal vessels with multiple attempts at penetration of the ventricles.[14,16] However, two recent studies showed that in patients undergoing VPS placement, multifocal IPH can also occur in different regions of the brain that are not adjacent to the catheter, showing that the hemorrhage is not directly related to surgical intervention.[7,8] Although the etiology of this rare phenomenon remains largely unknown, it has been hypothesized that after VPS surgery, the immature cerebral vasculature of the neonate may not fully tolerate the sudden change in cerebral perfusion pressure. An additional change in the venous circulation in the periventricular white matter where the medullary veins are located can also contribute to this vascular phenomenon.[8] Our findings suggest that a rapid decrease in the ventricular volume after serial reservoir taps may have caused IPH, as we observed a significant reduction in the ventricular volumes in infants with IPH 7 days after the initiation of reservoir taps. This observation persisted after correcting for head circumference. There was no significant difference in CSF volumes when the reservoir was inserted. As not all infants underwent MRI prior to the reservoir insertion, we cannot exclude the possibility that there was associated ischemic injury to the white matter, making the infant more vulnerable to development of IPH. In line with the previous observations on hemorrhage after VPS surgery, CSF removal with serial reservoir taps may have resulted in fluctuations in both arterial and venous hemodynamics globally in the brain, which in turn caused the IPH demonstrated in our cohort. This also explains why IPH was more commonly seen as a multifocal phenomenon in both the periventricular white matter and subcortical regions in our cohort.

As the clinical signs of increased intracranial pressure occur in the late phase in infants with hydrocephalus, there is now a trend to treat these infants early by using objective sonographic measurements.[1,17] Two-dimensional measurements of VI, AHW, and TOD can be simply performed at the bedside.[12] Although the correlation between sonographic and MRI measurements of ventricular volumes needs further investigation, it has been shown that linear measurements of ventricular size can be reliably used to calculate the ventricular volume.[12,18,19] In the present study, we used the sonographic ventricular measurements to calculate ventricular volumes as described by Benavente-Fernandez et al.[12] The derivation formula described by these investigators takes into

account the VI, AHW, and TOD to obtain ventricular volumes. Although these VIs grow alongside each other, disproportionate changes can occasionally be seen. We did not observe a significant difference in any of these measurements prior to reservoir taps and at 3 days and 7 days after the reservoir taps. Therefore, the ventricular volumes at these time points were similar between the groups; however, we found that the reduction in the VI and TOD 7 days after reservoir taps were significantly greater in infants with IPH, which explains why we found a difference in ventricular volume reduction at this time point. To prevent IPH after VPS placement in preterm infants, gradual decompression of the ventricles was recommended in the literature.[8] Because it is not possible to set pressure limits in ventricular reservoirs, we recommend the use of the aforementioned objective sonographic measurements in daily practice to gradually bring the ventricular size down while the infants are undergoing serial reservoir taps. It is also possible to estimate intraventricular pressure before removal of CSF by using a butterfly needle and tubing system. However, this technique will require disconnection of the sterile syringe from the tubing, which in turn might increase the risk of contamination and infection. Thus, we decided to base our CSF removal on cUS measurements as a proxy of pressure in the present study.

Differences in the temporal evolution of ventriculomegaly will have consistent clinical consequences. Slow and more gradual increase in the ventricular size allows the developing brain to adapt itself with inherent repair mechanisms via neuroplasticity.[1] However, we previously reported that larger ventricular volumes were negatively associated with cognitive and motor scores at 2 years of age in infants with PHVD.[2] Thus, it is of paramount importance to alleviate the ventricular distension that compresses periventricular brain parenchyma while also preventing the brain from further complications related to the surgical intervention. In the present study, although the cognitive and motor scores were slightly lower in infants with IPH, we did not find any significant difference between infants with and those without IPH. We also did not find any difference in the CP and postneonatal epilepsy rates between the groups. These might be due to the small number of infants, which may have prevented the difference from reaching statistical significance. Infants with multifocal IPH had lower cognitive scores probably due to volume loss in multiple brain tissues. Also of note was that infants with a VPS had lower motor scores in agreement with the previous literature.[2,20,21]

The present study has several limitations. The major limitation is its retrospective nature and the small number of infants, which may have prevented several tests to reach statistical significance. Second, infants were evaluated with various neurodevelopmental tests at 2 years corrected age; however, we used Z scores to standardize scores with an aim to compare different test results. Third, the infants were enrolled over a 20-year period, but the treatment of PHVD did not substantially

change in the participating centers. Furthermore, this would have similar effects on both study arms. Fourth, the vast majority of infants (30/36) were accrued from a single center (UMCU), and it was not possible to match infants also by center for 2 infants; therefore, site-specific factors may have influenced the decompression-related IPH. Fifth, we were only able to perform MRI before reservoir insertion in some of our infants and therefore cannot exclude the possibility of the occurrence of IPH before the placement of a reservoir. However, we do not consider it likely that these IPHs occurred prior to reservoir placement. The periventricular IPHs were all well seen with cUS and were first seen around 1 week after reservoir insertion. Looking at the signal intensity of the IPHs at the TEA, the periventricular and subcortical IPHs appeared to have the same time of onset. Moreover, neurodevelopmental outcomes in infants with hydrocephalus are inextricably linked to the etiology and preterm birth. Although their numbers are small, the inclusion of term infants and infants with congenital hydrocephalus adds heterogeneity to the present study. The major strength of the present study is the close neuroimaging screening to detect this rare phenomenon in centers with substantial experience in neonatal neurology practices.

Conclusions

To the best of our knowledge, we report for the first time that IPH can occur after a rapid reduction of the ventricular volume during the 1st week after the initiation of serial reservoir taps in infants with hydrocephalus. It is essential to perform serial cUS scans to guide the amount of CSF removal via reservoir taps in the management of these infants and perform TEA-MRI for recognition of subcortical as well as periventricular IPHs. Further studies are warranted to investigate possible other preventive strategies from this significant complication of reservoir taps.

Acknowledgment

We thank the neonatal intensive care nurses and developmental specialists for their dedicated help to obtain the pertinent data and records.

References

1. Flanders TM, Billinghurst L, Flibotte J, Heuer GG. Neonatal hydrocephalus. Neoreviews. 2018; 19: 467-477.
2. Cizmeci MN, Groenendaal F, Liem KD, van Haastert IC, Benavente-Fernández I, van Straaten HLM, et al. Randomized controlled early versus late ventricular intervention study in posthemorrhagic ventricular dilatation: outcome at 2 years. J Pediatr. 2020; 226: 28-35.e3.
3. McAllister JP II. Pathophysiology of congenital and neonatal hydrocephalus. Semin Fetal Neonatal Med. 2012; 17(5): 285-294.
4. Zhang J, Williams MA, Rigamonti D. Genetics of human hydrocephalus. J Neurol. 2006; 253(10): 1255-1266.
5. El-Dib M, Limbrick DD Jr, Inder T, Whitelaw A, Kulkarni AV, Warf B, et al. Management of post-hemorrhagic ventricular dilatation in the infant born preterm. J Pediatr. 2020; 226:16-27.e3.
6. Mazzola CA, Choudhri AF, Auguste KI, Limbrick DD Jr, Rogido M, Mitchell L, et al. Pediatric hydrocephalus: systematic literature review and evidence-based guidelines. Part 2: Management of posthemorrhagic hydrocephalus in premature infants. J Neurosurg Pediatr. 2014; 14(suppl 1): 8-23.
7. Oushy S, Parker JJ, Campbell K, Palmer C, Wilkinson C, Stence NV, et al. Frontal and occipital horn ratio is associated with multifocal intraparenchymal hemorrhages in neonatal shunted hydrocephalus. J Neurosurg Pediatr. 2017; 20(5): 432-438.
8. Choi JW, Kim SK, Wang KC, Lee JY, Cheon JE, Phi JH. Multifocal intraparenchymal hemorrhages after ventriculoperitoneal shunt surgery in infants. J Neurosurg Pediatr. 2014; 14(4): 329-335.
9. Volpe JJ. Intraventricular hemorrhage in the premature infant-current concepts. Part II. Ann Neurol. 1989; 25(2): 109-116.
10. Levene MI. Measurement of the growth of the lateral ventricles in preterm infants with real-time ultrasound. Arch Dis Child. 1981; 56(12): 900-904.
11. Davies MW, Swaminathan M, Chuang SL, Betheras FR. Reference ranges for the linear dimensions of the intracranial ventricles in preterm neonates. Arch Dis Child Fetal Neonatal Ed. 2000; 82(3): F218-F223.
12. Benavente-Fernandez I, Lubián-Gutierrez M, Jimenez-Gomez G, Lechuga-Sancho AM, Lubián-López SP, Neonatal Neurology Foundation. Ultrasound lineal measurements predict ventricular volume in posthaemorrhagic ventricular dilatation in preterm infants. Acta Paediatr. 2017; 106(2): 211-217.
13. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol. 1997; 39(4): 214-223.
14. Fukamachi A, Koizumi H, Nukui H. Postoperative intracerebral hemorrhages: a survey of computed tomographic findings after 1074 intracranial operations. Surg Neurol. 1985; 23(6): 575-580.
15. Misaki K, Uchiyama N, Hayashi Y, Hamada J. Intracerebral hemorrhage secondary to ventriculoperitoneal shunt insertion—four case reports. Neurol Med Chir (Tokyo). 2010; 50(1): 76-79.
16. Mascalchi M. Delayed intracerebral hemorrhage after CSF shunt for communicating "normal-pressure" hydrocephalus. Case report. Ital J Neurol Sci. 1991; 12(1): 109-112.
17. Lai GY, Chu-Kwan W, Westcott AB, Kulkarni AV, Drake JM, Lam SK. Timing of temporizing neurosurgical treatment in relation to shunting and neurodevelopmental outcomes in posthemorrhagic ventricular dilatation of prematurity: a meta-analysis. J Pediatr. 2021; 234: 54-64.e20.

18. Beijst C, Dudink J, Wientjes R, Benavente-Fernandez I, Groenendaal F, Brouwer MJ, et al. Two-dimensional ultrasound measurements vs. magnetic resonance imaging derived ventricular volume of preterm infants with germinal matrix intraventricular haemorrhage. Pediatr Radiol. 2020;50(2): 234-241.
19. Gontard LC, Pizarro J, Sanz-Peña B, Lubián López SP, Benavente-Fernández I. Automatic segmentation of ventricular volume by 3D ultrasonography in post haemorrhagic ventricular dilatation among preterm infants. Sci Rep. 2021; 11(1): 567.
20. Luyt K, Jary SL, Lea CL, Young GJ, Odd DE, Miller HE, et al. Drainage, irrigation and fibrinolytic therapy (DRIFT) for posthaemorrhagic ventricular dilatation: 10-year follow-up of a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2020; 105(5): 466-473.
21. Shankaran S, Bajaj M, Natarajan G, Saha S, Pappas A, Davis AS, et al. Outcomes following post-hemorrhagic ventricular dilatation among infants of extremely low gestational age. J Pediatr. 2020; 226: 36-44.e3.

"A man who does not think differently from his time and environment, cannot grow beyond his time and environment"

Mustafa Kemal Atatürk

7

Corpus Callosum Injury After Neurosurgical Intervention for Post-Hemorrhagic Ventricular Dilatation and Association with Neurodevelopmental Outcome at 2 Years

Mehmet N. Cizmeci, Floris Groenendaal, Niek E. van der Aa, Marlee M. Vandewouw, Julia M. Young, Sen Han, Manon J.N.L. Benders, Margot J. Taylor, *Linda S. de Vries, *Peter Woerdeman **Shared last authorship*

J Neurosurg Pediatr, 2022, In Press

Abstract

Objective: Direct injury to the corpus callosum (CC) due to neurosurgical interventions in infants with post-hemorrhagic ventricular dilatation (PHVD) has not been reported in the literature. The authors observed a subset of infants who had penetrating CC injury after neurosurgical interventions for PHVD and hypothesized that this pattern of injury may result in suboptimal CC maturation and neurodevelopmental impairment.

Methods: In this multicenter, retrospective, observational study 100 preterm and 17 term infants with PHVD were included and compared with 23 preterm controls. Both neonatal and post-neonatal brain MRIs were assessed for injury and measurements were performed on post-neonatal MRIs at 2 years corrected age. Neurodevelopmental outcome was assessed at 2 years corrected age.

Results: A total of 269 brain MRIs of 140 infants were included. Of infants with PHVD, 48 (41%) had penetrating CC injury following neurosurgical interventions for PHVD. The median (IQR) CC midsagittal surface area was smaller in infants with CC injury when compared with infants with PHVD who had intact CC and controls (190 mm^2 [149-262] vs 268 mm^2 [206-318] vs 289 mm^2 [246-320], respectively; $p < 0.001$). In the univariate analysis, area of the CC was associated with cognitive Z score (coefficient 0.009; 95% CI, 0.005-0.012; $p<0.001$) and motor Z score (coefficient 0.009; 95% CI, 0.006-0.012; $p<0.001$). In the multivariable model, CC injury was not independently associated with cognitive and motor Z score after adjusting for gestational age and presence of periventricular hemorrhagic infarction (coefficient, 0.04 [95% CI, -0.36 to 0.46], $p=0.7$ and coefficient, -0.37 [95% CI, -0.83 to 0.09], $p=0.1$, respectively).

Conclusions: CC injury was not uncommon following neurosurgical interventions for PHVD in both preterm and term infants. At the age of 2 years, CC midsagittal surface area was smaller in infants with injury, but CC injury was not independently associated with cognitive and motor outcomes at 2 years corrected age.

Introduction

Germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH) remains a common complication in preterm infants and is associated with increased risk of adverse neurodevelopmental outcomes particularly when high-grade GMH-IVH is complicated by post-hemorrhagic ventricular dilatation (PHVD).[1,2] Although the question of when best to treat PHVD remains unanswered, recent studies and a meta-analysis showed that later timing of neurosurgical interventions predicted higher rates of ventriculo-peritoneal shunt (VPS) placement and moderate to severe neurodevelopmental impairment (NDI), emphasizing the importance of timely intervention.[3-6] After documentation of enlargement of the ventricles beyond defined thresholds with the use of cranial ultrasonography, interventions for PHVD generally start with lumbar punctures to decompress the ventricles.[2] This relatively less invasive intervention is followed by more invasive temporizing neurosurgical measures if stabilization or regression of ventricular size does not occur.[4] For this purpose, placement of a ventricular reservoir (VR) as a ventricular access device with an aim to serially aspirate cerebrospinal fluid (CSF) is a commonly used technique.[2] Beyond VR, VPS placement is considered in infants who require ongoing VR aspirations.[2,4]

The corpus callosum (CC) is the principal commissural pathway connecting the cerebral hemispheres and linking cortical and subcortical regions of the brain.[7] Complications of neurosurgical interventions for PHVD such as mechanical obstruction, hemorrhage, and infection are well-documented; however, direct injury to the CC due to the insertion of a VR and VPS has not been reported in the neonatal population.[8] We observed a subset of infants who had penetrating CC injury after neurosurgical interventions for PHVD and hypothesized that this pattern of injury may result in suboptimal CC maturation and NDI. In this study, we assessed the neuroimaging features of penetrating CC injury, while also studying its relation to neurodevelopmental outcomes at 2 years corrected age.

Methods

Study Participants

In this multicenter, retrospective, observational study, preterm and term neonates with PHVD who were admitted to the Level III neonatal intensive care unit (NICU) of the Wilhelmina Children's Hospital, University Medical Center Utrecht (UMCU), between January 2005 and December 2018 were eligible, when they developed PHVD and required neurosurgical intervention. PHVD was diagnosed when infants had progressive measurements of the ventricular index >97th percentile and anterior horn width >6 mm on at least two cranial ultrasound scans using reference charts described by Levene[9] and

Davies et al.[10], respectively. Interventions for PHVD were initiated with lumbar punctures and followed by VR and VPS insertion when required. Treatment thresholds for neurosurgical interventions are described in detail in a previous article.[5] Neurosurgical interventions were performed without ultrasonography guidance using anatomical landmarks by experienced pediatric neurosurgeons. Catheters were inserted from the outermost lateral corner of the anterior fontanelle. The direction of the catheter was towards the midline and the catheter tip was aimed to remain slightly above the level of the foramen of Monro. A database search of brain magnetic resonance imaging (MRI) of enrolled infants was conducted. Because brain MRI at 2 years of age is not routinely performed at UMCU in infants without brain injury and/or NDI, the control group was selected from a different cohort. Control group comprised preterm infants <32 weeks' gestation without PHVD who were prospectively recruited at the Level III NICU of the Hospital for Sick Children, University of Toronto (UofT). These infants were recruited between January 2008 and December 2011 and routinely scanned at 2 years corrected age Neonates with evidence of a chromosomal anomaly, congenital malformation of the central nervous system, hydrocephalus due to anatomical issues, and congenital infection were excluded. Demographic data were obtained from the patients' files and/or electronic hospital databases. Data on antenatal and perinatal factors including gestational age, birth weight, sex, hemorrhage severity, and comorbidities including the use of postnatal steroids, prolonged mechanical ventilation for >7 days, sepsis, necrotizing enterocolitis, patent ductus arteriosus, and retinopathy of prematurity were collected. The study was approved by the Research Ethics Boards at both centers and a waiver of consent was provided for the study because of the use of anonymous data analysis.

Neuroimaging Protocol

Participating centers followed a predefined MRI protocol according to their institutional guidelines. At UMCU, until 2010, brain MR imaging was performed on a 1.5T system (Intera; Philips Healthcare, Best, the Netherlands) with an age-appropriate head coil and the protocol included sagittal T1-weighted and axial T2-weighted images for both neonatal and 2-year scans. Between 2010 and 2018, a 3T system (Achieva; Philips Healthcare, Best, the Netherlands) was used and sagittal T1-weighted and axial T2-weighted images were obtained. UofT followed a similar brain MR imaging protocol according to the institutional guidelines using a 1.5T system (SIGNA, GE Healthcare, USA) with an age-appropriate head coil for the neonatal and 2-year scans. In both centers, infants were sedated as per institutional protocols and received hearing protection for the procedure.

Assessment of the Corpus Callosum

MRIs were acquired from the study infants at 2 time points. Neonatal MRIs were obtained in all infants who required a neurosurgical intervention around 30 weeks' postmenstrual age and/or term-equivalent age (TEA-MRI). Both neonatal and post-neonatal MR scans were used for the detection of injury to the CC. All assessments were performed by an investigator (MNC) with formal training in neonatal neurology, who was blinded to the infants' clinical history and neuroimaging report. In equivocal cases, a senior investigator (LSdV) was consulted.

Post-neonatal MRIs were obtained routinely at 2 years of age in infants who required a VPS, and in infants with VR who developed NDI. Measurements were performed on post-neonatal MRIs obtained at 2 years of age. The CC was manually traced on the mid-sagittal slice created from the three-dimensional T1-weighted image at 2 years of age using Osirix Lite for Macintosh software, version 10.0.2 (Pixmeo, Bernex, Switzerland). Linear measurements of the genu and splenium length were performed at their widest distance in the anteroposterior direction as described by Vannucci et al.[11] Midportion thickness was assessed by measuring the height of the CC body at its widest distance vertical to the CC axis. Total cross-sectional CC surface area was measured in the midsagittal plane. The CC was traced 3 times per MRI and the mean values were used for each analysis. In infants with a penetrating injury to the CC, cross-sectional areas were measured separately and their sum was calculated. Patterns of injury are presented in Figure 1. Intra-rater reliability was tested in the first 15 scans to test the consistency of measurements.

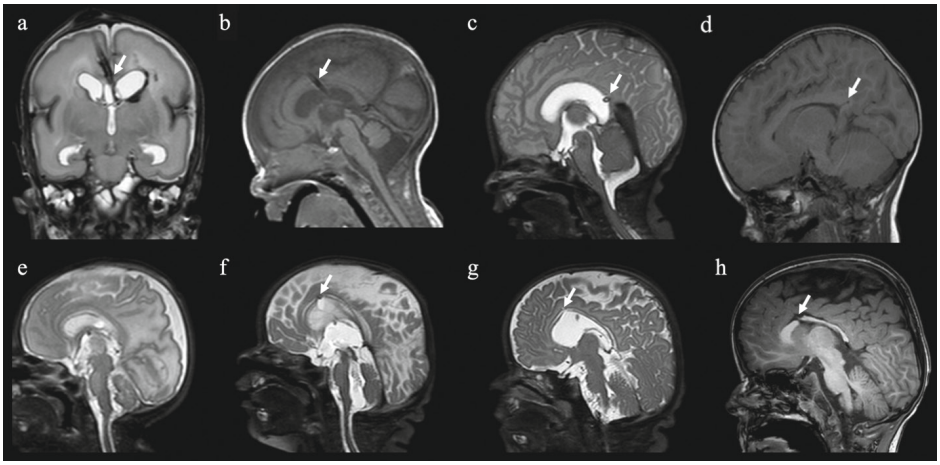


Figure 1: MRI findings of three cases with white arrows pointing to the lesions in each image. Upper panel (a and b) shows a $30^{0/7}$ preterm infant with PHVD following reservoir insertion. a) Coronal T2-weighted MRI scan demonstrates corpus callosum injury (arrow) following reservoir insertion; b) Parasagittal T1-weighted image shows piercing injury to the corpus callosum; upper panel (c and d) shows a $29^{3/7}$ preterm infant with PHVD following ventriculo-peritoneal shunt insertion c) Midsagittal T2-weighted image shows injury to the splenium of the corpus callosum (arrow) and d) Midsagittal T1-weighted image shows the effect of injury to the splenium of the corpus callosum (arrow) at 2 years of age; lower panel (e - h) shows a $26^{2/7}$ preterm infant with PHVD following two reservoir insertions e) Parasagittal T2-weighted image shows the intact corpus callosum after the 1st reservoir insertion, f) Midsagittal T2-weighted image demonstrates the piercing injury to the corpus callosum following the 2nd reservoir insertion (arrow), g) Parasagittal T2-weighted image shows apparent corpus callosum injury (arrow) at term-equivalent age MRI, and h) midsagittal T1-weighted image demonstrates piercing injury with a significant gap in the body of the corpus callosum (arrow) at 2 years of age.

