Progress in Neonatal Neurology with a Focus on Neuroimaging in the Preterm Infant

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Neuropediatrics 2015;46:234–241.

Abstract

There have been tremendous changes in the methods used to evaluate brain injury in the preterm infant in the past 30 years. In particular, major improvements have been made in how we use neuroimaging techniques and now magnetic resonance imaging (MRI) is used more often and considered complimentary to routine and sequential cranial ultrasound. The focus has shifted from severe lesions such as large intraventricular and parenchymal hemorrhages and cystic periventricular leukomalacia to assessing and understanding the etiology of more subtle noncystic white matter injury, punctate hemorrhage, and cerebellar lesions. The more severe lesions that dominated the early period of preterm neonatal brain imaging occur less frequently but are still associated with major disabilities, such as, cerebral palsy, while subtle white matter injury and cerebellar lesions are more often associated with cognitive and behavioral problems, which have become the most prevalent issues among the survivors of extremely preterm birth.

Keywords
- neuro-imaging
- cranial ultrasound
- MRI
- cerebral palsy

Introduction

The first images of the neonatal brain were obtained using computed tomography in the late 70s[1] and there was concern about the high percentage of hemorrhages, usually in the absence of apparent clinical symptoms. Cranial ultrasound (cUS) was introduced into the neonatal intensive care unit only a few years later, initially through the temporal bone using a linear probe, but soon after the anterior fontanelle was used as the main acoustic window. The linear probe was replaced by a mechanical sector probe, which had better resolution and a wider field of insonation. This bedside technique, without ionizing radiation, allowed repeated imaging of the preterm infant and within a few years, we learned that 80% of germinal matrix–intraventricular hemorrhages (GMH–IVH) occurred within the first 72 hours after birth and that the hemorrhage could become more severe over the next day or so and it was sometimes associated with adjacent parenchymal involvement and the development of ventriculomegaly. Recently, we have also become aware that GMH–IVH may already be present at birth or develop beyond 96 hours after birth and this atypical presentation was associated with factor V Leiden mutation in 41% of these infants.[2] By performing daily examinations, risk factors for hemorrhage were identified, mostly related to complications of mechanical ventilation (pneumothorax, hypercarbia, "fighting the ventilator") or fluctuations in blood pressure or blood flow. With this knowledge, these risk factors could be minimized and a gradual decrease in the incidence of GMH–IVH was noted. However, antenatal administration of corticosteroids to enhance lung maturation has been the single most important factor for this reduction in GMH–IVH.[3]

The associated parenchymal involvement now known as a periventricular hemorrhagic infarction (PVHI) adjacent to the ventricle was initially considered to be due to the rupture of the ependymal lining of the ventricle from pressure due to the IVH itself. Most of us now consider a PVHI to be because of the hemorrhage due to impaired venous drainage of the

received
March 28, 2015
accepted
April 14, 2015
published online
June 29, 2015

DOI http://dx.doi.org/10.1055/s-0035-1554102.
ISSN 0174-304X.