Neurodevelopmental Assessment

Neurodevelopmental outcomes were assessed at each center as part of the standard neurodevelopmental follow-up programs. Assessments were performed by developmental specialists and cognitive and motor outcomes were assessed with either the Bayley Scales of Infant Development, 2nd Edition (BSID-II) or Bayley Scales of Infant and Toddler Development, 3rd Edition (BSITD-III) or Griffiths Mental Development Scales (GMDS). BSID-II and BSITD-III tests were routinely used to assess outcomes of infants who were born <28 weeks' gestation, and those born >28 weeks' gestation, were tested with GMDS at UMCU, while BSITD-III testing was the standard approach regardless of the gestational age at UofT. Cognitive and motor index or composite scores were corrected for prematurity. The conversion from the BSID-II mental developmental index to the BSITD-III composite cognitive score was calculated by the formula (59% of the BSID-II mental developmental index score plus 52) suggested by Lowe et al.[12] To include children who had an index score <50 on the BSID-II or a cognitive or motor

composite score <55 or <46 respectively on the BSITD-III, developmental quotients were calculated (developmental age equivalent [in months, based on raw test scores] divided by the corrected test age and multiplied by 100).[13] The composite cognitive and motor scores at 24 months corrected age were categorized as the normal range (mean ± 1 standard deviation [SD]), subclinical range (<-1 SD), and clinical range (<-2 SD). Standardized Z scores were calculated for cognitive and motor scores for each infant to compare different test types. Cerebral palsy (CP), and type of CP if applicable, was defined based on the definition by Rosenbaum et al.[14] CP was classified as spastic, ataxic or dyskinetic, and topographically categorized as unilateral or bilateral.[15] The gross motor function classification system (GMFCS) was used to grade the severity of CP.[16]

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 27 (IBM Corp., Armonk, N.Y., USA). Categorical variables were presented as numbers and percentages. The Chi-squared and Fisher's exact tests were used to compare categorical variables among groups. Continuous variables were presented as mean (±SD) and median (interquartile range [IQR]) depending on their distribution. Mann-Whitney U test was used to compare nonparametric variables and Student t-test for comparison between variables with Gaussian distribution. The Kruskal Wallis test and one-way analysis of variance (ANOVA) test were used to determine the difference in subgroup analysis. A post hoc analysis was performed to determine the statistical differences in multi-group comparisons. Univariate linear regression was used to determine risk factors for an adverse neurodevelopmental outcome and multiple linear regression and logistic regression were applied for the significant variables detected with the univariate analysis. Adjustment for gestational age, sex, and presence of periventricular hemorrhagic infarction (PVHI) was performed in the multivariable regression models. Statistical significance was set at $p < 0.05$.

Results

Study Participants

A total of 140 infants were included in the final analysis of whom 117 infants had PHVD and 23 were controls. The median (IQR) gestational age and birth weight were similar between infants with CC injury and intact CC groups (p=0.3 for both), while infants in the control group had lower birth weight when compared to infants with PHVD (p=0.005). Characteristics of included infants and distribution of the clinical factors and comorbidities are presented in Table 1.

Table 1: Demographic and clinical characteristics of the study population.

	PHVD with Corpus Callosum Injury (n=48)	PHVD with Intact Corpus Callosum (n=69)	Control Group (n=23)	p
Gestational age, weeks	29.9 (26.6-33.9)	31.0 (27.7-35.1)	29.1 (27.3-30.3)	0.08
Gestational age category				
Born <37$^{0/7}$ weeks	41 (85)	59 (85)	23 (100)	0.1
Born >37$^{1/7}$ weeks	7 (15)	10 (15)	0 (0)	
Birth weight, g	1508 (968-2304)	1635 (1105-2725)	1100 (955-1390)	**0.005**
Sex				
Male	32 (67)	38 (55)	15 (65)	0.4
Female	16 (33)	31 (45)	8 (35)	
Accompanying PVHI	20 (41)	19 (28)	1 (4)	**0.003**
Reservoir placement	48 (100)	69 (100)	0 (0)	**<0.001**
VPS placement	30 (63)	30 (44)	0 (0)	**<0.001**
Mechanical ventilation >7 days	13 (27)	15 (22)	9 (39)	0.3
Culture positive late onset sepsis	5 (10)	6 (9)	6 (26)	0.08
Surgical treatment for NEC	0 (0)	3 (4)	0 (0)	0.2
Surgical treatment for PDA	3 (6)	2 (3)	0 (0)	0.4
Surgical treatment for ROP	0 (0)	2 (3)	0 (0)	0.3
Mortality	0 (0)	5 (7)	0 (0)	0.07

Data are presented as median (interquartile range) or number (%)

Characteristics of Corpus Callosum Injury

A total of 269 brain MRIs were assessed, of which 84 were obtained at 30 weeks' gestation, 112 at term-equivalent age, and 73 at 2 years of age. Of infants with PHVD, 48 (41%) had penetrating CC injury. Forty-six (94%) of the injuries were due to VR placement, while 3 (6%) occurred due to VPS insertion. All injuries due to VR insertion were observed in the body of the CC, while all injuries due to VPS placement were in the splenium. In infants with PHVD, all infants had a VR insertion, and 60 (51%) of those with a VR required a VPS for permanent CSF diversion. The median (IQR) number of interventions including VR and/or VPS insertion was greater in infants with CC injury compared to the intact CC group (2 [1-2] vs 1 [1-2]; p=0.005). Eleven (23%) with CC injury and 9 (13%) with intact CC had revision surgery for VPS or more than 2 surgical interventions (p=0.1). Nine (19%) infants with CC injury and 11 (16%) with intact CC had

their VR tip lying in the basal ganglia and thalami region (p=0.6). None of the infants showed ischemic findings of cystic white matter injury on cranial ultrasound scans or brain MRIs.

Measurements of Corpus Callosum

The MRI scans were performed at a median age of 23.5 months in infants with CC injury and controls, and at 23.3 months in the intact CC group (p=0.9). Intra-rater reliability for the linear measurements of the genu, midportion, splenium, and midsagittal CC surface area were 0.92, 0.86, 0.93, 0.89, respectively. Genu length was similar across the groups (p=0.2), while midportion thickness and splenium length were smaller in infants with PHVD when compared with controls (p <0.001 for both). In the post-hoc analysis, the median (IQR) midsagittal CC surface area was smaller in infants with CC injury when compared with infants with PHVD who had intact CC and controls (190 [149-262] vs 268 [206-318] vs 289 [246-320], respectively; p <0.001). The results of the post hoc analysis are presented in Table 2.

Table 2: Characteristics of the corpus callosum injury.[†]

	PHVD with CC Injury (n=48)	PHVD with Intact CC (n=69)	Control Group (n=23)	p
Total number of MRIs	112	134	23	
Number of neonatal MRIs	82	114	0	
Number of post-neonatal MRIs	30	20	23	
Age at 2 year MRI, months	23.5 (20.9-27.0)	23.3 (20.9-27.3)	24.0 (24.0-24.2)	0.9
Genu length, mm	6.2 (5.4-7.4)	6.4 (5.3-8.2)	5.8 (5.0-6.4)	0.2
Midportion thickness, mm	1.4 (1.1-2.1)	3.0 (1.5-4.2)	4.2 (3.5-4.5)	**<0.001**
CC injury vs Intact CC				**0.004**
CC injury vs Controls				**<0.001**
Intact CC vs Controls				**0.02**
Splenium length, mm	4.4 (2.6-4.8)	5.0 (3.9-5.8)	8.0 (7.1-8.5)	**<0.001**
CC injury vs Intact CC				0.6
CC injury vs Controls				**<0.001**
Intact CC vs Controls				**<0.001**
Midsagittal CC area, mm^2	190 (149-262)	268 (206-318)	289 (246-320)	**<0.001**
CC injury vs Intact CC				**0.04**
CC injury vs Controls				**0.001**
Intact CC vs Controls				0.9

[†]All measurements are performed at 2 year MRIs
Data are presented as median (interquartile range) or number (%)

Neurodevelopmental Outcomes

Five (4%) infants died in the neonatal period not related to the neurosurgical intervention. Two (2%) were lost to follow-up and 11 (9%) had incomplete follow-up data and were removed from the outcome analysis. Of the 122 (87%) infants who were included in the final neurodevelopmental outcome analysis, 60 (49%) were assessed with GMDS, 17 (14%) with BSID-II, and 45 (37%) with BSITD-III. Details of the neurodevelopmental outcomes in the post-hoc analyses are presented in Table 3. The mean ± SD cognitive Z score was -0.33 ± 0.9 in infants with PHVD, and 0.90 ± 0.8 in the control group; the motor Z score was -0.54 ± 1.2 and -0.26 ± 0.8, respectively. Cognitive Z scores were lower in infants with PHVD (mean difference, -1.24 [95% CI, -1.7 to -0.76]; p <0.001, respectively) when compared with controls. In the univariate analysis, midsagittal surface area of the CC was associated with cognitive Z score (coefficient 0.009; 95% CI, 0.005-0.012; p<0.001) and motor Z score (coefficient 0.009; 95% CI, 0.006-0.012; p<0.001). In the multivariable model, CC injury was not independently associated with cognitive and motor Z score after adjusting for gestational age and presence of PVHI (coefficient, 0.04 [95% CI, -0.36 to 0.46], p=0.7 and coefficient, -0.37 [95% CI, -0.83 to 0.09], p=0.1, respectively). PVHI was an independent risk factor associated with lower cognitive and motor Z scores after adjusting for gestational age (coefficient, -0.53 [95% CI, -0.96 to -0.09], p=0.02 and coefficient, -0.84 [95% CI, -1.34 to -0.35], p=0.001, respectively). In infants with PHVD, 12 (29%) infants with CC injury and 6 (11%) infants with intact CC developed CP (p=0.02). In the multivariable model, the presence of PVHI was the only independent risk factor for CP after adjusting for gestational age, CC injury, and sex (odds ratio: 7.7, [95% CI, 2.2 to 27.3], p<0.002).

Table 3: Subgroup analysis of the neurodevelopmental outcomes of the study infants.

	PHVD with CC Injury (n=42)	PHVD with Intact CC (n=57)	Control Group (n=23)	p
Corrected age at follow-up, mo	24.2 (23.5-25.4)	24.1 (23.5-26.3)	27.2 (26.8-28.4)	**<0.001**
CC injury vs Intact CC				1
CC injury vs Controls				**<0.001**
Intact CC vs Controls				**<0.001**
Cognitive Z-score	-0.36 ± 1.09	-0.33 ± 0.94	0.90 ± 0.88	**<0.001**
CC injury vs Intact CC				0.9
CC injury vs Controls				**<0.001**
Intact CC vs Controls				**<0.001**
Motor Z-score	-0.84 ± 1.3	-0.33 ± 1.1	-0.26 ± 0.9	0.09
CC injury vs Intact CC				0.1
CC injury vs Controls				0.2
Intact CC vs Controls				0.9
Cognitive score category[†]				0.06
Normal range	30 (75)	41 (73)	21 (100)	
Subclinical range	4 (10)	10 (18)	0 (0)	
Clinical range	6 (15)	5 (9)	0 (0)	
Motor score category[††]				0.06
Normal range	24 (63)	36 (68)	16 (80)	
Subclinical range	4 (11)	11 (21)	4 (20)	
Clinical range	10 (26)	6 (11)	0 (0)	
Cerebral palsy	12 (29)	6 (11)	0 (0)	**0.004**
Type of CP				0.08
Unilateral spastic CP	19 (75)	4 (66)	0 (0)	
Bilateral spastic CP	3 (25)	1 (17)	0 (0)	
Ataxic	0 (0)	1 (17)	0 (0)	

Data are presented as median (interquartile range, IQR), mean ± standard deviation or number (%)
[†]Cognitive scores were available in 117/122 of infants
[††]Motor scores were available in 111/122 of infants

The mean ± SD cognitive Z score was -0.33 ± 0.9 in infants with PHVD, and 0.90 ± 0.8 in the control group; the motor Z score was -0.54 ± 1.2 and -0.26 ± 0.8, respectively. Cognitive Z scores were lower in infants with PHVD (mean difference, -1.24 [95% CI, -1.7 to -0.76]; p <0.001, respectively) when compared with controls. In the univariate analysis, midsagittal surface area of the CC was associated with cognitive Z score

(coefficient 0.009; 95% CI, 0.005-0.012; p<0.001) and motor Z score (coefficient 0.009; 95% CI, 0.005-0.012; p<0.001). In the multivariable model, CC injury was not independently associated with cognitive and motor Z score after adjusting for gestational age and presence of PVHI (coefficient, 0.04 [95% CI, -0.36 to 0.46], p=0.7 and coefficient, -0.37 [95% CI, -0.83 to 0.09], p=0.1, respectively). Presence of PVHI was an independent risk factor associated with lower cognitive and motor Z scores after adjusting for the gestational age (coefficient, -0.53 [95% CI, -0.96 to -0.09], p=0.02 and coefficient, -0.84 [95% CI, -1.34 to -0.35], p=0.001, respectively). In infants with PHVD, 12 (29%) infants with CC injury and 6 (11%) infants with intact CC developed CP (p=0.02). In the multivariable model, the presence of PVHI was the only independent risk factor for CP after adjusting for gestational age, CC injury, and sex (odds ratio: 7.7, [95% CI, 2.2 to 27.3], p<0.002).

Discussion

In this multicenter, observational study, we assessed the effect of neurosurgical interventions in infants with PHVD with a specific focus on macroscopic integrity and development of the CC. Our findings show that CC injury can occur due to neurosurgical interventions for PHVD in both preterm and term infants. The majority of these injuries were due to VR insertion; however, we also observed that a small proportion (6%) of the cases had injury to the posterior part of the CC following VPS insertion. In keeping with our hypothesis, the midsagittal surface area of the CC was smaller in infants with CC injury compared to that of infants whose CC remained intact after neurosurgical interventions and controls, reflecting underdevelopment of these essential commissural nerve fibers following the insult. Of note, infants with PHVD had smaller linear measurements and CC surface area when compared with controls regardless of injury to the CC. Although the CC surface area was positively associated with cognitive and motor outcomes at 2 years of age and CP was more common in infants with CC injury in the univariate analysis, these associations did not persist after adjusting for gestational age, sex, and the presence of PVHI. As expected, PVHI was found to be an independent risk factor that was negatively associated with both cognitive and motor outcomes; however, contrary to our hypothesis, CC injury was not independently associated with cognitive and motor outcomes at 2 years corrected age. Although complications of neurosurgical interventions have been reported in the literature, to the best of our knowledge, this is the first neonatal study to describe penetrating CC injury as a distinct entity following neurosurgical interventions for PHVD and assess the association between metrics of CC development and neurodevelopmental outcomes.

Surgery for shunt placement is among the most common neurosurgical interventions in neonates and most interventions are performed freehand using anatomical

landmarks.[17] In the present study, interventions were performed without ultrasound guidance by pediatric neurosurgeons with many years of experience in performing this procedure. This intervention approach without seeing the tip of the catheter during insertion has been reported to have inaccuracy rates ranging between 15 to 40% in the pediatric literature and may also explain the high rate of CC injury we observed in our cohort.[17] Of note, a proportion of infants in both groups (overall 17%) had their VR catheter tip positioned in the basal ganglia and thalami region. To address this issue, Kellnar et al.[18] described the use of intraoperative cranial ultrasonography in newborns to optimize the position of the shunt catheter, and since the first description, multiple studies showed the efficacy of neuro-navigation using ultrasonography for real-time visualization of the ventricles.[17,19] A prospective controlled study by the Hydrocephalus Clinical Research Network investigated the use of ultrasound guidance in the pediatric population during neurosurgical interventions for hydrocephalus. Accurate placement was observed in 59% of the infants; however, this rate was well below the study goal of 80% and was only slightly better than the success rate (49%) in the control group.[20] We speculate that using ultrasonography for real-time visualization of the ventricles might be a promising technique to avoid CC injury during neurosurgical interventions for PHVD if supported by future well-designed studies. Our data also show that overall, 17% of infants with PHVD required either a revision surgery or more than 2 surgical interventions due to VR/VPS dysfunction. Similar to our findings, in a population-based database, Donoho et al.[21] found that the 30-day readmission rate of pediatric patients undergoing ventricular shunting was 18%.

The blood supply of the CC derives from the branches of both anterior and posterior circulations that anastomose to form a pericallosal pial plexus and in around 80% of humans, additional blood supply comes from the anterior communicating artery.[22,23] Due to the dominance of the anterior circulation, anterior portions of the CC are more resilient to ischemia.[22,24,25] Several neonatal studies using Doppler examinations have demonstrated impairment of the cerebral circulation in infants with PHVD.[26,27] We observed thinning of the midportion and splenium regions of the CC in infants with PHVD compared to that of controls. This likely reflects the fact that the circulation of the CC was impaired leading to thinning in the middle and posterior parts, but not necessarily in the anterior part of the CC due to the aforementioned preserved circulation pattern. It has also been shown that white matter injury in the context of PHVD causes microstructural changes in the CC, which may also explain thinning in the CC found in the present study.[28,29] PVHI, which was the only independent risk factor for adverse cognitive and motor outcomes in the present study, may also have played a role in the underdevelopment of the CC. Additionally, we found that infants with CC injury had smaller CC body thickness than that of infants with intact CC, while splenium length was similar across these groups. This may be explained by the effect

of penetrating injury leading to impaired circulation in the CC areas that are adjacent to the injury, but relatively preserved posterior circulation of the splenium. It is important to emphasize that we were not able to use volumetric analysis in the present study and applied 2-dimensional surface area and linear measurements instead. Although 2-dimensional measurements can be conducted with high reliability, further studies using volumetric analysis are warranted to confirm our findings.[30]

We were not able to document a negative effect of penetrating CC injury on cognitive and motor outcomes at 2 years in our study. The positive association between CC injury and cognitive and motor scores as well as CP did not persist after accounting for clinical factors. However, it is important to underline that three different neurodevelopmental tests were used in the present study as the study infants were recruited over a 14-year period. Although we used Z scores to be able to compare scores obtained by different test types, ideally outcomes should have been compared using the same test for all infants. Also of note, unlike adults with CC injury and pediatric patients with developmental anomalies of the CC who commonly exhibit cognitive impairments, language delay, visuo-spatial integration issues, dyslexia, and behavioral issues, newborn infants with penetrating CC injury did not show impairments in the cognitive and motor domains.[7,22,31,32] We speculate that this may be reflecting the higher neuroplastic capacity of the developing human brain. It is also possible that cognitive impairments may first become apparent later in childhood when the cognitive demands increase at school-age. It is important to re-emphasize that our follow-up data only represent neurodevelopmental outcomes during infancy and it is not possible to draw firm conclusions about later childhood outcomes. Therefore, the effect of penetrating CC injury on the cognitive domain and higher cognitive functions should be further investigated in children at school-age. Also of note, cognitive assessment at 2 years of age may not accurately measure cognitive functioning as compared with school-age testing.

The present study has several limitations. First, we were not able to use volumetric analysis to calculate the CC volume and used CC surface area and linear measurements instead. However, volumetric measurement of the CC is technically challenging, limiting its application in clinical practice and it has been shown that measurement of the CC area does not require sophisticated image processing and can be conducted with high reliability.[30] Second, we used standard neurodevelopmental tests to assess cognitive and motor outcomes at 2 years corrected age. However, we did not use neurodevelopmental tools specifically developed to assess cognitive domain and visuo-spatial integration that are commonly affected in CC injury, as these infants were not old enough to be assessed with these specific tests. Also of note, infants were evaluated with various neurodevelopmental tests and comparison could only be made by using standardized Z scores. Third, because this was a multi-center study, scanning

protocols were not the same in the two centers, which could have led to varying image qualities. Fourth, the effect of non-cystic white matter injury, which is a risk factor for adverse neurodevelopmental outcomes was not taken into account in the present study. However, we did not observe major ischemic findings of cystic white matter injury in this cohort on cranial ultrasound scans or brain MRIs. Finally, although their numbers are small, the inclusion of term infants adds heterogeneity to the present study. The major strength of the present study is the inclusion of a considerable number of infants with PHVD with a high follow-up rate to document the neuroimaging aspects and neurodevelopmental consequences of this clinical entity.

Conclusions

Although timely neurosurgical interventions are required to prevent neurodevelopmental impairments in infants with progressive PHVD, we report for the first time that CC injury can occur in neonates due to neurosurgical interventions for PHVD and this can potentially result in underdevelopment of these essential commissural nerve fibers. However, CC injury was not independently associated with cognitive and motor outcomes at 2 years of age in the present study. PVHI was the only independent risk factor for adverse cognitive and motor outcomes. As a wide range of neurodevelopmental impairments due to CC injury may manifest later in childhood, further studies are warranted to investigate the impact of this pattern of injury on multiple neurodevelopmental outcome domains beyond infancy.

Acknowledgment

The authors thank Astrid Nieuwets, Ingrid van Haastert, neonatal intensive care nurses, MRI technicians, and developmental specialists for their dedicated help to obtain the pertinent data and records.

Conflict of Interest

No funding was received for this study. The authors have no financial relationship or any other conflict of interest to declare.