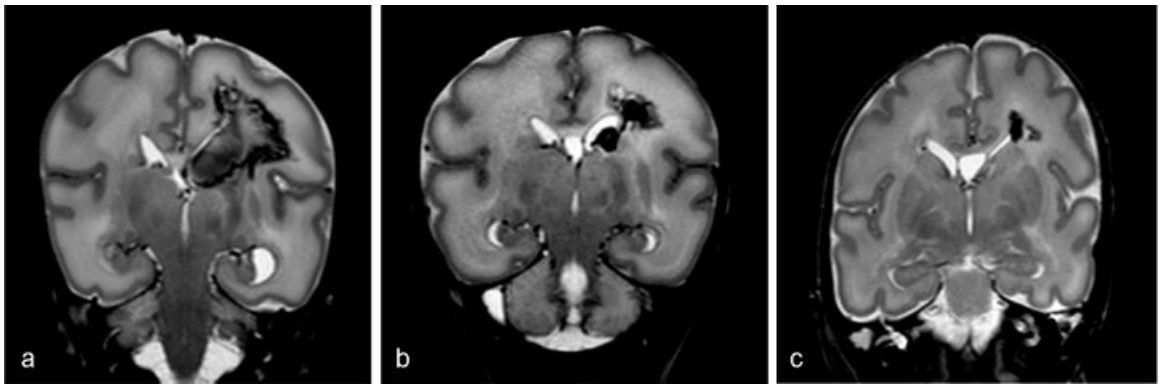

Fig. 1 Three preterm infants with a periventricular hemorrhagic infarction (PVHI). (a) A large PVHI (a) is communicating with the lateral ventricle. (b) A smaller one appears to be separate. (c) The third one is frontal and very small without an associated intraventricular hemorrhage.

medullary veins in the periventricular white matter. The PVHI tended to be large and globular in shape, the ventricular margin was not maintained allowing communication with the lateral ventricle and usually evolving into a porencephalic cyst. Now the lesions we see are more often smaller and triangular in shape and often are not or only partly communicating with the lateral ventricle and they evolve into one larger or several smaller cysts adjacent to the ventricle (►**Fig. 1**). The size and site of these PVHI lesions as seen on early cUS are predictive of outcome.[4–6] A PVHI in the frontal white matter carries the lowest risk of developing a unilateral spastic cerebral palsy (USCP) while infants with a PVHI involving the trigone are most at risk. Infants with a PVHI in the temporal lobe are more at risk of cognitive and visual problems.[6] A magnetic resonance imaging (MRI) at term-equivalent age (TEA) allows visual assessment of myelination of the posterior limb of the internal capsule (PLIC) and asymmetry in myelination with poor or absent myelin ipsilateral to the PVHI is highly predictive of the subsequent development of a contralateral USCP.[7] The use of diffusion tensor imaging (DTI) and a direction-encoded color map within 1 month of the PVHI onset, and well before visual assessment of PLIC myelination is possible, has shown asymmetry with delayed PLIC maturation in all who subsequently developed USCP.[8]

Posthemorrhagic Ventricular Dilatation

Posthemorrhagic ventricular dilatation (PHVD) develops in approximately 25 to 50% of preterm infants within 7 to 14 days after the onset of a severe GMH–IVH.[8] cUS is a very useful bedside technique for following this process (►**Fig. 2**). Measurements can be taken of the ventricular index (VI), anterior horn width and occipital horn width, and these measurements can be used to optimize timing of intervention.[9–11] When performing cUS before and after a lumbar puncture (LP) that was successful in draining a reasonable amount of cerebrospinal fluid (CSF) (10 mg/kg), one may see a decrease especially in the anterior horn width. Doppler ultrasound can be used to assess changes in cerebral hemodynamics in infants with PHVD, showing an increase in peak systolic flow velocity, followed by a decrease or absence of the

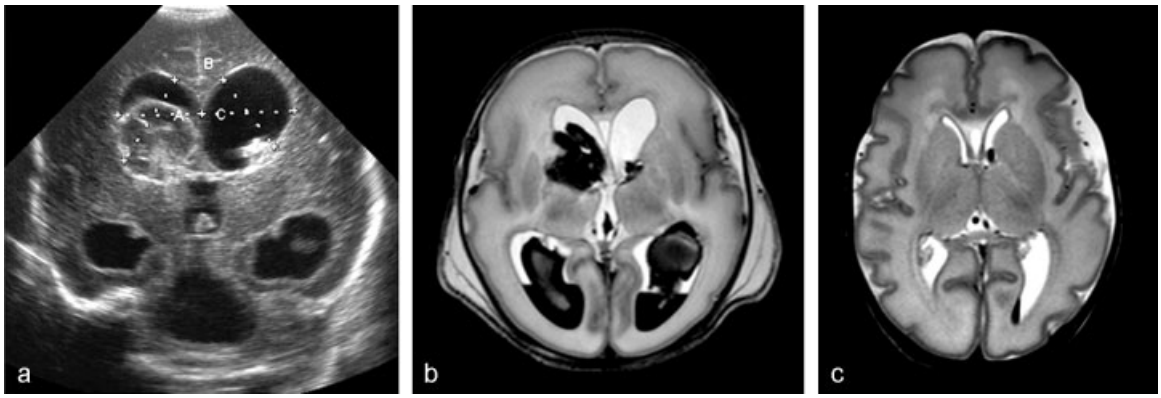

Fig. 2 Male infant, gestational age 29 weeks, with a grade III hemorrhage on the right and severe posthemorrhagic ventricular dilatation, including severe dilatation of the 4th ventricle, seen on a (a) coronal ultrasound scan. A and C are measurements of the ventricular width and B of the anterior horn width. (b) The T2-weighted sequence, performed at the age of 2 weeks, following intervention shows less "ballooning" of the ventricles and confirms the presence of bilateral germinal matrix–intraventricular hemorrhage (GMH–IVH). (c) Compared with another preterm infant, who had a magnetic resonance imaging at the same postmenstrual age, and who has a small IVH, there is a marked difference in signal intensity of the white matter cortical folding and the amount of extracerebral space.

end diastolic flow velocity with increasing intracranial pressure.[12] When LPs are not successful in alleviating the PHVD within a week, the pediatric neurosurgeon may be asked to insert a ventricular reservoir. cUS appearances and measurements will guide the neonatologist in how much CSF to tap from the reservoir to decrease the ventricular size below the 97th centile. There is an ongoing and often heated discussion both in the literature and between neonatologists and neurosurgeons about the optimal time to intervene in PHVD. It is well known that these very preterm infants have a large extracerebral space and it takes several weeks before classical clinical symptoms of increased intracranial pressure (apneas, bradycardia, vomiting, a full fontanelle or rapid increase in head circumference) will occur. Should one wait for clinical symptoms more applicable to the older child or should one treat earlier based on ventricular measurements made with cUS? Those who advocate early intervention are concerned about the adverse effect of intraventricular blood and progressive ventricular dilatation on the adjacent vulnerable periventricular white matter of the preterm infant and have reported better outcome data than others who were less proactive, but these data were retrospective and the need for a randomized controlled trial was acknowledged.[13,14] In a randomized controlled trial, early (i.e., initiated once the VI has crossed the 97th centile line[15]) versus late intervention (i.e., initiated after the VI has exceeded 4 mm above the 97th centile line) is compared (ELVIS trial, number ISRCTN43171322). Because of the decrease in the incidence of severe GMH–IVH, enrollment has been slow and the trial is still ongoing.

Cerebellar Hemorrhage

With the increased survival of extremely preterm infants (gestational age [GA], 24–28 weeks) and more routine use of the mastoid window when performing cUS, cerebellar hemorrhages (CBH) are now recognized as a common problem in a very immature infants.[16–18] The cerebellum has an extremely rapid and complex development during the preterm period. From 24 to 40 weeks' gestation, the cerebellar volume, as assessed with in vivo three-dimensional volumetric ultrasound, increases fivefold, and the surface area of the cerebellar cortex increases more than 30-fold during this period.[19–21]

The reported incidence of CBH when using cUS ranges from 2 to 9% depending on the GA of the population studied. When MRI is performed as well, the incidence is much higher and ranges from 15 to 20%.[18,22] cUS will only allow recognition of the hemorrhages which are more than 4 to 5 mm in size. Larger CBHs tend to be associated with supratentorial lesions, most often severe GMH–IVH. Smaller (punctate) hemorrhages in the cerebellum are far more common but can only be diagnosed with MRI.[23,24] Susceptibility-weighted imaging (SWI) further improves the recognition of small punctate cerebellar lesions (►**Fig. 3**).[23,25] Focal unilateral lesions occurring in the cerebellar hemisphere may originate in the external granular layer, covering the surface of the cerebellum, whereas the less common vermian hemorrhages may originate in residual GMH of the ventricular zone in the roof of the fourth ventricle. CBHs vary from a single to multiple punctate lesions present throughout both cerebellar hemispheres, a single larger hemorrhage in one cerebellar hemisphere, or large bilateral CBH.[26] When the MRI is repeated at TEA, atrophy of the affected cerebellar hemisphere can be seen following larger CBHs (►**Fig. 3c**). A unilateral PVHI can also be associated with a marked loss of contralateral cerebellar volume, so-called crossed cerebellar atrophy.[27] In contrast, Limperopoulos et al[28] showed that unilateral cerebellar lesions had an adverse effect on the contralateral cerebral volume.