References

1. Yeo KT, Thomas R, Chow SS, et al. Improving incidence trends of severe intraventricular haemorrhages in preterm infants <32 weeks gestation: a cohort study. *Arch Dis Child Fetal Neonatal Ed*. 2020;105:145-150.
2. El-Dib M, Limbrick DD, Jr., Inder T, et al. Management of Post-hemorrhagic Ventricular Dilatation in the Infant Born Preterm. *J Pediatr.* 2020; Nov;226:16-27.
3. Cizmeci MN, Groenendaal F, de Vries LS. Timing of Intervention for Posthemorrhagic Ventricular Dilatation: An Ongoing Debate. *J Pediatr.* 2021;234:14-16.
4. Lai GY, Chu-Kwan W, Westcott AB, Kulkarni AV, Drake JM, Lam SK. Timing of Temporizing Neurosurgical Treatment in Relation to Shunting and Neurodevelopmental Outcomes in Posthemorrhagic Ventricular Dilatation of Prematurity: A Meta-analysis. *J Pediatr.* 2021;234:54-64.
5. de Vries LS, Groenendaal F, Liem KD, et al. Treatment thresholds for intervention in posthaemorrhagic ventricular dilation: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed*. 2019;104:70-75.
6. Cizmeci MN, Groenendaal F, Liem KD, et al. Randomized Controlled Early versus Late Ventricular Intervention Study in Posthemorrhagic Ventricular Dilatation: Outcome at 2 Years. J Pediatr 2020;226:28-35.
7. Andronikou S, Pillay T, Gabuza L, et al. Corpus callosum thickness in children: an MR pattern-recognition approach on the midsagittal image. *Pediatr Radiol.* 2015;45:258-272.
8. Badhiwala JH, Hong CJ, Nassiri F, Hong BY, Riva-Cambrin J, Kulkarni AV. Treatment of posthemorrhagic ventricular dilation in preterm infants: a systematic review and meta-analysis of outcomes and complications. *J Neurosurg Pediatr.* 2015;16:545-555.
9. Levene MI. Measurement of the growth of the lateral ventricles in preterm infants with real-time ultrasound. *Arch Dis Child*. 1981;56:900-904.
10. Davies MW, Swaminathan M, Chuang SL, Betheras FR. Reference ranges for the linear dimensions of the intracranial ventricles in preterm neonates. *Arch Dis Child Fetal Neonatal Ed.* 2000;82:218-223.
11. Vannucci RC, Barron TF, Vannucci SJ. Development of the Corpus Callosum: An MRI Study. *Dev Neurosci.* 2017;39:97-106.
12. Lowe JR, Erickson SJ, Schrader R, Duncan AF. Comparison of the Bayley II Mental Developmental Index and the Bayley III Cognitive Scale: are we measuring the same thing? *Acta Paediatr.* 2012;101:55-58.
13. Jary S, Kmita G, Whitelaw A. Differentiating developmental outcome between infants with severe disability in research studies: the role of Bayley Developmental Quotients. *J Pediatr.* 2011;159:211-214.
14. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl*. 2007;109:8-14.
15. Novak I, Morgan C, Adde L, et al. Early, Accurate Diagnosis and Early Intervention in Cerebral Palsy: Advances in Diagnosis and Treatment. *JAMA Pediatr.* 2017;171:897-907.
16. Palisano RJ, Hanna SE, Rosenbaum PL, et al. Validation of a model of gross motor function for children with cerebral palsy. *Phys Ther.* 2000;80:974-985.
17. Kullmann M, Khachatryan M, Schuhmann MU. Ultrasound-guided placement of ventricular catheters in first-time pediatric VP shunt surgery. *Childs Nerv Syst.* 2018;34:465-471.
18. Kellnar S, Ring-Mrozik E, Deindl C. [Intraoperative sonographic diagnosis of the ventricular position of shunt systems in infants with hydrocephalus]. *Z Kinderchir.* 1989;44:131-134.
19. Babcock DS, Barr LL, Crone KR. Intraoperative uses of ultrasound in the pediatric neurosurgical patient. *Pediatr Neurosurg*. 1992;18:84-91.

20. Whitehead WE, Riva-Cambrin J, Wellons JC, 3rd, et al. No significant improvement in the rate of accurate ventricular catheter location using ultrasound-guided CSF shunt insertion: a prospective, controlled study by the Hydrocephalus Clinical Research Network. *J Neurosurg Pediatr.* 2013;12:565-574.
21. Donoho DA, Buchanan IA, Rangwala SD, et al. Readmissions after ventricular shunting in pediatric patients with hydrocephalus: a Nationwide Readmissions Database analysis. *J Neurosurg Pediatr.* 2021:1-10.
22. Blaauw J, Meiners LC. The splenium of the corpus callosum: embryology, anatomy, function and imaging with pathophysiological hypothesis. *Neuroradiology.* 2020;62:563-585.
23. Kahilogullari G, Comert A, Ozdemir M, et al. Arterial vascularization patterns of the splenium: An anatomical study. *Clin Anat*. 2013;26:675-681.
24. Ture U, Yasargil MG, Krisht AF. The arteries of the corpus callosum: a microsurgical anatomic study. *Neurosurgery.* 1996;39:1075-1085.
25. Chrysikopoulos H, Andreou J, Roussakis A, Pappas J. Infarction of the corpus callosum: computed tomography and magnetic resonance imaging. *Eur J Radiol.* 1997;25:2-8.
26. Van Bel F, Van de Bor M, Baan J, Stijnen T, Ruys JH. Blood flow velocity pattern of the anterior cerebral arteries. Before and after drainage of posthemorrhagic hydrocephalus in the newborn. *J Ultrasound Med.* 1988;7:553-559.
27. Nishimaki S, Iwasaki Y, Akamatsu H. Cerebral blood flow velocity before and after cerebrospinal fluid drainage in infants with posthemorrhagic hydrocephalus. *J Ultrasound Med*. 2004;23:1315-1319.
28. Nieuwets A, Cizmeci MN, Groenendaal F, et al. Post-hemorrhagic ventricular dilatation affects white matter maturation in extremely preterm infants. *Pediatr Res*. 2021. doi: 10.1038/s41390-021-01704-2
29. Lean RE, Han RH, Smyser TA, et al. Altered neonatal white and gray matter microstructure is associated with neurodevelopmental impairments in very preterm infants with high-grade brain injury. *Pediatr Res.* 2019;86:365-374.
30. Malavolti AM, Chau V, Brown-Lum M, et al. Association between corpus callosum development on magnetic resonance imaging and diffusion tensor imaging, and neurodevelopmental outcome in neonates born very preterm. *Dev Med Child Neurol.* 2017;59:433-440.
31. Gao Y, Yan K, Yang L, Cheng G, Zhou W. Biometry reference range of the corpus callosum in neonates: An observational study. *Medicine (Baltimore)*. 2018;97:e11071.
32. Luders E, Thompson PM, Toga AW. The development of the corpus callosum in the healthy human brain. *J Neurosci* 2010;30:10985-10990.

"Mankind is a single body and each nation a part of that body. We must never say "What does it matter to me if some part of the world is ailing?" If there is such an illness, we must concern ourselves with it as though we were having that illness."

Mustafa Kemal Atatürk

8

Bedside Ultrasound-Guided Percutaneous Needle Aspiration of Intra- and Extra-Axial Intracranial Hemorrhage in Neonates

Mehmet N. Cizmeci, Liesbeth Thewissen, Alexandra Zecic, Peter A. Woerdeman, Bart de Boer, Edward Baert, Paul Govaert, Jeroen Dudink, Floris Groenendaal, Maarten Lequin, Linda S. de Vries

Neuropediatrics, 2018 Aug; 49(4): 238-245 DOI: 10.1055/s-0038-1641568

Abstract

Intracranial hemorrhage is an important cause of brain injury in the neonatal population and bedside percutaneous needle aspiration has emerged as an alternative due to the major risks that can be caused by standard neurosurgical decompression. We aimed to assess the effectiveness of this minimally invasive bedside technique and conducted a retrospective analysis of all newborn infants with a large extra-axial hemorrhage associated with a parenchymal hemorrhage causing a midline shift, managed at three academic centers over a 15-year period. Collected data included clinical history, laboratory results, review of all imaging studies performed, and neurodevelopmental follow-up. Eight infants (3 preterm and 5 full-term) presented on day 1 to 2 with seizures (n=6) and apneas (n=5), signs of increased intracranial pressure (n=4), and coning (n=1). Risk factors were present in six. Cranial ultrasound and computed tomography showed a midline shift in all; two infants showed status epilepticus on amplitude-integrated electroencephalography with complete resolution after the procedure. Between 7 and 34 mL could be aspirated associated with a decrease in the midline shift as seen by ultrasonography performed during the puncture. No complications were seen related to the procedure and none of the infants required further acute neurosurgical intervention. On follow-up, three had mild sequelae, including motor coordination problems (n=1) and hemianopia (n=2); none developed cerebral palsy or postneonatal epilepsy. Neonates, presenting with severe symptoms, can be managed successfully using ultrasound-guided needle aspiration and this minimally invasive bedside method should be kept in mind before performing neurosurgical decompression.

Introduction

Intracranial hemorrhage (ICH) is defined as the pathological accumulation of blood within the cranial vault and is associated with substantial devastating consequences on morbidity, mortality, and long-term neurodevelopmental outcome in neonates. In contrast to preterm infants who exhibit intraventricular hemorrhage (IVH) as the most common form of ICH, term neonates usually present with an extra-axial hemorrhage involving the meninges, commonly seen after a normal delivery, or more rarely with a lobar hemorrhage occurring within the brain parenchyma.[1,2] Regardless of the gestational age of the infant, the combination of duration of compression of the brain tissue, the extent of bleeding, and often accompanying seizures can have detrimental effects on neurological outcome.[3,4] Therefore, proper management of this condition, which usually includes neurosurgical intervention, is of paramount importance. While a decision for conventional neurosurgical decompression is most often made in the neonatal population, this may not be the best option for every patient with a compromised clinical condition. Bedside percutaneous needle aspiration has emerged as an alternative due to the major risks that can be caused by standard neurosurgical decompression including, transfer of the neonate to the operating theatre, and further clinical deterioration due to general anesthesia and craniotomy. However, data on percutaneous needle aspiration is limited to a few cases with an extra-axial epidural or subarachnoid hemorrhage.[3,5–10] The aim of this study was to illustrate the use of ultrasound-guided percutaneous needle aspiration in eight newborn infants with a large extra-axial hemorrhage associated with a parenchymal hemorrhage causing a midline shift and to review the literature on this method.

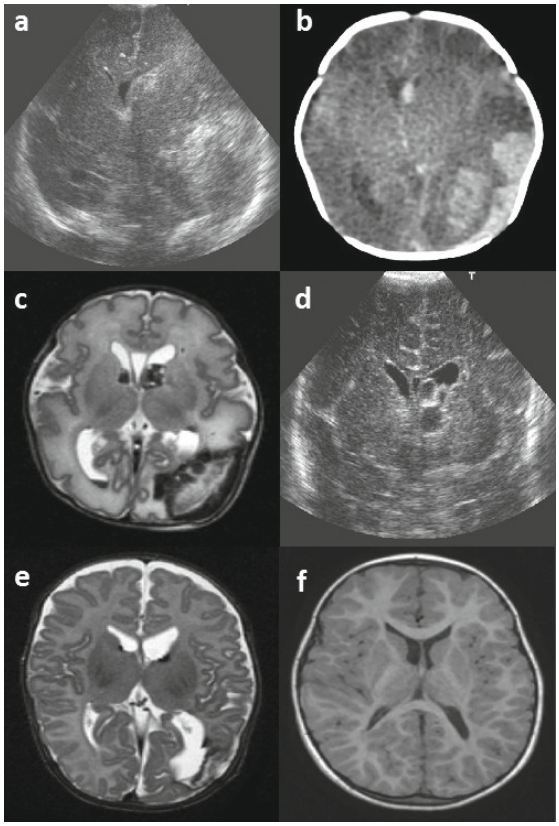
Methods

A retrospective analysis of all newborn infants with a large extraaxial hemorrhage associated with a parenchymal hemorrhage causing a midline shift, managed with bedside ultrasound-guided percutaneous needle aspiration at three centers over a 15-year period, was conducted. Eight patients were included, all of whom were admitted due to neonatal seizures and/or apneas. Neuroimaging techniques including cranial ultrasound (cUS), computed tomography (CT), and magnetic resonance imaging (MRI) were used. The medical records were used for information on neurodevelopmental outcome. Signed parental informed consent for inclusion in this study was obtained.

Selected Cases

Case 1

This male infant weighing 1050 g (3rd–10th percentile) was born to a gravida 1, para 0 mother by emergency cesarean section (C/S) at 311/7 weeks. The mother presented in labor with decreased fetal movements and Doppler ultrasonography revealed reversed end-diastolic flow velocities. The parental history and the course of the present pregnancy were unremarkable and the mother received one dose of antenatal steroids before delivery. The infant required intubation in the delivery room due to respiratory insufficiency and the Apgar scores were 1, 1, and 9 at 1, 5, and 10 minutes, respectively. His umbilical cord blood gas showed a pH of 7.10 with a base excess of –12 mmol/L and lactate of 13.7 mmol/L. Upon admission to a level 2 hospital, the infant was started on glucose infusion due to a low blood glucose level of 0.1 mmol/L. A complete blood count (CBC) analysis at 6 hours of life showed a hemoglobin of 6.5 mmol/L with a platelet count of 42,000/µL for which a thrombocyte and packed red blood cell transfusions were given. A cUS scan was performed, which showed a large left-sided parieto-occipital hemorrhage with a subarachnoid component causing a midline shift (Figure 1a).



< Figure 1: Ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) findings of case 1. (a) Cranial ultrasound (cUS) coronal view, showing a clear midline shift, a left-sided germinal matrix hemorrhage (GMH) and a large echogenic area in the left temporal–parietal lobe; (b) Axial CT confirming the midline shift and GMH, but showing both extra-axial and intraparenchymal hemorrhage as well as an area of low attenuation adjacent to the hemorrhage; (c) MRI-T2 sequence performed 8 days after the puncture no longer shows a midline shift, but shows a bilateral intraventricular hemorrhage, a subdural hemorrhage as well as intraparenchymal hemorrhage with adjacent increased signal intensity suggestive of ischemia; (d) cUS performed 2 weeks later showing left-sided residual hemorrhage; (e) MRI-T2 sequence at term equivalent age showing resolution of the hemorrhage with cystic evolution in the parenchyma, separate from the ventricle and mild ventricular dilatation; (f) T1-weighted sequence at 4 years showing normalization of ventricular size and progress in myelination.

He was started on mannitol infusion (0.5 g/kg) and transferred to our level three neonatal intensive care unit (NICU) for further evaluation. His head circumference on arrival was 27.8 cm (40th percentile) with a full fontanel and a cUS study revealed a small left germinal matrix-intraventricular hemorrhage (GMH-IVH) with a large focus of increased echogenicity in the left parieto-occipital lobe causing a midline shift, which was later confirmed to be a large parenchymal hemorrhage with a subdural and subarachnoid component on a CT scan (Figure 1b). After obtaining parental consent, an ultrasound-guided percutaneous needle aspiration through the parieto-mastoid suture was performed by the neurosurgeon. A 24-gauge needle was inserted with the guidance of a convex ultrasound probe placed on the anterior fontanel resulting in removal of 20 mL blood. The infant remained stable during the procedure and midline shift was no longer seen on subsequent cUS examinations. The amplitude-integrated electroencephalography (aEEG) showed a normal background pattern for age without seizure activity. Further etiologic studies including alloimmune antibodies, TORCH, and Parvovirus B19 were found to be negative and thrombocytopenia was considered to be due to fetal growth restriction and perinatal asphyxia. MRI of the brain on day 9 showed no midline shift, presence of bilateral GMHs, and a large left-sided parieto-occipital hematoma communicating with the left lateral ventricle with some blood in the occipital horn. Punctate white matter lesions were also noted together with a left-sided subdural collection (Figure 1c); MR angiography and MR venography were unremarkable. cUS examinations demonstrated grade I GMH on the right and grade II IVH on the left (Figure 1d). Serial cUS scans showed development of mild post-hemorrhagic ventricular dilatation (PHVD), especially on the left. He was started on oral isosorbide (8 g/kg/day) and required three lumbar punctures to stabilize the PHVD. The infant was mechanically ventilated for 9 days followed by continuous positive airway pressure for two more days before weaning to room-air and discharged home on day 36 on isosorbide and phenobarbital maintenance. Isosorbide therapy was discontinued 4weeks after discharge and a repeat cUS scan showed no dilatation after cessation of the therapy. The follow-up examination at term equivalent age showed a restless, but

otherwise well infant and the MR scan showed slightly asymmetrical myelination of the PLIC and mildly decreased size of cerebellar peduncle on the left, partial resolution of the hematoma leading to cystic appearance in the left parieto-occipital lobe, and ex-vacuo dilatation of the left lateral ventricle (Figure 1e). The infant received regular physiotherapy and at 6, 12, 18, 24, and 36 months corrected age, his Griffiths Scales of Mental Development (GSMD) score was within the normal range. A follow-up MR scan at 4 years of age showed focal white matter loss and gliosis (Figure 1f). Follow-up until 5.5 years of age revealed a friendly boy with a small stature (< –2 SD) receiving growth hormone. The infant did not develop cerebral palsy; however, he was diagnosed with developmental coordination disorder and received a special education program for 6 months after which he started and still attends mainstream school.

Case 2

This male infant was born at $39^{4/7}$ weeks to a 34-year-old gravida 2, para 1 mother who had received routine prenatal care. The infant was born by C/S due to failure to progress in labor. The Apgar scores were 9 and 10 at 1 and 5 minutes, respectively, and umbilical cord blood gas showed a mild metabolic acidosis with a pH of 7.15 and a base excess of –6 mmol/L. His birth weight was 3785 g (50^{th}–90^{th} percentile), head circumference 35.5 cm (50^{th}–90^{th} percentile), and the physical examination was completely normal. At the age of 30 hours, repetitive clonic movements of the left hand and leg were observed and the patient was admitted to the NICU for neuromonitoring. The CBC revealed a hemoglobin of 7.8 mmol/L with a platelet count of 362,000/µL and a C-reactive protein of 34 mg/L. Other laboratory studies including basic metabolic panel and coagulation profile were within the normal range. aEEG confirmed the presence of seizure activity in the right hemisphere (Figure 2a).

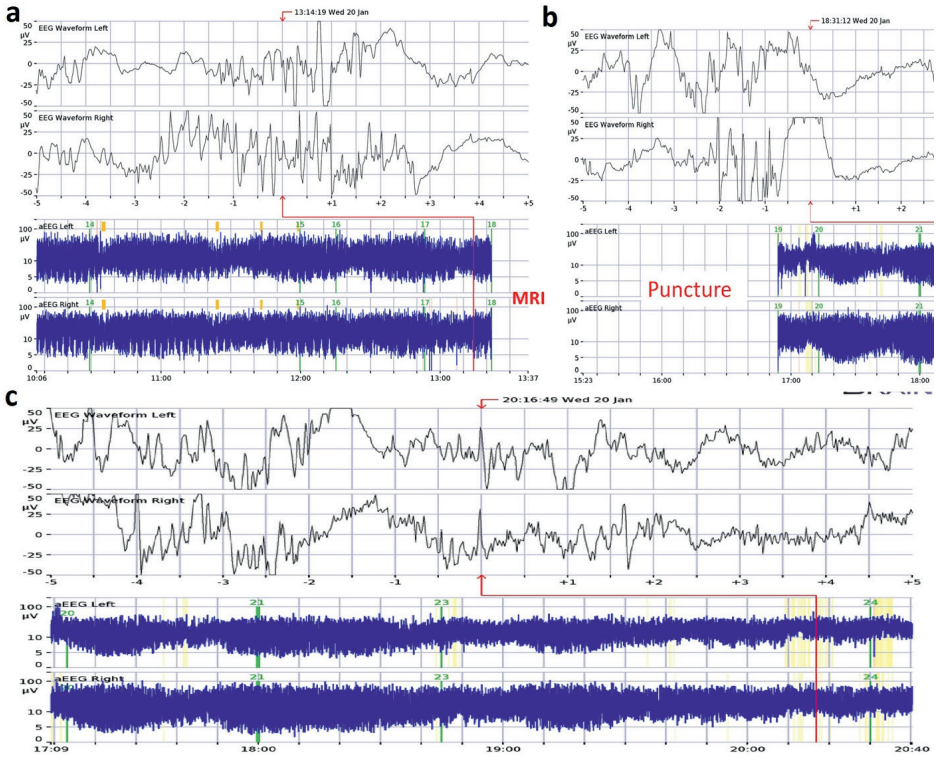
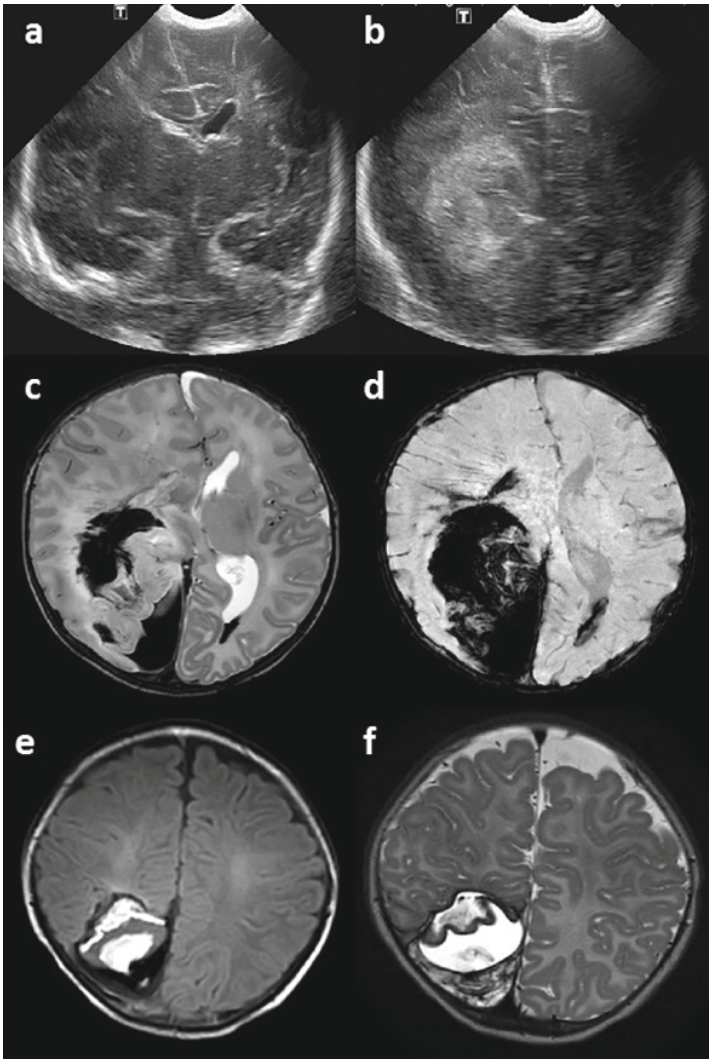


Figure 2: Amplitude-integrated electroencephalography (aEEG) recording of case 2. (a) Status epilepticus in the right hemisphere refractory to multiple antiepileptic drugs. aEEG recording was interrupted during the magnetic resonance imaging and the puncture; (b) aEEG trace showing cessation of the seizure activity following the procedure on a continuous normal voltage background and presence of sleep-wake cycling; (c) no recurrence of the seizure activity was noted in the following hours, showing continuous normal voltage background and sleep-wake cycling.

cUS revealed a large parenchymal hemorrhage in the right parieto-occipital lobe compressing the right lateral ventricle causing a midline shift (Figure 3 a and b). After a loading dose of phenobarbital (20mg/kg), seizures recurred electrographically and required add-on therapy with midazolam (loading dose: 0.05 mg/kg, followed by 0.15 mg/kg/h), lidocaine (loading dose: 2mg/kg, followed by continuous infusion for 24 hours, tapered gradually), and levetiracetam (10 mg/kg/dose). An MRI on day 2 showed a massive hemorrhage in the right parieto-occipital lobe with a large occipitoparietal subarachnoid and subdural collection. Hemorrhage was also detected in the right germinal matrix and lateral ventricle (Figure 3 c and d). MR angiography and MR venography were normal. Bedside ultrasound-guided percutaneous needle aspiration was performed by the neurosurgeon and 7 mL of blood was removed. aEEG after the procedure demonstrated complete cessation of the seizure activity and subsequently,

the antiepileptic drugs were tapered (Figure 2b and c). Serial cUS studies displayed a reduction in the size of the hematoma and disappearance of the midline shift with mild PHVD. Further etiologic evaluation yielded a heterozygous carrier state for factor V Leiden mutation. The infant was discharged home on day 12 on phenobarbital maintenance therapy. A follow-up MR scan at 3 months of age showed resolution of the previously noted hematoma, leaving a large arachnoid cyst in the right parieto-occipital lobe and ex-vacuo dilatation of the right lateral ventricle (Figure 3 e and f). He developed hemianopia of the left eye and convergent strabismus and otherwise, he showed favorable development with a GSMD score normal for his age currently at 18 months.



< Figure 3: Ultrasound and magnetic resonance imaging (MRI) findings of case 2. (a) Cranial ultrasound (cUS) coronal view, showing midline shift and a right-sided germinal matrix hemorrhage; (b) cUS image showing a large round-shaped echogenic area in the right parietooccipital lobe consistent with the hematoma; (c) MRI-T2 sequence performed on day 2 before the procedure shows a midline shift, bilateral intraventricular hemorrhage, and small subdural and large subarachnoid hemorrhage associated with intraparenchymal hemorrhage and ischemia of the parenchyma; (d) MRI-susceptibility weighted imaging at the same level demonstrates a right-sided large intraparenchymal hemorrhage in association with extra-axial blood collection; (e and f) MRI T1 and T2 sequences at 3 months showing the evolution of the parenchymal and extra-axial hemorrhage.

Results

The clinical and outcome characteristics of all eight infants (3 preterm and 5 full-term) are shown in Table 1. All infants presented on day 1 to 2 with seizures (n=6) and apneas (n=5), signs of increased intracranial pressure (n=4), and coning (n=1). Six had etiologic risk factors for hemorrhage. cUS and CT showed midline shift in all (Figure 1); two infants showed status epilepticus on EEG with complete resolution after the procedure (Figure 2 of Case 2). All infants were intubated, sedated, and mechanically ventilated during the procedure and between 7 and 34 mL (median 20 mL) could be aspirated associated with a decrease in the midline shift as seen by ultrasonography performed during the puncture. No complications were seen related to the procedure and none of the infants required further acute neurosurgical intervention. One infant developed posthemorrhagic hydrocephalus and needed a ventriculoperitoneal shunt (Case 8). The median age at follow-up was 12 months (range 4–168 months). Three had mild sequelae, including motor coordination problems (n=1) and hemianopia (n=2); none developed cerebral palsy or post-neonatal epilepsy.

Discussion

ICH is an important cause of brain injury in the neonatal population and despite the substantial advances in perinatal medicine in the past few decades, it continues to be a burdensome health issue in the NICU.[2] The infants reported in this case series all presented with severe symptoms due to a large intra- and extra-axial cerebral hematoma causing increased intracranial pressure with midline shift and were managed at the bedside with an ultrasound-guided needle puncture with an immediate improvement of their symptoms. To the best of our knowledge, this is the first series of newborn infants with a combined intra- and extra-axial hemorrhage presenting with a midline shift managed with this method.

Table 1: Characteristics of the newborns with intracranial hemorrhage, their clinical features, follow-up aspects and outcome

Case	Sex	GA	Weight (g)	Mode of Delivery	Presenting Symptom	Laboratory	Location of the Hemorrhage	Amount Aspirated (ml)	Follow-up Neuroimaging	Etiology	Neurologic Outcome
1	M	$31^{1/7}$	1050	C/S	Respiratory failure, full fontanelle on day 1	Hb:6.5 mmol/L Plt:42,000/μL PT/aPTT:Normal	Left temporal-parietal, left subdural, left GM-IVH (+) midline shift (+)	20	Cystic evolution in the parenchyma, mild PHVD gradually normalizing on MRI	SGA, perinatal asphyxia, thrombocytopenia	Current Status: 5.5 year-old, developmental coordination disorder, attending mainstream school
2	M	$39^{4/7}$	3785	C/S	Left-sided clonic seizure on day 2	Hb:7.8 mmol/L Plt:Normal PT/aPTT:Normal	Right parieto-occipital, subarachnoid, subdural, PWML, bilateral GM-IVH (+) midline shift (+)	7	Arachnoid cyst, ex-vacuo dilatation of right ventricle on MRI	Mild acidosis at birth, heterozygous for FV Leiden mutation	Current Status: 1.5 year-old, hemianopia on the left eye, convergent strabismus, favorable outcome
3	M	$31^{6/7}$	1285	C/S	Irritability, recurrent apneas, full fontanelle on day 1	Hb:12.8 mmol/L Plt:14,000/μL PT:22s, aPTT:55s	Left temporal and subarachnoid, bilateral GM-IVH (+) midline shift (+)	12	Arachnoid cyst in the left parieto-temporal region on MRI	SGA, arachnoid cyst, thrombocytopenia	Current Status: 3 year-old, helmet for plagiocephaly favorable outcome
4	F	$41^{0/7}$	3270	NSD	Right-sided hemiconvulsions on day 1	Normal	Left parietal, left subarachnoid midline shift (+)	24	Residual hemorrhage in the left parietal lobe, mild left ventricular dilatation	Unknown	Current Status: 10 mo. old, favorable outcome
5	M	$37^{0/7}$	1900	C/S	Feeding intolerance, recurrent apneas, respiratory failure, clonic seizure on day 1	Hb:7.4 mmol/L Plt:Normal PT/aPTT:Normal	Right subarachnoid, subdural right temporal lobe diffusion restriction on DWI, midline shift (+)	7	Resolution of the hematoma with volume loss in temporal lobe, ex-vacuo dilatation of right temporal horn on MRI	SGA, Vacuum extraction during C/S	Current Status: 6 mo. old, slightly asymmetrical motor function on lower extremities
6	M	$36^{6/7}$	2555	NSD	Hyperexcitability, hypoglycemia, apnea, seizures on day 1	Hb:9.9 mmol/L Plt:138,000/μL PT/aPTT:Normal	Left subdural, periphery of the cerebellum, midline shift (+)	20	Resolution of the hemorrhage, right posterior cerebral artery infarct, residual right thalamic hemorrhage on MRI	Assisted delivery for breech presentation	Current status: 14 year-old, Hemianopia on the right eye, slightly slower motor milestones compared with his twin brother, no cerebral palsy
7	F	$38^{1/7}$	2470	NSD	Recurrent apneas, right-sided hemiconvulsions on day 1	Hb:7.4 mmol/L Plt:161,000/μL PT:18s, aPTT:38s	Left subdural, ischemia in frontal, parietal and temporal lobes, midline shift (+)	34	Cortical and subcortical abnormalities on DWI, reduction in the size of the hematoma on MRI	Assisted delivery with vacuum extraction	Current status: 6 mo. old, cessation of seizures after the procedure, no asymmetry
8.	F	$40^{3/7}$	3265	NSD	Recurrent apneas, right-sided hemiconvulsions, bradycardia and high blood pressure on day 2	Hb:7.9 mmol/L Plt:247,000/μL PT:16s, aPTT:39s	Left subdural, ischemia in frontal, parietal and temporal lobes, midline shift (+)	23	Developed hydrocephalus on MRI	Unknown	Current status: 5 mo. old, required a VP-shunt for hydrocephalus

Bedside percutaneous needle aspiration is a non-surgical minimally invasive technique in which the exact site and depth of needle insertion can be determined under ultrasound guidance. Given the major risks of a standard neurosurgical decompression procedure in an unstable neonate, including transfer of the infant to the operating theatre, administering general anesthesia and further deterioration of the hemodynamic status, and possible severe changes in cerebral perfusion due to craniotomy, a less invasive method may inevitably be more favorable. Although there are anecdotal reports in the literature on needle aspiration of intracranial hematoma, the cases presented had extra-axial hemorrhages, without intra-axial components (Table 2).[5–8,11,12] In 1983, Aoki[8] reported the association of an epidural hematoma with a depressed skull fracture and in his report, he stated that the successful management of this condition was achieved by aspiration of the liquefied hematoma rather than surgical removal. Later on, Negishi et al[11] and Yamamoto et al[12] reported further successful management of newborn infants with an extra-axial epidural hemorrhage with the aspiration technique and the latter stated that surgical procedures should be attempted only if aspiration turns out to be ineffective. One might wonder whether the thick and semisolid nature of the hematoma could prevent it from being aspirated; however, since the very early reports, it has been noted that the majority of the neonatal intracranial hematomas displayed liquid characteristics.[6,8–10] Noguchi et al[6] indicated that neonatal ICH was more liquefied in nature compared with its adult counterpart and showed a tendency to solidify over time, which allows needle aspiration. Consistent with the literature, all of the newborns described in our series demonstrated a liquefied hematoma, which was easily aspirated. Parents were counselled on the risks, including failure of the technique to evacuate the hematoma, the risk of a new hemorrhage during or after the procedure and further damage to the cerebral tissue; yet none of the aforementioned complications were observed, although in case 8 brain tissue appeared to be part of the aspirated fluid, probably from the damaged occipital lobe due to the intracranial bleeding component. With cUS guidance during the procedure, both the assessment of the tip of the catheter and real-time visualization of the volume of the hematoma could be achieved.[6] Improvement in the success rate of needle insertion under ultrasonographic guidance would prevent blinded multiple puncture attempts, thus controlling the symptoms more rapidly in a compromised infant, while reducing the risk of coalescence of the needle tracks to form a porencephalic cystlike lesion and eliminating the risk of vascular injury with the addition of Doppler color flow.[13] Additionally with cUS, the best puncture site in relation with the nearest suture could be assessed.

Anatomically, ICH is classified as epidural, subdural, subarachnoid, intraventricular, or parenchymal, and involvement of more than one compartment is possible.[1,14] In the preterm infant, ICH occurs with an estimated incidence of 20% to 25% within the first 3 days after delivery in the form of GMH-IVH and the average incidence of

a parenchymal hemorrhage is reported to be between 5% and 11%.[15,16] However, in the term population, it is difficult to determine its true incidence, since not all term newborns with ICH present with clinical events and it is stated in the literature that asymptomatic ICH in term newborns is much more frequent than previously thought.1 Looney et al[14] reported the prevalence of asymptomatic ICH after vaginal delivery in term newborns to be as high as 26% in their MRI study. Whitby et al[17] described nine neonates with an asymptomatic subdural hemorrhage and could show birth trauma as the responsible factor in only two of these infants. The authors stated that a subdural hematoma was not necessarily due to evident birth trauma. Today, it is well-known that in the majority of the neonates, ICH occurs spontaneously or related to a clotting defect such as allo- or iso-immune thrombocytopenia, a mutation in the COL4A1 or COL4A2 gene, hemorrhagic transformation after arterial stroke, sinovenous thrombosis, especially when associated with a thalamic hemorrhage, or as the result of a vascular malformation.[1,17–22]

The risk of ICH is higher in newborns with hemophilia if they were born by assisted vaginal delivery rather than C/S; whereas von Willebrand disease is not reported to be a common cause of ICH probably due to the physiologic rise in the factor level shortly after birth.[23,24] We saw thrombocytopenia in two of our cases and in both cases, congenital causes of bleeding diathesis, perinatal infections and alloimmune thrombocytopenia were ruled out. Fetal growth restriction in both cases, as well as the perinatal asphyxia in one, might explain the thrombocytopenia. Dystocia necessitating vacuum extraction could well explain the intracranial events in two of our infants; however, we could not delineate any etiologic explanation for the 2nd and 4th case, although the former demonstrated mild metabolic acidosis and was heterozygous for factor V Leiden mutation. Occasionally, a parenchymal hemorrhage is accompanied by a subdural and/or subarachnoid extra-axial component and in most cases, it involves a single hemisphere.[1,18] This was most prominent in the second and the third case with a large hemorrhage into the arachnoid cyst accompanying the parenchymal hemorrhage (Table 1). Arachnoid cysts are reported in the literature either as a developmental process or secondary to trauma, hemorrhage and inflammation. Palin et al[25] reported a neonate who had ICH after the development of an arachnoid cyst and suggested a reverse causal relationship. Regardless of the primary focus, a therapeutic intervention to remove an intra- or extra-axial hematoma becomes essential when it causes neurologic findings such as seizures and compression of the adjacent cerebral tissues, leading to a midline shift or herniation.[6,11] We saw seizure activity on aEEG and a midline shift on cUS in all of our cases and dramatic improvement in these findings on serial monitoring after the intervention. Cessation of the status epilepticus was evident in two cases and is noteworthy as a potential major benefit of this bedside intervention. ICH has also the potential for severe long-term adverse neurological outcomes. Prematurity,

presence of perinatal asphyxia, the extent of injury, early onset of repetitive seizures or status epilepticus, and the need for more than one antiepileptic drug to control seizures were associated with an unfavorable outcome.[1,26] Klinge et al[27] showed that ICH is a major risk factor for neurodevelopmental morbidity including psychomotor retardation and cerebral palsy in infants with hemophilia. The newborns in our series presented with one or more of these risk factors; however, we saw a surprisingly favorable clinical outcome during the follow-up of these infants, normal scores for their ages on the neuro-developmental tests, and apparent improvements in their subsequent neuroimaging findings. We speculate that the relatively good outcome of these infants despite the presence of such risk factors might be due to the timely intervention and effective removal of the extra-axial component of these large space-occupying lesions with a minimally invasive method at the bedside without further compromising the clinical condition.

In summary, we described eight newborn infants presenting with overt clinical symptoms including seizure, apnea, and respiratory failure within the first 2 days after birth. All showed a clear midline shift due to an intra- and extra-axial ICH on neuroimaging. We saw a dramatic improvement in the symptoms with this minimally invasive aspiration technique guided by cUS performed at the bedside. We observed no complications during or after the procedure in our infants and the subsequent scans showed disappearance of the midline shift and resolution of the hematoma after the procedure. The neurologic outcome of the infants was rather favorable, all achieving results within the normal range on neurodevelopmental tests.

Conclusion

Bedside ultrasound-guided percutaneous needle aspiration technique should be considered for the management of large hemorrhages with both intra- and extra-axial components, especially in infants with ongoing seizures, before performing neurosurgical trepanation.

Table 2: Characteristics of reported cases in the neonatal literature that were managed with needle aspiration.

Author, Year	No. of Patients	Delivery Method	Assist in Delivery	Type of Hemorrhage	Location of Hemorrhage	Other Lesions	Ultrasound Guidance	Complication After Procedure	Outcome
Aoki[8], 1983	1	NSD	Vacuum	Epidural	Parietal	Cephalhematoma, skull fracture	No	-	Favorable
Negishi et al.[11] 1989	3	NSD in all	Forceps in 1	Epidural	Parietal in 2 Fronto-parietal in 1	Cephalhematoma, skull fracture in all	No	-	Favorable in all
Yamamoto et al.[12] 1995	1	NSD	-	Epidural	Parietal	Cephalhematoma, skull fracture	No	-	Favorable
Vachharajani et al.[5] 2002	1	C/S	Vacuum prior to C/S	Epidural and PH	Frontal	Subgaleal hemorrhage, depressed skull fracture	Yes	-	Favorable
Vinchon et al.[3] 2005	5	NSD in all	Vacuum in 2, Forceps in 1	Epidural in 1, subdural in 4, PH in 2	Variable	Skin swelling in 3, skull fracture in 1, cheek wound in 1	No	-	Favorable in 4, poor in 1 with severe hypotonia
Noguchi et al.[6] 2010	1	NSD	Vacuum	Epidural	Parietal	Cephalhematoma, depressed skull fracture	Yes	-	Favorable
Smets et al.[7] 2010	1	NSD	Vacuum	Epidural	Parieto-occipital	Cephalhematoma	No	Required second puncture	Favorable
Present Study	8	NSD in 4 C/S in 4	Vacuum in 2	PH in 5, GMH-IVH in 3, subarachnoid in 5, subdural in 6	Variable	Midline-shift in all infants	Yes	-	Favorable in 1, mild sequelae in 3, 4 below 12 months old

References

1. Gupta SN, Kechli AM, Kanamalla US. Intracranial hemorrhage in term newborns: management and outcomes. Pediatr Neurol 2009;40:1-12
2. Inder TE, Perlman JM, Volpe JJ. Preterm Intraventricular Hemorrhage/Posthemorrhagic Hydrocephalus. In: Volpe JJ, Inder TE, Darras BT, de Vries LS, du Plessis AJ, Neil J, Perlman JM eds. Neurology of the Newborn. Philadelphia: Elsevier/Saunders; 2017:637-698
3. Vinchon M, Pierrat V, Tchofo PJ, Soto-Ares G, Dhellemmes P. Traumatic intracranial hemorrhage in newborns. Childs Nerv Syst 2005;21:1042-1048
4. Bassan H. Intracranial hemorrhage in the preterm infant: understanding it, preventing it. Clin Perinatol 2009;36:737-762
5. Vachharajani A, Mathur A. Ultrasound-guided needle aspiration of cranial epidural hematoma in a neonate: treating a rare complication of vacuum extraction. Am J Perinatol 2002;19:401-404
6. Noguchi M, Inamasu J, Kawai F, et al. Ultrasound-guided needle aspiration of epidural hematoma in a neonate after vacuum-assisted delivery. Childs Nerv Syst 2010;26:713-716
7. Smets KJ, Vanhauwaert D. Treatment of cranial epidural hematoma in a neonate by needle aspiration of a communicating cephalhematoma. Eur J Pediatr 2010;169:617-619
8. Aoki N. Epidural hematoma communicating with cephalhematoma in a neonate. Neurosurgery 1983;13:55-57
9. Takagi T, Nagai R, Wakabayashi S, Mizawa I, Hayashi K. Extradural hemorrhage in the newborn as a result of birth trauma. Childs Brain 1978;4:306-318
10. Merry GS, Stuart G. Extradural hematoma in the neonate. Case report. J Neurosurg 1979;51:713-714
11. Negishi H, Lee Y, Itoh K, et al. Nonsurgical management of epidural hematoma in neonates. Pediatr Neurol 1989;5:253-256
12. Yamamoto T, Enomoto T, Nose T. Epidural hematoma associated with cephalohematoma in a neonate - case report. Neurol Med Chir (Tokyo) 1995;35:749-752
13. Brouwer M. Treatment and Outcome of Neonatal Haemmorrhagic Brain Injury [Ph.D. dissertation]. Utrecht: University Medical Centre Utrecht; 2011
14. Looney CB, Smith JK, Merck LH, et al. Intracranial hemorrhage in asymptomatic neonates: prevalence on MR images and relationship to obstetric and neonatal risk factors. Radiology 2007;242:535-541
15. De Vries LS, Van Haastert IL, Rademaker KJ, Koopman C, Groenendaal F. Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. J Pediatr 2004;144:815-820
16. Groenendaal F, Termote JU, van der Heide-Jalving M, van Haastert IC, de Vries LS. Complications affecting preterm neonates from 1991 to 2006: what have we gained? Acta Paediatr 2010;99:354-358.
17. Whitby EH, Griffiths PD, Rutter S, et al. Frequency and natural history of subdural haemorrhages in babies and relation to obstetric factors. Lancet 2004;363:846-851
18. Brouwer AJ, Groenendaal F, Koopman C, Nievelstein RJ, Han SK, de Vries LS. Intracranial hemorrhage in full-term newborns: a hospital-based cohort study. Neuroradiology 2010;52:567-576
19. de Vries LS, Koopman C, Groenendaal F, et al. COL4A1 mutation in two preterm siblings with antenatal onset of parenchymal hemorrhage. Ann Neurol 2009;65:12-18
20. Carpenter AM, Singh IP, Gandhi CD, Prestigiacomo CJ. Genetic risk factors for spontaneous intracerebral haemorrhage. Nat Rev Neurol 2016;12:40-49
21. Sandberg DI, Lamberti-Pasculli M, Drake JM, Humphreys RP, Rutka JT. Spontaneous intraparenchymal hemorrhage in full-term neonates. Neurosurgery 2001;48:1042-1048