The large CBHs occur within days of birth and as with GMH–IVH, cardiovascular factors appear to be important in the pathogenesis. In the study by Limperopoulos et al,[28] a persistent ductus arteriosus, the minimum pH on day 5 and being born by emergency cesarean delivery were identified as independent risk factors. Ventilation using high-frequency oscillation and the presence of a supratentorial hemorrhage were identified as independent risk factors for punctate cerebellar lesions.[22] While one would expect motor problems such as hypotonia, gait abnormalities, and ataxia, other deficits are more commonly reported in infants with CBH in the absence of severe supratentorial lesions. Among a group of 35 infants with an isolated CBH, impaired expressive language (37%), receptive language (42%), and cognitive deficits (40%), behavioral deficits (34%), and abnormal results on autism screener measures (37%) were common, and involvement of the vermis almost exclusively accounted for those with socialization difficulties and abnormal autism screening.[29] As MRI is more often used routinely, we will get more insight in how the site and size of the CBHs will affect outcome. Steggerda et al diagnosed small CBHs in 16 of 108 preterm infants did not find an association with neurodevelopmental outcome at 2 years of corrected age.[22] In another study enrolling 131 preterm infants with a cUS diagnosis of a CBH in 3 and an MRI diagnosis in a further 10 infants, there was a fivefold increase in the odds for abnormal neurological examination for those infants with hemorrhages only detected by MRI compared with preterm infants without CBHs and adjusted for GA, presence of associated IVH, and white matter injury (WMI). They did, however, not find an association with the Wechsler Preschool and Primary Scale of Intelligence assessment at the age of 3 to 6 years.[30]

White Matter Injury

With higher resolution ultrasound probes and a wider view of insonation, assessment of the white matter has improved considerably although it remains difficult as subtle white matter seen as increased echogenicity with cUS is a very subjective finding. Cystic WMI referred to as cystic periventricular leukomalacia (c-PVL), a term coined in 1962 by Banker and Larroche[31], "softening" (malacia) of the "white" (leukos) matter is nowadays no longer a common finding and sequential cUS is needed to recognize the cysts which take 2 to 4 weeks to develop.[32] These cysts in the white matter were

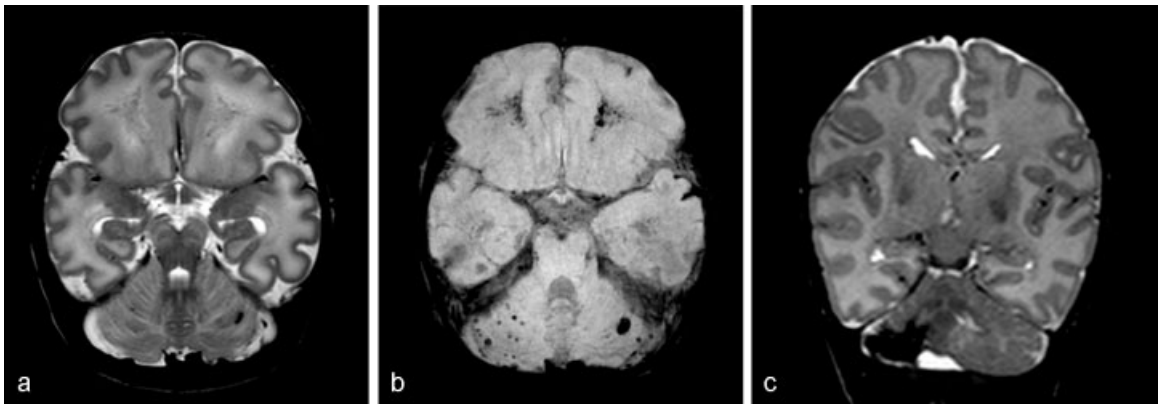

Fig. 3 (a and b) Punctate hemorrhagic cerebellar lesions, not recognized with mastoid window cranial ultrasound and more clearly seen with the (b) susceptibility-weighted imaging sequence than the (a) T2-weighted axial magnetic resonance imaging. Also note bilateral punctate lesions in the frontal white matter. (c) A larger cerebellar hemorrhage is shown in another infant with atrophy of the cerebellar hemisphere at term-equivalent age.

first diagnosed with cUS in the early 80s. When severe echogenicity is seen with cUS, an MRI, and especially diffusion-weighted imaging (DWI) performed within 7 to 10 days after the presumed insult may assist in the prediction of cystic evolution. Even though not all with increased signal intensity (SI) on DWI will show cystic evolution, most do in the presence of confluent areas of restricted diffusion.[33,34] The fluid in these cysts subsequently resorbs with adhesion of the walls of the cysts over the next weeks or months, resulting in the white matter loss and irregular dilatation of the adjacent ventricle. As with PVHI, the extent and especially the site of the cysts are important. Infants with extensive cysts in the parieto-occipital white matter are especially at risk for developing cerebral palsy.[35] MRI at TEA allows assessment of myelination of the PLIC and delayed or absent myelination is highly predictive of subsequent bilateral spastic cerebral palsy (BSCP).[7] By this time, areas of increased SI are sometimes seen on a T1-weighted image, suggestive of early gliosis. When performing tractography of the corticospinal tracts and segmentation of the thalamus on an early and TEA-MRI, a significant difference in fractional anisotropy (FA) values of the corticospinal tracts was found between cases and controls on both sets of scans. Thalamic volumes were similar to the controls on the early MRI but significantly reduced at TEA.[36]

In contrast to GMH–IVH, risk factors were more difficult to elucidate for WMI. Hypotension of the boundary zones was considered to be a likely risk factor, but this has not been confirmed and over the last decade or so, it has become clear that WMI is a more multifactorial problem, with (antenatal) inflammation and excitotoxic injury being the key players.[37–39] The time of onset may be antenatal, but it extends into the neonatal period and some infants may have so-called late-onset c-PVL following an acute deterioration, for example, after developing sepsis or necrotizing enterocolitis.[40] Enterovirus, parechovirus, or rotavirus infection may also result in c-PVL, even though CSF polymerase chain reaction will only be positive for enterovirus and parechovirus but not for rotavirus infection.[41–44] It is therefore recommended to repeat cUS following any clinical deterioration occurring at any time until discharge home as well as in infants readmitted with a rash, fever, and diarrhea.

A significant decline in the incidence of c-PVL has been noted in several centers over the last couple of decades and this coincided in one, but not in the other study with a decrease in the number of infants who developed CP as well as the severity of their disability, assessed using the gross motor function classification system.[45,46] In the study by van Haastert et al,[46] the decline was associated with an increased use of antenatal corticosteroids, the antenatal use of antibiotics, birth by cesarean delivery and insertion of an arterial catheter after birth, the latter allowing better control of blood pressure and carbon dioxide levels. It is well known that hypocarbia is associated with c-PVL, most likely due to vasoconstriction.[47] As a result of this reduction in c-PVL, several studies performing routine MRI at TEA only found a very small number of infants with c-PVL and it seemed therefore more appropriate to talk about WMI, also including subtle WMI, which is much more common in the preterm population.[37] Several studies performed in the last 10 to 15 years showed that the role of cUS was limited when it comes to recognizing milder WMI and MRI is considered to be the "gold standard." Counsell et al[48] coined the term DEHSI (diffuse excessive high SI) and reported that high SI in the white matter was a common finding in very preterm infants. They were also able to measure apparent diffusion coefficient (ADC) values using DWI and showed that ADC values were significantly higher than in preterm infants without DEHSI and comparable to those with overt WMI, such as infants with c-PVL. They subsequently reported that these infants with increased ADC values in the white matter at TEA had volume reduction in the periventricular white matter, the corona radiate, and within the central region of the centrum semiovale dorsomedial nucleus and also the thalamus and the globus pallidus and these imaging findings were associated with a significantly lower developmental quotient using the Griffiths mental development scale at 24 months of corrected age.[49] Several groups have since then however reported that