22. Wu YW, Hamrick SE, Miller SP, et al. Intraventricular hemorrhage in term neonates caused by sinovenous thrombosis. Ann Neurol 2003;54:123-126
23. MacLean PE, Fijnvandraat K, Beijlevelt M, Peters M. The impact of unaware carriership on the clinical presentation of haemophilia. Haemophilia 2004;10:560-564
24. Chalmers EA. Neonatal coagulation problems. Arch Dis Child Fetal Neonatal Ed 2004;89:475-478
25. Palin M, Anderson I, O'Reilly G, Goodden JR. A suprasellar arachnoid cyst resulting from an intraventricular haemorrhage and showing complete resolution following endoscopic fenestration. BMJ Case Rep 2015;29:1
26. Pisani F, Cerminara C, Fusco C, Sisti L. Neonatal status epilepticus vs recurrent neonatal seizures: clinical findings and outcome. Neurology 2007;69:2177-2185
27. Klinge J, Auberger K, Auerswald G, Brackmann HH, Mauz-Korholz C, Kreuz W. Prevalence and outcome of intracranial haemorrhage in haemophiliacs--a survey of the paediatric group of the German Society of Thrombosis and Haemostasis (GTH). Eur J Pediatr 1999;158:162-165

“The supreme guide in life is knowledge”

Mustafa Kemal Atatürk

9

General Discussion
Conclusions
Directions for Future Research

General Discussion

Origins of the Research Questions

Despite major advances in medical technology used in neonatal intensive care units over the last decades as well as ongoing progress in our understanding of neonatal neurological disorders, and significant strides forward in providing both perinatal and neonatal care, germinal matrix hemorrhage and intraventricular hemorrhage (GMH-IVH) still remain a common complication in the preterm population.[1] The implications of this condition for the long-term neurodevelopmental outcomes are diverse and determined also by a multitude of factors among which the degree of prematurity and coexisting systemic conditions are of utmost importance.[2-4] However, to what extent the coexisting conditions, such as chronic lung disease of prematurity, necrotizing enterocolitis, and culture-positive sepsis, will play role in the neurodevelopmental outcomes is challenging to predict for clinicians caring for these infants and outcome prediction remains an "art" that requires many years of practice, education, and experience. Therefore, neuroimaging of the newborn brain, by providing "visible" data on the severity and extent of neurological conditions has served as an essential modality for clinicians while caring for newborn infants and counselling parents and caregivers. In this respect, this thesis can be regarded as the product of an objective to create a more robust diagnostic neuroimaging approach to be used in newborns with hemorrhagic brain injury.

Large cohort studies over the last two decades show that neurodevelopmental impairment (NDI) affects up to 40% of those with high-grade GMH-IVH (grade-3 and periventricular hemorrhagic infarction [PVHI], previously called grade-4 GMH-IVH). Cerebral palsy (CP), the most common childhood motor disability, is also more common among these infants at pre-school age, especially for those with a PVHI.[2-4] Higher rates of impairment in motor function and learning issues at school-age are also expected in preterm infants with high-grade GMH-IVH.[5] However, data on the association of low-grade GMH-IVH (grade-1 and grade-2) and neurodevelopmental outcomes are inconsistent. While it does not appear to be directly related to NDI in some studies,[4,6] others have reported an increased rate of NDI in infants with low-grade GMH-IVH.[2,3] It is also important to take into account the effect of white matter injury when assessing infants with low-grade GMH-IVH.[7,8] In the present thesis, the emphasis was on the high-grade GMH-IVH, which is discussed in Chapters 2 through 5.

The most critical research question we aimed to address in this thesis was 'when best to treat post-hemorrhagic ventricular dilatation (PHVD)' which has been a hot topic of neonatal neurology for several decades.[9] In a seminal study, Whitelaw et al.[10] randomly assigned 70 preterm infants with a gestational age of 24 to 34 weeks who had progressive PHVD to either (1) drainage, irrigation, and fibrinolytic therapy (DRIFT group) to wash out hemorrhagic cerebrospinal fluid (CSF) or (2) tapping of CSF

by ventricular reservoir to control further ventricular expansion (standard treatment group). The composite outcome of death or ventriculoperitoneal shunt (VPS) rate was similar between the groups (44% and 50%, respectively); however, 35% of infants in the DRIFT group had secondary intraventricular hemorrhage (IVH) compared with 8% in the standard treatment group. Despite an increase in secondary IVH, among the survivors, 31% in the DRIFT group had severe cognitive disability versus 59% in the standard treatment group at 2 years of age.[11] The reduction in severe cognitive disability in the DRIFT arm persisted until school age, and the investigators showed that survival without severe cognitive disability was 66% in the DRIFT group and 35% in the standard treatment group.[12] In this respect, DRIFT was the first intervention for PHVD to objectively demonstrate sustained cognitive improvement; however, the increase in secondary IVH related to this approach remains a concern.[13]

The ELVIS (Early versus Late Ventricular Intervention Study, ISRCTN43171322) project was an international collaborative effort to address this long-lasting debate on when and how to intervene in PHVD. In this prospective controlled trial, a total of 126 preterm infants of ≤34 weeks' gestational age with progressive PHVD were included between the years of 2006 and 2016 at 14 centers in 6 countries across Europe and North America. Infants were eligible for the trial when they had a GMH-IVH grade-3, with or without PVHI. Recruited infants were then randomly allocated to either low-threshold group (intervention when an increase in ventricular index (VI) according to Levene[14] above the 97th percentile line showing an increase towards the 97th percentile + 4 mm line, but before crossing the p97 + 4 mm line; and an increase in diagonal anterior horn width (AHW) according to Davies et al.[15] of >6 mm and towards 10 mm) or high-threshold group (intervention when the VI crossed the 97th percentile + 4 mm line and the AHW was >10 mm). Interventions started with lumbar punctures (LP) with a maximum number of 3, and if necessary, this was followed by tapping from a subcutaneous ventricular reservoir, aiming for ventricular index <97th percentile line in both study arms within the next 7 days. Once or twice daily, 10 mL/kg were removed based on cUS measurements. Reservoir taps were continued until ventricular stabilization was documented. An infant with an ongoing requirement of reservoir taps when weight reached 2000-2500 g was challenged and when punctures were needed once again, deemed eligible for a VPS, if permanent CSF diversion is required.

It is important to re-emphasize that the interventions for both arms of the ELVIS trial were solely based on ultrasonographic criteria and initiated while the infants were still asymptomatic. Another important aspect of the ELVIS trial was that it aimed to bring the ventricular size down <97th percentile in both groups, whereas the previous studies focused on preventing further ventricular dilatation.[10,16-18] The aim was to test the hypothesis that low-threshold intervention reduces death and/or the need for VPS when compared with high-threshold intervention. Although no further reduction in

the need for a VPS in the low-threshold group was found, the need for VPS placement in both study arms was the lowest reported in the literature (19% and 23% in the low-threshold and high-threshold groups, respectively). In the low-threshold group, the number of infants who received temporizing interventions with LPs or ventricular reservoir was significantly higher than in the high-threshold group and whether this increase in additional interventions in the low-threshold group will be associated with preservation of brain volumes and improved neurodevelopmental outcome needed to be determined.[19] These two research questions were the origins of the hypotheses that were addressed in **Chapters 3 and 4**.

While there is an emphasis in this thesis on neuroimaging characteristics and associated neurodevelopmental outcomes of high-grade GMH-IVH, two chapters (Chapters 6 and 7) also focused on complications related to neurosurgical interventions for PHVD and their associations with neurodevelopmental outcomes. Finally, one chapter (Chapter 8) investigated the use of ultrasound-guided percutaneous needle aspiration as a bedside technique in unstable newborn infants with extra-axial hemorrhage.

Part-I: Neuroimaging Characteristics of High-Grade GMH-IVH and Association with Neurodevelopmental Outcomes

Neuroimaging with cranial ultrasonography (cUS) is the mainstay of diagnosis of GMH-IVH and follow-up of complications; however, most preterm infants with high-grade hemorrhage will also need a brain magnetic resonance imaging (MRI) at term-equivalent age (TEA-MRI) to determine the extent of the hemorrhagic injury and to detect accompanying white matter changes and possible cerebellar lesions not detected with cUS, as outlined in a recent review article by Inder et al.[8] The detrimental effect of PVHI on the developing brain has been demonstrated with advanced MRI techniques; however, cUS remains the preferred initial imaging tool for the detection and monitoring of PVHI.[20] cUS studies by Bassan et al.[21,22] from almost two decades ago described the sonographic characteristics of PVHI, with the majority of cases being unilateral and involving the frontal and parietal lobes and its close association with NDI. In **Chapter 2**, we investigated the sonographic characteristics of PVHI and their trends between 2008 and 2013 and sought to describe their association with neurodevelopmental outcomes on a large number of preterm infants with PVHI. The distinguishing feature of this study was the quantitative measurement of PVHI size while also using an objective scoring system specifically developed for the assessment of PVHI that has been shown to correlate with neurodevelopmental outcomes.[21] Our aim was to test the hypothesis that later study years would be associated with a decrease in incidence, more benign sonographic findings and better neurodevelopmental outcomes in infants with PVHI. However, in contrast to our hypothesis, no changes were seen over the study period

with respect to sonographic characteristics. In keeping with the previous literature, PVHI was commonly associated with an ipsilateral grade-3 GMH-IVH, located in the parietal lobe, globular in shape, reached its maximum extent by the end of the first postnatal week, and evolved into a single large porencephalic cyst in most cases in the chronic phase.[21,23,24]

As expected, the presence of PVHI was found to be an independent risk factor for NDI that was observed in around one-third of surviving infants. In comparison to the previous studies reporting cognitive impairment in half and motor impairment in nearly two thirds of affected infants, our findings appear more favorable.[23-27] The most notable finding was the CP rate of 42%, which was relatively lower than reported in the literature.[22,23] Of note, 81% of the infants with CP were functioning at gross motor function classification system (GMFCS) level 1 or 2, which indicates that these infants were walking independently. Also of note, PVHI size and severity score were negatively associated with gross motor scores and infants with trigone involvement were more likely to develop CP. This latter finding shows the relationship between the location of PVHI, and especially trigone involvement, and CP as was first described by Rademaker et al.[26] and later refined by Dudink et al.[27] by relating PVHI subtypes to the affected veins. Efforts to describe the anatomic location of PVHI in more detail by using cUS is essential as it will help clinicians in predicting possible outcome trajectories and introduce targeted rehabilitation programs early in infancy to maximize the effect of neural plasticity.

In **Chapter 3**, in a nested substudy of the ELVIS trial, we aimed to compare the extent of brain injury and quantify brain volumes at term-equivalent age in infants with PHVD randomized to low-threshold and high-threshold intervention groups. In this study, we applied a validated scoring system described by Kidokoro et al.[28] to objectively assess brain injury. To reliably examine the quantitative impact of the injury on various brain regions, we also performed volumetric analysis using the automatic segmentation method, which was previously developed by our group.[29] Because of the use of a convolutional neural network technique, which was trained on segmented images of preterm infants without any brain pathology in the main study site, almost half of all segmented MRIs in infants with PHVD showed suboptimal image quality and could not be included in the volumetric analysis. Therefore, with an aim to maximize the number of infants assessed for ventricular volumes we also calculated the frontal and occipital horn ratio (FOHR), which was shown to have a strong correlation with the ventricular volumes in infants with PHVD.[30]

Among the survivors, MRI could not be obtained in 22 infants due to logistic reasons and the final sample consisted of 88 infants with an equal number of infants in each study arm. The most noteworthy finding was the smaller ventricular volumes in the low-threshold group, despite the fact that slightly over half of all infants could be included

in the volumetric analysis. As expected, FOHR showed a more significant difference between the groups, being lower in the low-threshold group. We found that infants who were in the low-threshold group had lower global brain abnormality scores and after excluding infants with PVHI, the combination of the white matter and gray matter volumes was higher in the low-threshold group, which demonstrates the negative effect of enlarged ventricles on the surrounding brain parenchyma. When stratified based on their brain abnormality scores, normal or mildly abnormal scores were more commonly seen in the low-threshold group. Infants in the high-threshold group also more commonly demonstrated a delay in myelination and more often had thinning of the corpus callosum (CC), which can be attributed to the effect of white matter volume loss as well as compression caused by enlarged ventricles. In this nested substudy of the ELVIS trial, using an objective brain injury assessment together with the quantification of the ventricular dilatation, we were able to document the beneficial neuroimaging effects of earlier intervention in the setting of PHVD.

Our findings were in line with those of the previous study by Jary et al.[31] who measured total cerebral volumes by using manual segmentation and demonstrated that brain growth is significantly impaired in PHVD. One might think that the beneficial effects of the earlier intervention on brain injury and brain volumes observed in our nested substudy can partly justify the increase in the need for LPs and reservoir insertions observed in the ELVIS trial. However, to fully justify the increase in the number of interventions, better neuroimaging findings should also translate into more favorable neurodevelopmental outcomes in infants receiving earlier interventions. Whether the smaller ventricular volumes and less brain injury in infants who underwent low-threshold therapy will be associated with improved neurodevelopmental outcomes in the ELVIS trial was addressed in **Chapter 4**.

In **Chapter 4**, we assessed neurodevelopmental outcomes of the ELVIS cohort at 2 years corrected age to test the hypothesis that earlier intervention would result in improved neurodevelopmental outcomes. In 92% of the surviving infants, outcomes were assessed as part of the standard follow-up protocol and the composite adverse neurodevelopmental outcome was defined as death, CP, or cognitive/motor score <-2 SD on the Bayley Scales of Infant Development, second edition or the Bayley Scales of Infant and Toddler Development, third edition. An important aspect of this study was that all GMFCS levels of CP and all infants with cognitive/motor score <-2 SD were included as a composite outcome measure rather than focusing only on non-ambulatory CP and cognitive/motor score <-3 SD. Although there was no difference between the low-threshold (35%) and high-threshold (51%) groups in regards to the composite outcome; in the post-hoc analysis, the low-threshold intervention was associated with a decreased risk of an adverse outcome after correcting for gestational age, the severity of GMH-IVH, and cerebellar hemorrhage. Of note, a larger FOHR was

found to be negatively associated with the cognitive and motor scores irrespective of group allocation. This observation supports our hypothesis that draining CSF earlier based on cUS measurements may prevent further brain injury by removal of blood components and inflammatory substances, and alleviating direct injury to the adjacent brain parenchyma. Preserved ventricular volumes with potentially better outcomes seem to justify the increase in additional interventions in the low-threshold group.

Also of note, similar to the findings of Leijser et al[32], infants in the low-threshold group requiring a VPS had cognitive and motor scores that were similar to those without a VPS, and in contrast, infants in the high-threshold group who required a VPS had lower cognitive and motor scores compared with those without. In summary, **Chapter 4** demonstrates the beneficial effect of an earlier intervention for PHVD on reducing mortality and neurodevelopmental disability.

Over the last decade, advanced MRI modalities such as diffusion tensor imaging (DTI) gained popularity in brain research. DTI allows the assessment of fiber tracts in the developing brain by utilizing the three-dimensional anisotropy of water diffusion and provides objective and predictable indices of white matter development and injury.[33,34] In **Chapter 5**, we aimed to assess white matter microstructure using DTI in infants with PHVD and hypothesized that PHVD may adversely affect the vulnerable maturational processes in the white matter and neurodevelopmental outcomes at 2 years corrected age. This study was conducted on an exclusive cohort of extremely preterm infants <28 weeks' gestation with PHVD, and in keeping with our hypothesis, we found lower fractional anisotropy and higher radial diffusivity values in CC in infants with PHVD compared to that of controls. These findings indicate impaired microstructure of the CC, which is located in close proximity to the dilated ventricles. Expectedly, cognitive and motor scores were less favorable in infants with PHVD and fractional anisotropy values of the CC were associated with both cognitive and motor scores at 2 years corrected age.

Chapter 5 also underscores the deleterious effects of a coexisting PVHI on the developing brain as also outlined in **Chapter** 2. The corticospinal tract (CST) has been shown to be vulnerable to axonal injury caused by ipsilateral PVHI.[35] In infants with PVHI, ipsilateral fractional anisotropy values of the CST showed a trend towards decrease reflecting the possible impact of PVHI affecting the maturational processes in the CST. The number of infants in this subgroup analysis was limited, which might have prevented this trend from reaching statistical significance. The axonal injury due to PVHI is commonly referred to as pre-Wallerian degeneration, which can be visualized early with DTI.[35] Interestingly, we did not observe impaired DTI values in CST in infants with isolated PHVD, which might be due to the protective effect of early intervention for PHVD in the majority of the infants studied. In **Chapter 3**, we had found that almost twice as many infants undergoing high-threshold intervention (52% vs 27%) showed

significant myelination delay in their CST. These similar observations in **Chapters 3 and 5** also support our hypothesis that timely interventions may prevent vulnerable regions of the developing brain from disturbances caused by PHVD.

Part-II: Neurosurgical Interventions for Hemorrhagic Brain Injury and Related Complications

The most common cause of hydrocephalus in newborns is PHVD; however, hydrocephalus can also occur due to obstruction of CSF pathways by genetic, developmental, and acquired conditions.[36,37] The mainstay of management is alleviation of increased CSF volume with interventions.[36-38] In Part-II of this thesis, we addressed neurosurgical interventions used for the treatment of PHVD and possible adverse events due to these interventions and their association with neurodevelopmental outcomes. However, we also included preterm and term infants with congenital causes of hydrocephalus while examining this association in **Chapters 6 and 7**.

Placement of a reservoir with an aim to withdraw CSF is a commonly used technique in infants with hydrocephalus.[39] This technique is usually the initial neurosurgical approach due to high CSF concentrations of blood products, clinical instability that is usually observed in the acute phase of the disease as well as unsuitability of the small peritoneal cavity for a permanent shunt system.[37] We observed a subgroup of infants who developed intraparenchymal hemorrhage (IPH) after serial ventricular reservoir taps, which has been previously reported in infants with VPS, but not in infants with reservoir insertion.[40] In **Chapter 6**, we sought to describe the characteristics of IPH and its association with neurodevelopmental outcomes. We hypothesized that rapid reduction of ventricular volumes with serial reservoir taps might cause IPH and assessed the neuroimaging features of this phenomenon and its association with neurodevelopmental outcomes at 2 years. We found that IPH can be caused by a rapid reduction of the ventricular volume during the first week after the commencement of serial reservoir taps. It has been postulated that the immature cerebral vasculature of the newborn may not fully tolerate and rupture as a consequence of the sudden change in cerebral perfusion pressure, which likely explains why we observed this phenomenon following rapid reservoir taps.[40] Among the infants with IPH, around two-thirds had multifocal IPH and hemorrhage was equally distributed in the periventricular and subcortical regions of the brain. None of the hemorrhages were around the reservoir track, which was similar to what has been described in the literature following VPS insertion.[40] cUS enabled early detection of the periventricular IPH similar to what we observed for PVHI in **Chapter 2**; however, the majority of the subcortical IPHs were only noted with TEA-MRI, which highlights the importance of obtaining TEA-MRI. We found that the presence of multifocal IPH was negatively associated with cognitive outcomes probably due to volume loss in multiple areas of the brain. In summary, **Chapter 6** shows

the importance of performing serial cUS scans to guide the amount of CSF removal via reservoir taps in the management of infants with hydrocephalus and obtaining TEA-MRI for better recognition of the findings, especially when subcortical.

Chapter 7 was based on our observation that a subset of infants with PHVD had penetrating CC injury following neurosurgical interventions. Although complications of neurosurgical interventions for PHVD such as obstruction in the catheters and secondary infection are well-documented, direct injury to the CC was a novel observation that has not been reported previously. Thus, in **Chapter 7** we aimed to provide insight into this phenomenon and hypothesized that this pattern of injury may impact CC maturation and subsequently cause impaired neurodevelopmental outcomes at 2 years of age. Based on our assessment of a considerable number of brain MRIs (n=269), we observed a high rate of piercing CC injury (41%) following neurosurgical interventions in this study. The majority of these injuries were due to reservoir insertions and the most notable finding was that the CC was thinner in infants with injury when compared with infants with PHVD who had intact CC and control infants. It is well-known that genetic, metabolic, and infectious disorders, as well as hemorrhagic and ischemic brain injury, can cause thinning of the CC; however, an iatrogenic cause due to neurosurgical intervention has not been reported in the neonatal literature.[41] We had presented in **Chapter 3** that, PHVD can also cause thinning of the CC as one-third of the infants undergoing high-threshold intervention showed thinning of the CC, a much higher rate than that of infants in the low-threshold group. Thinning of the CC in infants with PHVD can be explained by white matter volume loss as well as compression caused by dilated ventricles.[41] Findings of the present study shows us that maturational disturbances in the CC in infants with PHVD are not only caused by the effect of PHVD but can also be seen secondary to interventions for PHVD. We speculate that using cUS for real-time visualization of the ventricles during neurosurgical interventions may be used to avoid CC injury if supported by future studies. Contrary to our hypothesis, CC injury was not independently associated with cognitive and motor outcomes at 2 years of age; however, it is important to emphasize that at this early age we used standard neurodevelopmental tests to assess outcomes and could not yet use tests that are specifically developed to evaluate cognitive functioning and visuospatial integration that are commonly affected in infants with CC injury.