they were unable to find an association between DEHSI and neurodevelopmental outcome at 18 to 24 months.[50–54] More often white matter abnormalities have been graded as mild, or moderate to severe.[55] Woodward et al reported that moderate-to-severe WMI were associated with problems at school age.[56] Others have focused on punctate white matter lesions (PWMLs), seen in approximately 25% of the preterm infants.[50,57] The presence of inhomogeneous periventricular echogenicity on cUS may suggest the presence of PWMLs, but the sensitivity is quite low.[58] PWMLs are seen as areas of low SI on a T2-weighted sequence and as high SI on a T1-weighted sequence. Because of this, the lesions were initially considered to be hemorrhagic in origin, but with the use of additional MRI sequences it appears that some PWMLs are hemorrhagic and some more ischemic. When the MRI is performed within a week after the presumed insult, ischemic lesions are seen as high SI on DWI. The lesions are often seen in clusters and are even more florid on the T1-weighted sequence performed at TEA, possibly due to early gliosis. Findings from SWI further support the ischemic nature of these lesions, due to the lack of low SI. When low SI is seen on the SWI, this is suggestive of hemorrhage in the lesion. Hemorrhagic PWMLs are more often seen in the presence of GMH–IVH and tend to have a more linear appearance.[59]

Perinatal Arterial Ischemic Stroke

While most data about perinatal arterial ischemic stroke (PAIS) only includes full-term infants, PAIS is not uncommon in preterm infants (0.7% in preterm infants with a GA of $\leq$ 35 weeks).[60] Similar to full-term infants, PAIS was more common on the left (61%), and 7% had bilateral lesions. The majority of strokes involved the middle cerebral artery (MCA) distribution. Twin-to-twin transfusion syndrome, fetal heart rate abnormality, and hypoglycemia were identified as independent risk factors for preterm PAIS. It was of interest that involvement of one or more MCA lenticulostriate branches was common in the preterm infant, referred to as "perforator stroke" by Ecury-Goossen et al.[61] In this study, 25 of the 55 infants with perforator stroke were born preterm. Similar to our study, perforator stroke was first diagnosed beyond the first week in 40% of the infants, illustrating the importance of sequential cUS.[60,61] In a recent study, comparing cUS with an early MRI perforator stroke was more reliably diagnosed with cUS than with MRI.[24]

Bilateral injury to the thalami is unlikely to be because of the bilateral stroke, but it can occur in preterm infants with severe HIE. These abnormalities have only been reported a few times so far.[62,63] Logitharajah et al[63] only reported the MRI findings. The basal ganglia and brain stem were also often involved and outcome was poor with only one-third of the infants having a normal outcome at the age of 2 years. A third died, and nearly a quarter developed quadriplegic CP. Symmetrical echogenicity in the thalami can also be seen in late-preterm or full-term infants who are considered to have had an acute antenatal insult, even though the history is not always clear.[64,65] The abnormalities are usually recognized with cUS and become more marked with time (►**Fig. 4**). They tend to present with low Apgar scores, no spontaneous movements, are hypertonic often associated with contractures, sometimes following initial hypotonia, are unable to suck and swallow, and may have facial diplegia. The prognosis is very poor, with lack of psychomotor development and they usually die within weeks or months.

Future Directions

In this review, the focus was on the most commonly used neuroimaging techniques, cUS, and conventional MRI. While we tend to perform both cUS and MRI to look for