Finally, in **Chapter 8**, we reported on the use of a minimally invasive bedside approach in a series of newborn infants presenting with overt clinical symptoms due to a combined intra- and extra-axial intracranial hemorrhage. It should be emphasized that GMH-IVH was present in around one-third of these infants and the pathology depicted in this chapter was different from GMH-IVH, which was discussed in all the other chapters of this thesis. These infants showed a midline shift on neuroimaging and were managed with percutaneous needle aspiration at the bedside, which was

well-tolerated without any complications during or after the procedure. Given the major risks of a neurosurgical decompression procedure in an unstable neonate, including risks related to general anesthesia and craniotomy, this less invasive method can be a promising alternative. The neurologic outcome of the infants in this series was found to be favorable, all achieving results within the normal range on standard neurodevelopmental tests. Future prospective studies are required to confirm our findings before drawing firm conclusions on the use of this minimally invasive bedside approach.

Conclusions and Clinical Implications

The following conclusions can be drawn from this thesis:

- In infants with post-hemorrhagic ventricular dilatation (PHVD), earlier interventions to bring the intraventricular pressure, therefore the ventricular size, down based on ultrasonographic assessments result in smaller ventricular volumes and less brain injury at term-equivalent age (Chapter 3).
- Earlier interventions for PHVD based on ultrasonographic assessments result in reduced composite outcome of mortality and neurodevelopmental disability at 2 years corrected age (Chapter 4).
- Periventricular hemorrhagic infarction (PVHI) continues to be a significant complication in very preterm infants and is an independent risk factor for both cognitive and motor impairment at 2 years corrected age (Chapter 2, 4, and 5).
- Cognitive and motor outcomes are within the normal range in two-thirds, and cerebral palsy (CP) is seen in around 40% of PVHI survivors at 2 years corrected age. The majority (81%) of infants with CP can walk independently. These neurodevelopmental findings appear more favorable when compared to previous studies conducted more than a decade ago (Chapter 2).
- PHVD causes impaired microstructure of the corpus callosum (CC) in extremely preterm infants with PHVD. Fractional anisotropy values of the CC obtained by diffusion-tensor imaging are associated with both cognitive and motor scores at 2 years corrected age (Chapter 5).
- In infants with PHVD, rapid reduction of the ventricular pressure and volume during the first week after the commencement of serial reservoir taps may result in intraparenchymal hemorrhage (IPH) in the periventricular and/or subcortical white matter tissues, and these IPHs can affect cognitive outcomes when multifocal. Therefore, it is essential to perform serial cUS scans to guide the amount of cerebrospinal fluid removal via reservoir taps (Chapter 6).
- Neurosurgical interventions, especially reservoir insertions, can cause injury to the CC and subsequent thinning of the CC. However, this phenomenon does not appear to be related to impaired neurodevelopmental outcomes at 2 years of age (Chapter 7).
- In newborn infants with combined intra- and extra-axial intracranial hemorrhage and a midline shift on neuroimaging, percutaneous needle aspiration at the bedside is well-tolerated without any complications during or after the procedure. This minimally invasive bedside technique can be a promising approach if supported by future prospective studies (Chapter 8).

Future Directions For Research and Clinical Practice

Prevention of GMH-IVH

As outlined in several chapters of this thesis, GMH-IVH continues to be a common form of brain injury affecting around 20% of very preterm infants and remains associated with high rates of NDI, especially when accompanied by parenchymal involvement and progressive ventricular dilatation. Because treatment of GMH-IVH is mainly supportive and aims primarily on timely detection of complications and avoidance of further brain injury, prevention and further reduction of GMH-IVH is of paramount importance. Gentle care strategies including minimal handling of the very preterm infant, minimizing environmental light and noise exposure, maintaining glucose, electrolytes, and body temperature within the normal range have been adopted by many centers caring for these infants over the last decades.[1] A recent multicenter cohort study by de Bijl-Marcus et al.[42] showed a reduced risk of developing GMH-IVH in infants receiving nursing intervention bundles that consisted of maintaining the head in the midline, lifting the head of the incubator and avoidance of flushing and rapid withdrawal of blood, and sudden elevation of the legs. These feasible strategies should be further studied in large-scale prospective studies and implemented in daily practice.

Advanced Neuroimaging and Neuromonitoring for the Early Diagnosis of GMH-IVH and Related Complications

As outlined in Chapter 1, cUS is the most widely used neuroimaging modality to diagnose GMH-IVH due to its high sensitivity for detecting hemorrhagic brain injury and Doppler modes are commonly applied in conventional ultrasonography to visualize the hemodynamic effects of brain injury. In the last two decades, Doppler ultrasound imaging has undergone a paradigm shift with the emergence of ultrafast ultrasonography, which enables complete blood flow mapping of the region of interest and simultaneous access to velocity measurements at a single-pixel level.[43] If used for continuous monitoring of the germinal-matrix region via small electrode-sized probes over the anterior fontanelle, this new modality has the potential to improve our understanding of GMH-IVH, by providing insights on exact timing and associated risk factors. Furthermore, ultrasound elastography, a novel ultrasonography modality that reflects the secondary effects of tissue injury based on its elastic capacity, can be studied in future trials to improve our understanding of the tissue characteristics of injury caused by GMH-IVH.[44]

There is also an ongoing effort to more effectively implement non-invasive neurophysiological monitoring, such as near-infrared spectroscopy (NIRS), to the management of infants with progressive PHVD. Recent studies show that NIRS could

potentially provide clinical data to assist in determining the optimal timing of surgical intervention in these infants.[45,46]

Potential Biomarkers of GMH-IVH and Impending PHVD

Potential diagnostic CSF, plasma, and urine biomarkers of GMH-IVH and impending PHVD can be used to monitor newborn infants who are at increased risk of developing GMH-IVH and progressive PHVD, which in turn can be used to optimize the timing of interventions.[47] Interleukin-6, *S100β* protein, activin, erythropoietin, chemokine ligand-18, brain-type creatine kinase have been shown to be promising for early detection of infants who will go on to develop GMH-IVH; while transforming growth factor-*β*1 and *β*2, matrix metalloproteinase, plasminogen activator inhibitor, and glial fibrillary acidic protein were found to be early biomarkers of impending PHVD.[48]

Recent efforts also focus on tract-specific associations using diffusion-weighted MRI and CSF biomarkers to delineate white matter injury in the context of PHVD. A recent study investigating CSF amyloid precursor protein, neural cell adhesion-1, and L1 cell adhesion molecule at the initiation of PHVD treatment showed that these molecules may provide additional data for examining PHVD-related white matter injury and subsequent developmental impairment.[49] Future proteomics research focusing on biomarkers to understand the possible mechanisms related to hemorrhagic brain injury and associated complications is warranted.[50]

Mesenchymal Stem Cells for GMH-IVH and PHVD

In a series of benchmark studies, Ahn et al.[51] investigated whether intraventricular transplantation of human umbilical cord blood-derived mesenchymal stem cells (MSCs) prevents PHVD development and attenuates brain injury in newborn rats with severe GMH-IVH.[51] In their first study, it was demonstrated that MSCs significantly attenuated PHVD and brain injury due to GMH-IVH. The investigators attributed these neuroprotective effects to the anti-inflammatory effects of MSCs.[51] In their second study, both intraventricular and intravenous transplantation of MSCs had similar therapeutic efficacy in protecting against severe GMH-IVH. The investigators concluded that these findings suggest that the less invasive intravenous route may be an alternative for clinically unstable very preterm infants.[52] In their third study, significant neuroprotection was only demonstrated when MSCs were administered 2 days after the onset of GMH-IVH, but not after 7 days, suggesting beneficial effects of earlier intervention. These three animal studies led to a phase-I human trial in which 9 preterm infants with PHVD received MSCs in incremental doses and no side effects were observed, confirming the safety and tolerability of MSCs.[53] It is evident that administering MSCs in infants with GMH-IVH seems safe and feasible, and these optimistic findings warrant a further phase-II study, which is currently underway (NCT02890953). Ongoing studies also focus

on administering fresh human milk as a source of stem cells via intranasal route in infants with GMH-IVH with an aim to stimulate the repair of damaged brain tissue (NCT04225286).

Pharmacological Agents and Neuroreparative Strategies

Recent advances in neuroscience have shed new insights on the neuroreparative strategies and this progress motivated researchers to further investigate the treatment of GMH-IVH.[54] Several anti-inflammatory agents have been used in animal studies and among these, erythropoietin and melatonin gained popularity as promising agents due to their safety profile and efficacy in reducing neuroinflammation and oxidative injury.[54,55] Among other promising agents, minocycline, for its effects on reducing neuroinflammation, and deferoxamine, via iron chelation and reducing the toxic effects of iron deposits on the developing brain, can be counted.[56-58] If supported by well-designed human studies, these non-surgical treatment options for PHVD may be possible to transform the care of preterm infants with this condition in the near future.[54]

Innovative Neurosurgical Techniques to Reduce Shunt Rate and Improve Outcomes

Over the last decade, newer endoscopic neurosurgical techniques such as ventricular lavage and third ventriculostomy with or without choroid plexus cauterization have been shown to be promising to reduce the need for VPS in infants with PHVD.[59-62] Reported success rates have been variable, which may be attributed to patient selection, operation technique, and experience of the operating surgeon; thus, future prospective randomized multicenter studies are warranted.[60] These intervention strategies may potentially serve as an alternative to VPS in this population in the near future.[38]

Using Neuroimaging Modalities for Their Therapeutic Effects

Intraventricular clot formation in infants with GMH-IVH diminishes CSF circulation leading to its accumulation and thereby causing progressive PHVD.[1] This mechanism presents an opportunity to develop novel treatment strategies to reduce the clot size and enable CSF recirculation. Prior work from Lauer et al.[63] described in a rabbit model that ultrasound energy can be used to accelerate the lysis of clots. Further research on porcine models demonstrated that it is possible to mechanically dissolve intracranial clots by using the therapeutic effects of focused ultrasonography.[64] Combining focused ultrasonography with MR technology, for navigation, has been recently proposed as a novel therapeutic modality to achieve clot lysis and investigated in an intraventricular hemorrhage model by Looi et al.[65] This novel technique steps forward as a promising technique and further studies are warranted to elucidate its effect in animal and human models.

Final Remarks

With significant advances in the field of neonatal neurology, newborns with hemorrhagic brain injury continue to receive the most updated evidence-based therapies from the intra-uterine period through school-age. This thesis shows that timely detection of hemorrhagic brain injury, close monitoring of associated complications, timely initiation of interventions based on neuroimaging criteria without waiting for clinical signs, and proper long-term follow-up of the affected infants are essential and require teamwork. The collective effort of interdisciplinary collaborations and integration of families at each decision step will allow infants to receive the best possible therapy. Effective diagnostic approaches and therapeutic interventions will help optimize neuroplasticity and reduce neurologic disease burden throughout the affected newborn's life.

References

1. Leijser LM, de Vries LS. Preterm brain injury: Germinal matrix-intraventricular hemorrhage and post-hemorrhagic ventricular dilatation. Handb Clin Neurol 2019;162:173-99.
2. Beaino G, Khoshnood B, Kaminski M, et al. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. Dev Med Child Neurol 2010;52:e119-25.
3. Bolisetty S, Dhawan A, Abdel-Latif M, et al. Intraventricular hemorrhage and neurodevelopmental outcomes in extreme preterm infants. Pediatrics 2014;133:55-62.
4. Payne AH, Hintz SR, Hibbs AM, et al. Neurodevelopmental outcomes of extremely low-gestational-age neonates with low-grade periventricular-intraventricular hemorrhage. JAMA Pediatr 2013;167:451-9.
5. Hollebrandse NL, Spittle AJ, Burnett AC, et al. School-age outcomes following intraventricular haemorrhage in infants born extremely preterm. Arch Dis Child Fetal Neonatal Ed 2021;106:4-8.
6. Scott TE, Aboudi D, Kase JS. Low-Grade Intraventricular Hemorrhage and Neurodevelopmental Outcomes at 24-42 Months of Age. J Child Neurol 2020;35:578-84.
7. Gomaa N, Miller SP. Intraventricular haemorrhage in preterm children: viewing longer term with a wider lens. Arch Dis Child Fetal Neonatal Ed 2021;106:2-3.
8. Inder TE, de Vries LS, Ferriero DM, et al. Neuroimaging of the Preterm Brain: Review and Recommendations. J Pediatr 2021;237:276-87 e4.
9. Cizmeci MN, Groenendaal F, de Vries LS. Timing of Intervention for Posthemorrhagic Ventricular Dilatation: An Ongoing Debate. J Pediatr 2021;234:14-6.
10. Whitelaw A, Evans D, Carter M, et al. Randomized clinical trial of prevention of hydrocephalus after intraventricular hemorrhage in preterm infants: brain-washing versus tapping fluid. Pediatrics 2007;119:e1071-8.
11. Whitelaw A, Jary S, Kmita G, et al. Randomized trial of drainage, irrigation and fibrinolytic therapy for premature infants with posthemorrhagic ventricular dilatation: developmental outcome at 2 years. Pediatrics 2010;125:e852-8.
12. Luyt K, Jary SL, Lea CL, et al. Drainage, irrigation and fibrinolytic therapy (DRIFT) for posthaemorrhagic ventricular dilatation: 10-year follow-up of a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2020;105:466-73.
13. Chari A, Mallucci C, Whitelaw A, Aquilina K. Intraventricular haemorrhage and posthaemorrhagic ventricular dilatation: moving beyond CSF diversion. Childs Nerv Syst 2021;37:3375-83.
14. Levene MI. Measurement of the growth of the lateral ventricles in preterm infants with real-time ultrasound. Arch Dis Child 1981;56:900-4.
15. Davies MW, Swaminathan M, Chuang SL, Betheras FR. Reference ranges for the linear dimensions of the intracranial ventricles in preterm neonates. Arch Dis Child Fetal Neonatal Ed 2000;82:F218-23.
16. Mantovani JF, Pasternak JF, Mathew OP, et al. Failure of daily lumbar punctures to prevent the development of hydrocephalus following intraventricular hemorrhage. J Pediatr 1980;97:278-81.
17. Randomised trial of early tapping in neonatal posthaemorrhagic ventricular dilatation. Ventriculomegaly Trial Group. Arch Dis Child 1990;65:3-10.
18. Dykes FD, Dunbar B, Lazarra A, Ahmann PA. Posthemorrhagic hydrocephalus in high-risk preterm infants: natural history, management, and long-term outcome. J Pediatr 1989;114:611-8.
19. de Vries LS, Groenendaal F, Liem KD, et al. Treatment thresholds for intervention in posthaemorrhagic ventricular dilation: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2019;104:F70-F5.

20. Arichi T, Counsell SJ, Allievi AG, et al. The effects of hemorrhagic parenchymal infarction on the establishment of sensori-motor structural and functional connectivity in early infancy. Neuroradiology 2014;56:985-94.
21. Bassan H, Benson CB, Limperopoulos C, et al. Ultrasonographic features and severity scoring of periventricular hemorrhagic infarction in relation to risk factors and outcome. Pediatrics 2006;117:2111-8.
22. Bassan H, Feldman HA, Limperopoulos C, et al. Periventricular hemorrhagic infarction: risk factors and neonatal outcome. Pediatr Neurol 2006;35:85-92.
23. de Vries LS, Roelants-van Rijn AM, Rademaker KJ, Van Haastert IC, Beek FJ, Groenendaal F. Unilateral parenchymal haemorrhagic infarction in the preterm infant. Eur J Paediatr Neurol 2001;5:139-49.
24. Bassan H, Limperopoulos C, Visconti K, et al. Neurodevelopmental outcome in survivors of periventricular hemorrhagic infarction. Pediatrics 2007;120:785-92.
25. Guzzetta F, Shackelford GD, Volpe S, Perlman JM, Volpe JJ. Periventricular intraparenchymal echodensities in the premature newborn: critical determinant of neurologic outcome. Pediatrics 1986;78:995-1006.
26. Rademaker KJ, Groenendaal F, Jansen GH, Eken P, de Vries LS. Unilateral haemorrhagic parenchymal lesions in the preterm infant: shape, site and prognosis. Acta Paediatr 1994;83:602-8.
27. Dudink J, Lequin M, Weisglas-Kuperus N, Conneman N, van Goudoever JB, Govaert P. Venous subtypes of preterm periventricular haemorrhagic infarction. Arch Dis Child Fetal Neonatal Ed 2008;93:F201-6.
28. Kidokoro H, Neil JJ, Inder TE. New MR imaging assessment tool to define brain abnormalities in very preterm infants at term. AJNR Am J Neuroradiol 2013;34:2208-14.
29. Moeskops P, Viergever MA, Mendrik AM, de Vries LS, Benders MJ, Isgum I. Automatic Segmentation of MR Brain Images With a Convolutional Neural Network. IEEE Trans Med Imaging 2016;35:1252-61.
30. Kulkarni AV, Drake JM, Armstrong DC, Dirks PB. Measurement of ventricular size: reliability of the frontal and occipital horn ratio compared to subjective assessment. Pediatr Neurosurg 1999;31:65-70.
31. Jary S, De Carli A, Ramenghi LA, Whitelaw A. Impaired brain growth and neurodevelopment in preterm infants with posthaemorrhagic ventricular dilatation. Acta Paediatr 2012;101:743-8.
32. Leijser LM, Miller SP, van Wezel-Meijler G, et al. Posthemorrhagic ventricular dilatation in preterm infants: When best to intervene? Neurology 2018;90:e698-e706.
33. Miller SP, Vigneron DB, Henry RG, et al. Serial quantitative diffusion tensor MRI of the premature brain: development in newborns with and without injury. J Magn Reson Imaging 2002;16:621-32.
34. Pecheva D, Kelly C, Kimpton J, et al. Recent advances in diffusion neuroimaging: applications in the developing preterm brain. F1000Res 2018;7.
35. Roze E, Benders MJ, Kersbergen KJ, et al. Neonatal DTI early after birth predicts motor outcome in preterm infants with periventricular hemorrhagic infarction. Pediatr Res 2015;78:298-303.
36. McAllister JP, 2nd. Pathophysiology of congenital and neonatal hydrocephalus. Semin Fetal Neonatal Med 2012;17:285-94.
37. Tracy M Flanders LB, John Flibotte, Gregory G. Heuer. Neonatal Hydrocephalus. NeoReviews 2018;19:467-77.
38. El-Dib M, Limbrick DD, Jr., Inder T, et al. Management of Post-hemorrhagic Ventricular Dilatation in the Infant Born Preterm. J Pediatr 2020.

39. Mazzola CA, Choudhri AF, Auguste KI, et al. Pediatric hydrocephalus: systematic literature review and evidence-based guidelines. Part 2: Management of posthemorrhagic hydrocephalus in premature infants. J Neurosurg Pediatr 2014;14 Suppl 1:8-23.
40. Choi JW, Kim SK, Wang KC, Lee JY, Cheon JE, Phi JH. Multifocal intraparenchymal hemorrhages after ventriculoperitoneal shunt surgery in infants. J Neurosurg Pediatr 2014;14:329-35.
41. Andronikou S, Pillay T, Gabuza L, et al. Corpus callosum thickness in children: an MR pattern-recognition approach on the midsagittal image. Pediatr Radiol 2015;45:258-72.
42. de Bijl-Marcus K, Brouwer AJ, De Vries LS, Groenendaal F, Wezel-Meijler GV. Neonatal care bundles are associated with a reduction in the incidence of intraventricular haemorrhage in preterm infants: a multicentre cohort study. Arch Dis Child Fetal Neonatal Ed 2020;105:419-24.
43. Baranger J, Mertens L, Villemain O. Blood Flow Imaging with Ultrafast Doppler. J Vis Exp 2020.
44. Kim HG, Park MS, Lee JD, Park SY. Ultrasound Elastography of the Neonatal Brain: Preliminary Study. J Ultrasound Med 2017;36:1313-9.
45. June A, Heck T, Shah TA, Vazifedan T, Bass WT. Decreased Cerebral Oxygenation in Premature Infants with Progressive Posthemorrhagic Ventricular Dilatation May Help with Timing of Intervention. Am J Perinatol 2021.
46. Kochan M, McPadden J, Bass WT, et al. Changes in Cerebral Oxygenation in Preterm Infants With Progressive Posthemorrhagic Ventricular Dilatation. Pediatr Neurol 2017;73:57-63.
47. Limbrick DD, Jr., Castaneyra-Ruiz L, Han RH, Berger D, McAllister JP, Morales DM. Cerebrospinal Fluid Biomarkers of Pediatric Hydrocephalus. Pediatr Neurosurg 2017;52:426-35.
48. Douglas-Escobar M, Weiss MD. Biomarkers of brain injury in the premature infant. Front Neurol 2012;3:185.
49. Morales DM, Smyser CD, Han RH, et al. Tract-Specific Relationships Between Cerebrospinal Fluid Biomarkers and Periventricular White Matter in Posthemorrhagic Hydrocephalus of Prematurity. Neurosurgery 2021;88:698-706.
50. Letunica N, Cai T, Cheong JLY, Doyle LW, Monagle P, Ignjatovic V. The use of proteomics for blood biomarker research in premature infants: a scoping review. Clin Proteomics 2021;18:13.
51. Ahn SY, Chang YS, Sung DK, et al. Mesenchymal stem cells prevent hydrocephalus after severe intraventricular hemorrhage. Stroke 2013;44:497-504.
52. Ahn SY, Chang YS, Sung DK, et al. Optimal Route for Mesenchymal Stem Cells Transplantation after Severe Intraventricular Hemorrhage in Newborn Rats. PLoS One 2015;10:e0132919.
53. Ahn SY, Chang YS, Sung SI, Park WS. Mesenchymal Stem Cells for Severe Intraventricular Hemorrhage in Preterm Infants: Phase I Dose-Escalation Clinical Trial. Stem Cells Transl Med 2018;7:847-56.
54. Robinson S, Conteh FS, Oppong AY, et al. Extended Combined Neonatal Treatment With Erythropoietin Plus Melatonin Prevents Posthemorrhagic Hydrocephalus of Prematurity in Rats. Front Cell Neurosci 2018;12:322.
55. Carloni S, Favrais G, Saliba E, et al. Melatonin modulates neonatal brain inflammation through endoplasmic reticulum stress, autophagy, and miR-34a/silent information regulator 1 pathway. J Pineal Res 2016;61:370-80.
56. Guo J, Chen Q, Tang J, et al. Minocycline-induced attenuation of iron overload and brain injury after experimental germinal matrix hemorrhage. Brain Res 2015;1594:115-24.
57. Strahle JM, Garton T, Bazzi AA, et al. Role of hemoglobin and iron in hydrocephalus after neonatal intraventricular hemorrhage. Neurosurgery 2014;75:696-705; discussion 6.
58. Strahle JM, Mahaney KB, Morales DM, et al. Longitudinal CSF Iron Pathway Proteins in Posthemorrhagic Hydrocephalus: Associations with Ventricle Size and Neurodevelopmental Outcomes. Ann Neurol 2021;90:217-26.
59. Kulkarni AV, Riva-Cambrin J, Rozzelle CJ, et al. Endoscopic third ventriculostomy and choroid plexus cauterization in infant hydrocephalus: a prospective study by the Hydrocephalus Clinical Research Network. J Neurosurg Pediatr 2018;21:214-23.