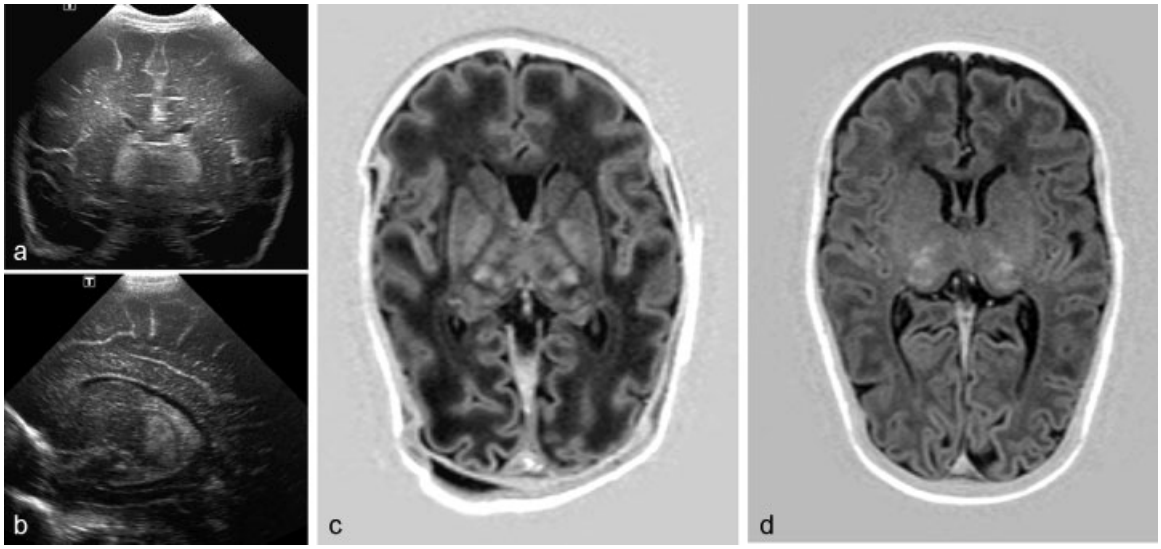

Fig. 4 Male infant, gestational age 34 weeks. (a) Coronal and (b) parasagittal ultrasound scans performed on day 1, showing bilateral thalamic echogenicity. (a) Axial magnetic resonance imaging T1-weighted images in the first week (c) and (d) at term-equivalent age (TEA) show increased signal intensity in the thalami. At TEA (d), the thalami look small and there is no myelination of the posterior limb of the internal capsule.

the presence of abnormalities, we should not forget that sequentially normal cUS and a normal MRI at TEA, especially when combined with a normal neurological examination are also very important in predicting a good outcome and very reassuring for the parents. Abnormalities found on an MRI may however also cause parental concern and some parents would prefer to have an informed choice about performing an MRI and may prefer not to hear the results.[66]

Other quantitative and more advanced MRI techniques are still mainly used for research but the additional value of DTI, allowing early detection of asymmetry of the corticospinal tracts was mentioned. These advanced techniques are especially promising for a better understanding of the impact of neonatal intensive care on subsequent brain development, but at present provide less specific information for the individual child.[67,68] Several studies have shown the predictive value for cognitive outcome at 2 years of corrected age of using tract-based spatial statistics (TBSS)[69] and a recent study demonstrated that thalamocortical connectivity assessed in the preterm brain at TEA is correlated with cognitive performance at the age of 2 years.[70] Using these advanced MR techniques may allow better prediction of cognitive outcome which has become increasingly important now that severe motor deficits are fewer—a reduction in cognitive abilities and also the presence of behavioral difficulties have now become the more common problematic sequelae for extremely preterm infants who survive the neonatal period.[71]

Acknowledgments

I am very grateful to Professor Frances Cowan who made very useful suggestions and performed a critical review of the article. I am also grateful to the medical and nursing staff members who participated in caring for the infants, and all the technicians working in the MRI unit.