60. Riva-Cambrin J, Kestle JRW, Rozzelle CJ, et al. Predictors of success for combined endoscopic third ventriculostomy and choroid plexus cauterization in a North American setting: a Hydrocephalus Clinical Research Network study. J Neurosurg Pediatr 2019;24:128-38.
61. Schulz M, Buhrer C, Pohl-Schickinger A, Haberl H, Thomale UW. Neuroendoscopic lavage for the treatment of intraventricular hemorrhage and hydrocephalus in neonates. J Neurosurg Pediatr 2014;13:626-35.
62. Park YS, Kotani Y, Kim TK, et al. Efficacy and safety of intraventricular fibrinolytic therapy for post-intraventricular hemorrhagic hydrocephalus in extreme low birth weight infants: a preliminary clinical study. Childs Nerv Syst 2021;37:69-79.
63. Lauer CG, Burge R, Tang DB, Bass BG, Gomez ER, Alving BM. Effect of ultrasound on tissue-type plasminogen activator-induced thrombolysis. Circulation 1992;86:1257-64.
64. Monteith SJ, Harnof S, Medel R, et al. Minimally invasive treatment of intracerebral hemorrhage with magnetic resonance-guided focused ultrasound. J Neurosurg 2013;118:1035-45.
65. Looi T, Piorkowska K, Mougenot C, Waspe A, Hynynen K, Drake J. An MR-based quantitative intraventricular hemorrhage porcine model for MR-guided focused ultrasound thrombolysis. Childs Nerv Syst 2018;34:1643-50.

10

Nederlandse Samenvatting

Algemene discussie

Deel-I: Kenmerken van neurobeeldvorming van hooggradige GMH-IVH en associatie met ontwikkelingsneurologische uitkomsten

Neurobeeldvorming met craniële ultrasonografie (cUS) is de meest gebruikte methode om de diagnose germinale matrix-intraventriculaire bloeding (germinal matrix hemorrhage-intraventricular hemorrhage [GMH-IVH]) te stellen. Met het serieel verrichten van cUS kunnen te verwachten complicaties vroegtijdig worden herkend. Magnetische resonantie beeldvorming (MRI) op de à terme datum (term-equivalent age MRI [TEA-MRI]) is van belang om de omvang van de hemorrhagische schade te bepalen, de ermee gepaard gaande veranderingen in de witte stof en mogelijk cerebellaire laesies op te sporen die niet met cUS werden gezien, zoals beschreven is in een recent overzichtsartikel van Inder et al.[1] Het gevolg van een periventriculair hemorrhagisch infarct (PVHI) op de zich ontwikkelende hersenen is aangetoond met geavanceerde MRI-technieken. cUS blijft echter het initiële beeldvormingsonderzoek bij uitstek voor detectie en monitoring van PVHI.[2] cUS-onderzoeken door Bassan et al.[3,4] van bijna twee decennia geleden beschrijven de cUS kenmerken van PVHI. In de meerderheid van de gevallen zijn die unilateraal en betreffen die de frontale en pariëtale kwabben waarbij een nauw verband bestaat met een neurologische ontwikkelingsstoornis (neurodevelopmental impairment, NDI).

In **Hoofdstuk 2** onderzochten we de cUS kenmerken van PVHI en de trends tussen 2008 en 2013. Wij wilden tevens de associatie met neurologische ontwikkelingsuitkomsten beschrijven bij een groot aantal te vroeg geborenen met PVHI. De onderscheidende factor van dit onderzoek was de kwantitatieve meting van de omvang van PVHI met gebruik van een objectief scoringssysteem dat specifiek is ontwikkeld voor het beoordelen van PVHI en blijkt te correleren met neurologische ontwikkelingsuitkomsten.[3] Ons doel was, de hypothese te testen dat latere onderzoeksjaren geassocieerd zouden zijn met een daling in incidentie, minder ernstige cUS bevindingen en betere neurologische ontwikkelingsresultaten bij te vroeg geborenen met PVHI. Onze hypothese moest worden verworpen omdat er tijdens de onderzoeksperiode geen veranderingen werden waargenomen met betrekking tot de cUS kenmerken. Conform de reeds bestaande literatuur werd PVHI vaak geassocieerd met een ipsilaterale, graad 3 GMH-IVH. De PVHI trad meestal op in de pariëtale kwab. De maximum omvang werd tegen het einde van de eerste postnatale week bereikt en ontwikkelde zich meestal tot een enkele grote porencefale cyste.[3,5,6]

Zoals verwacht, bleek de aanwezigheid van PVHI een onafhankelijke risicofactor voor NDI te zijn. Deze werd waargenomen bij ongeveer een derde van de overlevende prematuur geborenen. Onze bevindingen bleken gunstiger te zijn vergeleken met eerdere studies die cognitieve stoornissen meldden bij de helft, en motorische

stoornissen bij nagenoeg twee derde van de aangedane prematuur geborenen.[5-9] De meest opvallende bevinding was het percentage cerebrale parese (CP) van 42% dat relatief lager was dan wat in de literatuur wordt vermeld.[4,5] Belangrijk is dat 81% van de kinderen met CP functioneerde op een niveau I of II van het classificatiesysteem voor grof-motorisch functioneren (Gross Motor Function Classification System [GMFCS]) wat erop wijst dat deze kinderen zonder hulpmiddelen konden lopen. Ook belangrijk is dat de score voor omvang en ernst van het PVHI negatief geassocieerd was met de grof motorische scores en dat kinderen bij wie het trigonum betrokken was, meer kans hadden om CP te ontwikkelen. Deze laatste bevinding toont de relatie aan tussen de plaats van het PVHI, in het bijzonder betrokkenheid van het trigonum, en CP zoals het voor het eerst werd beschreven door Rademaker et al.[8] en later verfijnd door Dudink et al.[9] Hij bracht subtypes van een PVHI in verband met de aangedane venen. Inspanningen om de anatomische locatie van een PVHI meer in detail te beschrijven met gebruik van cUS zijn van essentieel belang. Dit zal clinici helpen om de te verwachten ontwikkeling beter te voorspellen en doelgerichte revalidatieprogramma's op de vroege kinderleeftijd te introduceren om het effect van neurale plasticiteit te maximaliseren.

In **Hoofdstuk 3** wilden we, in een ingebed deelonderzoek van de ELVIS-studie, bij prematuur geborenen met post-hemorrhagische ventrikel dilatatie (PHVD) de omvang van de hersenschade vergelijken en hersenvolumes kwantificeren met behulp van TEA-MRI, gerandomiseerd naar vroege- en late interventiegroepen. In dit onderzoek pasten we een gevalideerd scoringssysteem toe, beschreven door Kidokoro et al.,[10] om hersenschade objectief te beoordelen. Om de kwantitatieve impact van de schade op de verschillende hersengebieden op een betrouwbare wijze te onderzoeken, voerden we ook volumetrische analyses uit met gebruik van de automatische segmentatiemethode die eerder door onze groep werd ontwikkeld.[11] Een techniek van convolutionele neurale netwerken die in het centrum van de hoofdonderzoeker (Utrecht) werd uitgeprobeerd op gesegmenteerde beelden van vroeg geborenen zonder hersenpathologie had als resultaat dat bijna de helft van alle gesegmenteerde MRI's bij kinderen met PHVD een suboptimale beeldkwaliteit vertoonde. Reden waarom deze niet in de volumetrische analyse konden worden geïncludeerd. Daarom hebben we, om het aantal voor ventriculaire volumes te beoordelen kinderen te maximaliseren, ook de frontale en occipitale hoorn ratio (FOHR) berekend die een sterke correlatie vertoonde met de ventrikel volumes bij kinderen met PHVD.[12]

Om logistieke redenen kon van 22 pasgeboren overlevers geen MRI worden verkregen. De definitieve steekproef bestond uit 88 kinderen met een gelijk aantal kinderen in elke onderzoeksgroep. De meest opmerkelijke bevinding was de kleinere ventriculaire volumes in de vroege interventie groep, ondanks het feit dat iets meer dan de helft van alle kinderen kon worden geïncludeerd in de volumetrische analyse. Zoals verwacht, toonde de FOHR een significanter verschil tussen de groepen. Deze

was lager in de vroege interventie groep. We stelden vast dat zuigelingen in deze groep lagere globale scores voor hersenafwijkingen hadden. Na exclusie van de kinderen met PVHI was de combinatie van witte stof en grijze stof volumes groter in de vroege interventie groep, wat het negatieve effect van vergrote ventrikels op het omringende hersenparenchym aantoont. Na stratificatie op basis van hun scores voor hersenafwijkingen werden normale of licht abnormale scores vaker waargenomen in de vroege interventie groep. Kinderen in de late interventie groep vertoonden tevens vaker een vertraagde myelinisatie en atrofie van de hersenbalk (corpus callosum, [CC]). Dit kan worden toegeschreven aan het effect van volumeverlies van witte stof alsook aan compressie veroorzaakt door vergrote ventrikels. In dit ingebed deelonderzoek van de ELVIS-studie konden we, met behulp van TEA-MRI, aan de hand van een objectieve beoordeling van de hersenschade gecombineerd met een kwantificering van de ventrikel dilatatie de gunstige effecten van vroegtijdige interventie vastleggen.

Onze bevindingen waren conform eerder onderzoek door Jary et al.[13] die totale hersenvolumes hebben gemeten met manuele segmentatie. Zij toonden aan dat PHVD een negatief effect heeft op hersengroei. Men zou kunnen aannemen dat de gunstige effecten van vroegtijdige interventie op hersenschade en hersenvolumes die in ons ingebed deelonderzoek werden waargenomen te danken zijn aan het eerder maar ook vaker verrichten van lumbaal puncties (LP's) en het plaatsen van een reservoir. Dit werd waargenomen in het ELVIS-onderzoek. Om echter het verhoogd aantal interventies te kunnen verantwoorden, moeten betere bevindingen op basis van de neurobeeldvorming zich ook vertalen naar gunstiger uitkomsten van de neurologische ontwikkeling van kinderen die vroegtijdige interventies krijgen. Of de kleinere ventriculaire volumes en minder vaak voorkomen van herseschade bij kinderen die de vroege interventie ondergingen geassocieerd kunnen worden met betere ontwikkelingsneurologische uitkomsten in het ELVIS-onderzoek, werd behandeld in **Hoofdstuk 4**.

In **Hoofdstuk 4** beoordeelden we de neurologische ontwikkelingsuitkomsten van het ELVIS-cohort op de gecorrigeerde leeftijd van 2 jaar om de hypothese te toetsen dat een vroegtijdige interventie zou leiden tot betere neurologische ontwikkelingsuitkomsten. Bij 92% van de overlevende zuigelingen werden de uitkomsten beoordeeld als deel van het standaardprotocol voor follow-up. De samengestelde negatieve uitkomstmaat voor de ontwikkeling was gedefinieerd als overlijden, CP, of een cognitieve/motorische score <-2 SD op de Bayley Scales of Infant Development, tweede editie of de Bayley Scales of Infant and Toddler Development, derde editie. Een belangrijk aspect van dit onderzoek was dat alle vijf GMFCS niveaus van CP en alle kinderen met een cognitieve/motorische score <-2 SD werden geïncludeerd als een samengestelde uitkomstmaat, in plaats van de focus alleen te richten op niet-ambulante CP en cognitieve/motorische scores <-3 SD. Er was geen verschil tussen de vroege- (35%) en late interventie (51%) groepen met betrekking tot de samengestelde uitkomst. In de posthoc analyse was de vroege

interventie geassocieerd met een lager risico op een negatieve uitkomst na correctie van de zwangerschapsduur, de ernst van de GMH-IVH en de aanwezigheid van een cerebellaire bloeding. Op te merken valt dat een hogere FOHR negatief geassocieerd bleek te zijn met de cognitieve en motorische scores, ongeacht de toegewezen groep. Deze waarneming ondersteunt onze hypothese dat het vroeger draineren van cerebrospinaal vocht (CSV) op basis van cUS-metingen, additionele hersenschade kan voorkomen door verwijdering van bloedcomponenten en inflammatoire stoffen en daarmee directe schade van het omliggende hersenparenchym kan verminderen. De behouden ventriculaire volumes met mogelijk betere uitkomsten lijken het hogere aantal bijkomende interventies in de vroege interventie groep te rechtvaardigen.

Opmerkelijk is dat, vergelijkbaar met de bevindingen van Leijser et al[14], de kinderen in de vroege interventie groep die een ventriculo-peritoneale shunt (VPS) nodig hadden, cognitieve en motorische scores hadden die vergelijkbaar waren met deze zonder een VPS. Daartegenover hadden kinderen in de late interventie groep die een VPS nodig hadden, lagere cognitieve en motorische scores in vergelijking met kinderen zonder. Samengevat, **Hoofdstuk 4** toont het gunstige effect van een vroege interventie voor PHVD aan op het verminderen van mortaliteit en neurologische ontwikkelingsstoornissen.

In de afgelopen 10 jaar zijn geavanceerde MRI-modaliteiten zoals diffusion-tensor beeldvorming (diffusion tensor imaging [DTI)] gangbaarder geworden voor hersenonderzoek. Met DTI kunnen de vezelbanen in de zich ontwikkelende hersenen worden beoordeeld met gebruik van de driedimensionale anisotropie van waterdiffusie. Bovendien levert het objectieve en voorspelbare indicatoren op voor de ontwikkeling van de witte stof en eventuele schade.[15,16]

In **Hoofdstuk 5** wilden we de microstructuur van de witte stof met gebruik van DTI bij zuigelingen met PHVD beoordelen. We stelden de hypothese dat PHVD een negatieve invloed kan hebben op de kwetsbare rijpingsprocessen in de witte stof en de neurologische ontwikkelingsuitkomsten op de gecorrigeerde leeftijd van 2 jaar. Dit onderzoek werd uitgevoerd op een exclusief cohort van extreem prematuur geborenen (<28 weken zwangerschapsduur) met PHVD. We vonden lagere fractionele anisotropie- en hogere radiale diffusie waarden in het CC bij kinderen met PHVD in vergelijking met de controles. Hiermee werd onze hypothese bevestigd. Deze bevindingen wijzen op een verstoorde microstructuur van het CC dat zich in de directe nabijheid van de gedilateerde ventrikels bevindt. Zoals verwacht waren de cognitieve en motorische scores minder gunstig bij kinderen met PHVD. De fractionele anisotropie waarden van het CC waren geassocieerd met zowel cognitieve als motorische scores op de gecorrigeerde leeftijd van 2 jaar.

Hoofdstuk 5 benadrukt ook de schadelijke effecten van een co-existerend PVHI op de zich ontwikkelende hersenen zoals werd beschreven in **Hoofdstuk** 2. De tractus

corticospinalis (TCS) bleek kwetsbaar voor axonale schade die werd veroorzaakt door een ipsilateraal PVHI.[17] Bij zuigelingen met een PVHI vertoonden ipsilaterale fractionele anisotropie waarden van de TCS een neerwaartse trend die de mogelijke impact van PVHI weergeeft op de maturatie processen in de TCS. Het aantal kinderen in deze deelgroep analyse was beperkt waardoor deze trend mogelijk de statistische significantie niet kon bereiken. Naar axonale schade door een PVHI wordt vaak verwezen als pre-Wallerse degeneratie die vroeg kan worden gevisualiseerd met DTI.[17] Opmerkelijk is dat we geen verstoorde DTI-waarden in de TCS hebben waargenomen bij zuigelingen met een geïsoleerde PHVD. Dit is mogelijk te wijten aan het beschermende effect van vroege interventie voor PHVD bij de meerderheid van de onderzochte kinderen. In **Hoofdstuk 3** stelden we vast dat bij bijna tweemaal zoveel kinderen die late interventie ondergingen (52% vs. 27%) een significante vertraging in de myelinisatie in hun TCS was waar te nemen. Deze vergelijkbare bevindingen in **Hoofdstuk 3 en 5** ondersteunen eveneens onze hypothese dat tijdige interventies kunnen voorkomen dat in kwetsbare gebieden van de zich ontwikkelende hersenen verstoringen ontstaan die veroorzaakt worden door PHVD.

Deel-II: Neurochirurgische interventies voor hemorrhagisch hersenletsel en gerelateerde complicaties

De meest voorkomende oorzaak van hydrocefalus bij pasgeborenen is PHVD. Hydrocefalus kan echter ook optreden door obstructie van de CSV-routes door genetische, ontwikkelings- en verworven omstandigheden.[18,19] De pijler van de behandeling is het verhoogde CSV volume te verminderen met interventies.[18-20] In Deel-II van dit proefschrift behandelden we neurochirurgische interventies die worden toegepast voor de behandeling van PHVD en mogelijke bijkomende schade door deze interventies en hun associatie met neurologische ontwikkelingsuitkomsten. In ons onderzoek van deze associatie in **Hoofdstuk 6 en 7** hebben we vroeggeboren en voldragen pasgeborenen met aangeboren hydrocefalus geïncludeerd.

Plaatsing van een reservoir om CSV te verwijderen is een algemeen gebruikte techniek bij zuigelingen met hydrocefalus.[21] Deze techniek is doorgaans de initiële neurochirurgische benadering wegens de hoge concentraties aan bloedproducten in het CSV, de klinische instabiliteit die doorgaans wordt waargenomen in de acute fase van de ziekte, maar ook de ongeschiktheid van de kleine peritoneale holte voor een permanent shuntsysteem.[19] We observeerden een deelgroep prematuur geborenen die een intraparenchymale bloeding (intraparenchymal haemorrhage [IPH]) kregen na seriële reservoir puncties. Dit werd reeds eerder gerapporteerd bij voldragen pasgeborenen met een VPS maar nooit eerder bij prematuur pasgeborenen na een reservoirplaatsing.[22] In **Hoofdstuk 6** wilden we de kenmerken van IPH beschrijven en de associatie ervan met neurologische ontwikkelingsuitkomsten. We stelden de

hypothese dat een snelle reductie van ventriculaire volumes met seriële reservoir puncties IPH kan veroorzaken en beoordeelden de bevindingen bij beeldvormend onderzoek en de associatie ervan met neurologische ontwikkelingsuitkomsten op de (gecorrigeerde) leeftijd van 2 jaar. We stelden vast dat IPH kan worden veroorzaakt door een snelle reductie van het ventriculaire volume tijdens de eerste week na de start van seriële reservoir puncties. Vermoed wordt dat de onrijpe cerebrale vasculatuur van pasgeborenen dit niet verdraagt en kan scheuren als gevolg van de plotselinge verandering in cerebrale perfusiedruk. Dit verklaart waarschijnlijk waarom we dit verschijnsel hebben waargenomen na een te snelle ventrikel volume afname met behulp van reservoir puncties.[22] Van de pasgeborenen met IPH had twee derde multifocale IPH; de bloedingen waren evenredig verdeeld over de periventriculaire en subcorticale gebieden van de hersenen. Geen van de bloedingen bevond zich rond het reservoir traject, vergelijkbaar met wat de literatuur beschrijft na plaatsing van een VP-shunt .[22] cUS maakte vroegtijdige detectie van periventriculaire IPH mogelijk, net zoals we hebben waargenomen voor PVHI in **Hoofdstuk 2**. De meerderheid van de subcorticale IPH's werd echter alleen gezien met een TEA-MRI, wat aantoont hoe belangrijk het is om een MRI te verrichten rond de à terme datum. We stelden vast dat de aanwezigheid van multifocale IPH's negatief geassocieerd was met cognitieve uitkomsten, waarschijnlijk door volumeverlies in meerdere hersengebieden. Concluderend kunnen we stellen dat de bevindingen in **Hoofdstuk 6** het belang aantonen van seriële cUS-scans om te beslissen hoeveel CSV moet worden gepuncteerd na plaatsing van een reservoir bij pasgeborenen met PHVD. Daarnaast wordt aangetoond dat het verrichten van een TEA-MRI van belang is om vooral de subcorticale IPH's in beeld te brengen.

Hoofdstuk 7 was gebaseerd op onze observatie dat een subset van baby's met PHVD penetrerend letsel van het CC vertoonde na een neurochirurgische interventie. Hoewel complicaties van neurochirurgische interventies voor PHVD, zoals katheterobstructie en secundaire infectie, goed gedocumenteerd zijn, was direct letsel van het CC een nieuwe observatie die nog niet eerder werd gerapporteerd. Ons doel in **Hoofdstuk 7** was om deze bevinding te beschrijven waarbij onze hypothese was dat dit penetrerend letsel de rijping van het CC nadelig kan beïnvloeden en vervolgens ook kan leiden tot een vertraagde/afwijkende neurologische ontwikkeling op de (gecorrigeerde) leeftijd van 2 jaar. Op basis van onze beoordeling van een aanzienlijk aantal MRI's van de hersenen (n=269), hebben we in dit onderzoek een hoog percentage penetrerend letsel van het CC (41%) waargenomen na neurochirurgische interventies. De meerderheid van deze letsels waren te wijten aan reservoirplaatsingen. De belangrijkste bevinding was dat het CC dunner was bij baby's met letsel in vergelijking met baby's met PHVD met intact CC en de baby's van de controlegroep. Het is wel bekend dat genetische, metabole, en infectieuze aandoeningen, alsook hemorrhagische en ischemische hersenschade, atrofie van het CC kunnen veroorzaken. Een iatrogene oorzaak door neurochirurgische

interventie is echter nog niet beschreven in de neonatale literatuur.[23] We stelden in **Hoofdstuk 3** dat PHVD ook atrofie van het CC kan veroorzaken aangezien een derde van de baby's die een hoogdrempelige interventie ondergingen atrofie van het CC vertoonde, een veel hoger percentage dan dat van de kinderen in de vroege interventie groep. Atrofie van het CC bij kinderen met PHVD kan worden verklaard door witte stof verlies alsook compressie veroorzaakt door gedilateerde ventrikels.[23] De bevindingen van dit onderzoek tonen ons dat stoornissen in de rijping van het CC bij baby's met PHVD niet alleen worden veroorzaakt door het effect van PHVD, maar dat ze ook secundair kunnen zijn aan interventies voor PHVD. Een veelbelovend alternatief voor toekomstig onderzoek zou het toepassen van cUS tijdens neurochirurgische interventies zijn om letsel van het CC te voorkomen. In tegenstelling tot onze hypothese, was CC-letsel niet geassocieerd met cognitieve en motorische uitkomsten op 2-jarige leeftijd. We moeten echter benadrukken dat we op deze jonge leeftijd een standaard neurologische ontwikkelingstest gebruikten om uitkomsten te beoordelen en nog geen testen die specifiek ontworpen zijn om het cognitief functioneren en de visuospatiële integratie te evalueren die vaak aangetast zijn bij baby's met letsel van het CC.

Tot slot hebben we in **Hoofdstuk 8** verslag uitgebracht over het gebruik van een minimaal invasieve behandeling met 'bedside approach' bij een reeks pasgeborenen met duidelijke klinische symptomen van een gecombineerde intra- en extra-axiale intracraniële bloeding. Hier moet worden benadrukt dat GMH-IVH aanwezig was bij ongeveer een derde van deze zuigelingen. De in dit hoofdstuk besproken pathologie verschilde van GMH-IVH die werd besproken in alle andere hoofdstukken van deze thesis. Deze zuigelingen vertoonden een verschuiving van de middenlijn op neurobeeldvorming en de subdurale bloeding kon met behulp van een percutane naaldaspiratie 'at the bedside' worden behandeld. Dit werd goed verdragen en er werden geen complicaties tijdens of na de procedure gezien. Wegens de belangrijke risico's van een neurochirurgische decompressie procedure bij een neonaat die niet stabiel is en bij wie anesthesie en craniotomie risico's met zich meebrengen, kan deze minder invasieve methode een veelbelovend alternatief zijn. De neurologische uitkomst van de zuigelingen in deze reeks bleek gunstig, waarbij allen een normale ontwikkeling hadden op jonge leeftijd. Er zijn toekomstige prospectieve onderzoeken nodig om onze bevindingen te bevestigen voordat er definitieve conclusies kunnen worden getrokken uit het gebruik van deze minimaal invasieve 'bedside' benadering.

Conclusies en klinische implicaties

Uit deze thesis kunnen de volgende conclusies worden getrokken:

- Gebaseerd op ultrasonografische beoordelingen leidden eerdere interventies om de intraventriculaire druk en dus ook de ventrikelomvang bij prematuur geborenen met post-hemorrhagische ventrikel dilatatie (PHVD) te verminderen tot kleinere ventrikelvolumes en minder hersenletsel op de à terme leeftijd (Hoofdstuk 3).
- Eerdere interventies voor PHVD gebaseerd op ultrasonografische beoordelingen leidden tot een lagere samengestelde uitkomst van mortaliteit en neurologische ontwikkelingsstoornis op de gecorrigeerde leeftijd van 2 jaar (Hoofdstuk 4).
- Een periventriculair hemorrhagisch infarct (PVHI) blijft een aanzienlijke complicatie bij zeer vroeg geborenen en is een onafhankelijke risicofactor voor zowel cognitieve als motorische problemen op de gecorrigeerde leeftijd van 2 jaar (Hoofdstuk 2, 4 en 5).
- Cognitieve en motorische uitkomsten lagen binnen het normale bereik bij twee derde van te vroeg geborenen die na een PVHI in leven waren en op de gecorrigeerde leeftijd van 2 jaar werden getest. Een cerebrale parese (CP) werd bij ongeveer 40% waargenomen. De meerderheid (81%) van de kinderen die CP ontwikkelden kon zonder hulpmiddelen lopen. Deze bevindingen met betrekking tot de neurologische ontwikkeling zijn gunstiger in vergelijking met eerdere onderzoeken die meer dan 10 jaar geleden werden uitgevoerd (Hoofdstuk 2).
- PHVD leidt tot een verstoorde microstructuur van het corpus callosum (CC) bij extreem vroeggeboren baby's met PHVD. Fractionele anisotropie waarden van het CC, verkregen met diffusie-tensor beeldvorming, zijn geassocieerd met zowel cognitieve als motorische scores op de gecorrigeerde leeftijd van 2 jaar (Hoofdstuk 5).
- Bij baby's met PHVD kan een snelle verlaging van ventriculaire druk en volume tijdens de eerste week na de start van seriële reservoir puncties tot intraparenchymale bloeding (IPH) leiden in de periventriculaire en/of subcorticale witte stof. Deze IPH's kunnen cognitieve uitkomsten beïnvloeden wanneer de IPH's multifocaal zijn. Daarom is het van essentieel belang om seriële cUS-scans te maken om de te verwijderen hoeveelheid cerebrospinaal vocht te kunnen bepalen die via reservoir puncties moet worden verwijderd (Hoofdstuk 6).
- Neurochirurgische interventies, in het bijzonder reservoirplaatsing, kunnen leiden tot letsel aan het CC en bijgevolg atrofie van het CC. Dit verschijnsel lijkt echter niet gerelateerd te zijn met afwijkende neurologische ontwikkeling op de gecorrigeerde leeftijd van 2 jaar (Hoofdstuk 7).
- Bij pasgeborenen met gecombineerde intra- en extra-axiale intracraniële bloeding en een verschuiving van de middenlijn bij neurobeeldvorming wordt percutane naaldaspiratie 'at the bedside' goed verdragen, zonder complicaties tijdens of na de procedure. Deze minimaal invasieve 'bedside' techniek kan een veelbelovende benadering zijn (Hoofdstuk 8).

Referentiewerken

1. Inder TE, de Vries LS, Ferriero DM, et al. Neuroimaging of the Preterm Brain: Review and Recommendations. J Pediatr 2021;237:276-87 e4.
2. Arichi T, Counsell SJ, Allievi AG, et al. The effects of hemorrhagic parenchymal infarction on the establishment of sensori-motor structural and functional connectivity in early infancy. Neuroradiology 2014;56:985-94.
3. Bassan H, Benson CB, Limperopoulos C, et al. Ultrasonographic features and severity scoring of periventricular hemorrhagic infarction in relation to risk factors and outcome. Pediatrics 2006;117:2111-8.
4. Bassan H, Feldman HA, Limperopoulos C, et al. Periventricular hemorrhagic infarction: risk factors and neonatal outcome. Pediatr Neurol 2006;35:85-92.
5. de Vries LS, Roelants-van Rijn AM, Rademaker KJ, Van Haastert IC, Beek FJ, Groenendaal F. Unilateral parenchymal haemorrhagic infarction in the preterm infant. Eur J Paediatr Neurol 2001;5:139-49.
6. Bassan H, Limperopoulos C, Visconti K, et al. Neurodevelopmental outcome in survivors of periventricular hemorrhagic infarction. Pediatrics 2007;120:785-92.
7. Guzzetta F, Shackelford GD, Volpe S, Perlman JM, Volpe JJ. Periventricular intraparenchymal echodensities in the premature newborn: critical determinant of neurologic outcome. Pediatrics 1986;78:995-1006.
8. Rademaker KJ, Groenendaal F, Jansen GH, Eken P, de Vries LS. Unilateral haemorrhagic parenchymal lesions in the preterm infant: shape, site and prognosis. Acta Paediatr 1994;83:602-8.
9. Dudink J, Lequin M, Weisglas-Kuperus N, Conneman N, van Goudoever JB, Govaert P. Venous subtypes of preterm periventricular haemorrhagic infarction. Arch Dis Child Fetal Neonatal Ed 2008;93:F201-6.
10. Kidokoro H, Neil JJ, Inder TE. New MR imaging assessment tool to define brain abnormalities in very preterm infants at term. AJNR Am J Neuroradiol 2013;34:2208-14.
11. Moeskops P, Viergever MA, Mendrik AM, de Vries LS, Benders MJ, Isgum I. Automatic Segmentation of MR Brain Images With a Convolutional Neural Network. IEEE Trans Med Imaging 2016;35:1252-61.
12. Kulkarni AV, Drake JM, Armstrong DC, Dirks PB. Measurement of ventricular size: reliability of the frontal and occipital horn ratio compared to subjective assessment. Pediatr Neurosurg 1999;31:65-70.
13. Jary S, De Carli A, Ramenghi LA, Whitelaw A. Impaired brain growth and neurodevelopment in preterm infants with posthaemorrhagic ventricular dilatation. Acta Paediatr 2012;101:743-8.
14. Leijser LM, Miller SP, van Wezel-Meijler G, et al. Posthemorrhagic ventricular dilatation in preterm infants: When best to intervene? Neurology 2018;90:e698-e706.
15. Miller SP, Vigneron DB, Henry RG, et al. Serial quantitative diffusion tensor MRI of the premature brain: development in newborns with and without injury. J Magn Reson Imaging 2002;16:621-32.
16. Pecheva D, Kelly C, Kimpton J, et al. Recent advances in diffusion neuroimaging: applications in the developing preterm brain. F1000Res 2018;7.
17. Roze E, Benders MJ, Kersbergen KJ, et al. Neonatal DTI early after birth predicts motor outcome in preterm infants with periventricular hemorrhagic infarction. Pediatr Res 2015;78:298-303.
18. McAllister JP, 2nd. Pathophysiology of congenital and neonatal hydrocephalus. Semin Fetal Neonatal Med 2012;17:285-94.

19. Tracy M Flanders LB, John Flibotte, Gregory G. Heuer. Neonatal Hydrocephalus. NeoReviews 2018;19:467-77.
20. El-Dib M, Limbrick DD, Jr., Inder T, et al. Management of Post-hemorrhagic Ventricular Dilatation in the Infant Born Preterm. J Pediatr 2020.
21. Mazzola CA, Choudhri AF, Auguste KI, et al. Pediatric hydrocephalus: systematic literature review and evidence-based guidelines. Part 2: Management of posthemorrhagic hydrocephalus in premature infants. J Neurosurg Pediatr 2014;14 Suppl 1:8-23.
22. Choi JW, Kim SK, Wang KC, Lee JY, Cheon JE, Phi JH. Multifocal intraparenchymal hemorrhages after ventriculoperitoneal shunt surgery in infants. J Neurosurg Pediatr 2014;14:329-35.
23. Andronikou S, Pillay T, Gabuza L, et al. Corpus callosum thickness in children: an MR pattern-recognition approach on the midsagittal image. Pediatr Radiol 2015;45:258-72.

A

Appendices

List of Abbreviations
Curriculum vitae
Dankwoord (Acknowledgments)

List of Abbreviations

AAP:	American Academy of Pediatrics
AD:	Axial diffusivity
aEEG:	Amplitude-integrated electroencephalography
AHW:	Anterior horn width
BGT:	Basal ganglia and thalami
BSID-II:	Bayley Scales of Infant Development, Second Edition
BSITD-III:	Bayley Scales of Infant and Toddler Development, Third Edition
BW:	Birth weight
CA:	Corrected age
CC:	Corpus callosum
CP:	Cerebral palsy
CSF:	Cerebrospinal fluid
CS:	Cesarean section
CST:	Corticospinal tract
CT:	Computerized tomography
cUS:	Cranial ultrasound
DQ:	Developmental quotient
DRIFT:	Drainage, Irrigation and Fibrinolytic Therapy
DTI:	Diffusion tensor imaging
ELVIS:	Early vs. Late Ventricular Intervention Study
EP:	Extremely preterm
FA:	Fractional anisotropy
FTHR:	Frontal and temporal horn ratio
FOHR:	Frontal and occipital horn ratio
GA:	Gestational age
GMDS:	Griffiths Mental Development Scales
GMFCS:	Gross motor function classification system
GMH-IVH:	Germinal matrix hemorrhage and intraventricular hemorrhage
HT:	High-threshold
ICC:	Interclass correlation coefficient
ICH:	Intracranial hemorrhage
IPH:	Intraparenchymal hemorrhage
IQR:	Inter-quartile range
IRB:	Institutional Review Board
IVH:	Intraventricular hemorrhage
LP:	Lumbar puncture
LT:	Low-threshold

MD:	Mean diffusivity
MRI:	Magnetic resonance imaging
NDI:	Neurodevelopmental impairment
NEC:	Necrotizing enterocolitis
NICU:	Neonatal intensive care unit
OR:	Odds ratio
PHH:	Post-hemorrhagic hydrocephalus
PHVD:	Post-hemorrhagic ventricular dilatation
PLIC:	Posterior limb of the internal capsule
PVHI:	periventricular hemorrhagic infarction
RCT:	Randomized controlled trial
RD:	Radial diffusivity
SD:	Standard deviation
SWI:	Susceptibility-weighted imaging
TEA:	Term-equivalent age
TEA-MRI:	Term-equivalent age magnetic resonance imaging
TOD:	Thalamo-occipital distance
UMCU:	University Medical Center Utrecht
UofT:	University of Toronto
VI:	Ventricular index
VPS:	Ventriculo-peritoneal shunt
VR:	Ventricular reservoir

About the Author

Mehmet Nevzat Çizmeci was born on February 29th 1980 in Ankara and received his primary and secondary education in Istanbul. After becoming a certified neonatologist in 2013 and being promoted to associate professor in pediatrics in 2015, Mehmet wanted to pursue his passion for neonatal neurology and started a research fellowship at Utrecht University in 2017. His fruitful fellowship period transformed into a PhD trajectory in neuroscience led by Prof. Linda de Vries and Dr. Floris Groenendaal. In 2019, Mehmet joined the neonatal neurology team at SickKids as a clinical fellow and was trained by Prof. Steven Miller, Hilary Whyte, Emily Tam and Vann Chau. Mehmet received the prestigious CanMEDS Subspecialty Fellow Excellence Award in 2020 and joined the Neonatal Neurodevelopmental Follow-Up team at SickKids as the inaugural Dr. Karen Pape Fellow in Neuroplasticity. He is currently working with a multidisciplinary group of professionals led by Dr. Linh Ly. Mehmet lives with his two lovely daughters, Esin and Ela, and wife, Elif in Toronto. He loves teaching, reading and spending time outdoors with his family and friends.

Dankwoord (Acknowledgments)

First and foremost, I am extremely grateful to my supervisor and mentor, **Prof. Linda de Vries**, for her invaluable guidance and immense support during my PhD studies. Her unparalleled knowledge and experience in neonatal neurology have encouraged me throughout my PhD trajectory. Dear Linda, you were the first result of my internet search on neonatal neurology in 2011, and after 11 years, you are still the one who continues to motivate me to be my best version not only academically, but also in my personal life. Thank you for accepting me to the research fellowship and then to this distinguished PhD program, supporting me to do my neonatal neurology fellowship at SickKids, always being one call away and above all, being a part of *my family*.

I would like to thank to my copromotor, **Dr. Floris Groenendaal**, for his great support during my PhD years. Dear Floris, without your tremendous help, understanding and encouragement in the past 5 years, it would be impossible for me to complete my studies. I learnt a lot from your critical thinking, strong statistical knowledge, and clinical background.

I would also like to thank **Dr. Peter Woerdeman**. Dear Peter, I would like to express my sincere gratitude to you for the continuous support of my neurosurgery-related research, for your insightful comments and motivation.

My sincere thanks also go to **Prof. Manon Benders** who provided me an opportunity to join their team and gave access to the intensive care unit, research facilities, and electronic database. Without her continuous approvals, it would not have been possible to conduct this research.

I spent three years of my PhD period *in Toronto at SickKids*, doing clinical work with a wonderful group of people while also continuing my academic studies. I would like to express my sincere gratitude to **Prof. Hilary Whyte** who trusted me and brought me to SickKids and supported me tremendously. I could not have imagined having a better neonatal neurology training and I am cordially thankful to **Prof. Steven Miller** for being such a great leader and mentor and also to **Dr. Emily Tam, Dr. Vann Chau, Dr. Cecil Hahn, Diane Wilson, and Vanna Kazazian** for generously sharing their knowledge with me. I also would like to thank **Prof. Estelle Gauda and Prof. Martin Offringa** for their great mentorship and continuous support for my academic career. During the last two years of my neuroplasticity fellowship, **Dr. Linh Ly, Dr. Amr El-Shahed, and Dr. Andrew James** supported me tremendously to complete my studies and created a wonderful atmosphere in the clinic for me to learn and teach. I would like to extend my special gratitude to **Dr. Brian Kalish** for building a dedicated neonatal neuroscience group in our NICU and paying special attention to my ideas and thoughts. I also would like to thank to my senior staff in the NICU, **Dr. Kyoong-Soon Lee, Dr. Chris Tomlinson, Dr. Rebecca Hoban, Dr. Bonny Jasani, and Dr. Mary Woodward** for continuously updating my neonatology knowledge.

I am deeply grateful to **Dr. Lara Leijser** for always motivating and encouraging me, critically reviewing my drafts and offering her insightful comments. The three colleagues who were always there for me, **Dr. Niek van der Aa, Dr. Maria Luisa Tataranno,** and **Dr. Marko Culjat** will always be remembered with a smile on my face. I am sure, we will continue to have many more collaborations and share fond memories in the future.

I was privileged to be the first neonatal neurologist of my home country. Without **Prof. Esin Koç**'s great support nothing could be possible and I am deeply grateful for her ongoing support. I also co-founded a neonatal neurology working group in 2019 with my colleagues **Prof. Abdullah Kumral and Dr. Defne Engür**, and I would like to extend my heartfelt thanks for their dedication and support. I am also thankful to **Prof. Mehmet Satar, Prof. Merih Çetinkaya, Prof. Ebru Ergenekon, and Prof. Mustafa Ali Akın** for joining us and sharing their vast knowledge with our colleagues. My close friends, **Dr. İpek Güney Varal and Dr. Pelin Doğan** also deserve a special thank for being such a great support during the writing of my academic studies.

Inge-Lot van Haastert, many thanks for your great support, warm conversations, and for all the delicious foods you prepared for us! I have not told this to you before, but it was your special collaboration with Linda, which made me love neurodevelopmental follow-up. So I owe you a lot!

I also would like to offer my special thanks to the neonatology staff and faculty at WKZ, especially to **Dr. Jeroen Dudink, Dr. Karin Rademaker, Dr. Jaime Smal, Dr. Corine Koopman, and Frank van Bel**. I always enjoyed our conversations and learned a lot from your experiences.

Nienke Wagenaar, always nice to chat with you over a coffee and cordial thanks for your help during the writing of this thesis. I would like to thank all the previous PhD candidates and research fellows I worked with at Utrecht, especially **Dr. Ken Imai, Dr. Michael Hayman, Dr. Nathalie Claessens, Dr. Lauren Weeke, Dr. Kristin Keunen, Dr. Lisa Hortensius, Dr. Kim Annink, and Dr. Raymond Stegeman**. It is their warm support that have made my life in Utrecht a wonderful time.

Finally, I would like to express my gratitude to my parents, my wife and my children. Thank you my dear wife, **Dr. Elif Ayşe Çizmeci**, for always standing by me, listening and understanding what I think and how I feel and supporting me in pursuing my dreams. **Elif**, without your tremendous support this thesis could not be possible. My two lovely daughters, **Esin** (kuğum) and **Ela** (muhabbet kuşum), there are no words that can describe what you mean to me. Having you two in my life is a true blessing. Be whatever you want in life, but do never forget to be kind to others. My mother, **Berrin Çizmeci**, father **Münir Çizmeci**, and my dear sister, **Meral Çizmeci**, thank you for always believing in me. Without you, I might not be the person I am today!

UMC Utrecht

ISBN: 978-90-393-7439-9