References

1 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(4):529–534
2 Harteman JC, Groenendaal F, van Haastert IC, et al. Atypical timing and presentation of periventricular haemorrhagic infarction in preterm infants: the role of thrombophilia. Dev Med Child Neurol 2012;54(2):140–147
3 Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006;19(3):CD004454
4 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(6): 602–608
5 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(6):2111–2118
6 Soltirovska Salamon A, Groenendaal F, van Haastert IC, et al. Neuroimaging and neurodevelopmental outcome of preterm infants with a periventricular haemorrhagic infarction located in the temporal or frontal lobe. Dev Med Child Neurol 2014;56(6): 547–555
7 de Vries LS, van Haastert IC, Benders MJ, Groenendaal F. Myth: cerebral palsy cannot be predicted by neonatal brain imaging. Semin Fetal Neonatal Med 2011;16(5):279–287
8 Roze E, Benders MJNL, Kersbergen KJ, et al. Neonatal DTI early after birth predicts motor outcome in preterm infants with periventricular hemorrhagic infarction. Pediatr Res, May 15. doi: 10.1038/pr.2015.94. [Epub ahead of print]
9 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
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 Neonatol Ed 2000;82(3): F218–F223
11 Brouwer MJ, de Vries LS, Groenendaal F, et al. New reference values for the neonatal cerebral ventricles. Radiology 2012;262(1): 224–233
12 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(10):1315–1319
13 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(5):648–654
14 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(5):e1167–e1177
15 Murphy BP, Inder TE, Rooks V, et al. Posthaemorrhagic ventricular dilatation in the premature infant: natural history and predictors of outcome. Arch Dis Child Fetal Neonatal Ed 2002; 87(1):F37–F41
16 Limperopoulos C, Benson CB, Bassan H, et al. Cerebellar hemorrhage in the preterm infant: ultrasonographic findings and risk factors. Pediatrics 2005;116(3):717–724
17 Ecury-Goossen GM, Dudink J, Lequin M, Feijen-Roon M, Horsch S, Govaert P. The clinical presentation of preterm cerebellar haemorrhage. Eur J Pediatr 2010;169(10):1249–1253
18 Steggerda SJ, Leijser LM, Wiggers-de Bruïne FT, van der Grond J, Walther FJ, van Wezel-Meijler G. Cerebellar injury in preterm infants: incidence and findings on US and MR images. Radiology 2009;252(1):190–199
19 Chang CH, Chang FM, Yu CH, Ko HC, Chen HY. Assessment of fetal cerebellar volume using three-dimensional ultrasound. Ultrasound Med Biol 2000;26(6):981–988
20 Lemire RJ, Loeser JD, Leech RW, Alvord EC Jr. Normal and Abnormal Development of the Human Nervous System. Hagerstown: Harper & Row; 1975
21 Volpe JJ. Cerebellum of the premature infant: rapidly developing, vulnerable, clinically important. J Child Neurol 2009;24(9): 1085–1104
22 Steggerda SJ, De Bruïne FT, van den Berg-Huysmans AA, et al. Small cerebellar hemorrhage in preterm infants: perinatal and postnatal factors and outcome. Cerebellum 2013;12(6):794–801
23 Parodi A, Rossi A, Severino M, et al. Accuracy of ultrasound in assessing cerebellar haemorrhages in very low birthweight babies. Arch Dis Child Fetal Neonatal Ed 2015 (e-pub ahead of print). 10.1136/archdischild-2014-307176
24 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 (e-pub ahead of print). 10.1136/archdischild-2014-306129
25 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(2):81–88
26 Kidokoro H, Anderson PJ, Doyle LW, Woodward LJ, Neil JJ, Inder TE. Brain injury and altered brain growth in preterm infants: predictors and prognosis. Pediatrics 2014;134(2):e444–e453
27 Rollins NK, Wen TS, Dominguez R. Crossed cerebellar atrophy in children: a neurologic sequela of extreme prematurity. Pediatr Radiol 1995;25(Suppl 1):S20–S25
28 Limperopoulos C, Soul JS, Haidar H, et al. Impaired trophic interactions between the cerebellum and the cerebrum among preterm infants. Pediatrics 2005;116(4):844–850
29 Limperopoulos C, Bassan H, Gauvreau K, et al. Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning, and behavioral disability in survivors? Pediatrics 2007;120(3):584–593
30 Tam EW, Rosenbluth G, Rogers EE, et al. Cerebellar hemorrhage on magnetic resonance imaging in preterm newborns associated with abnormal neurologic outcome. J Pediatr 2011;158(2): 245–250
31 Banker BQ, Larroche JC. Periventricular leukomalacia of infancy. A form of neonatal anoxic encephalopathy. Arch Neurol 1962; 7:386–410
32 Pierrat V, Duquennoy C, van Haastert IC, Ernst M, Guilley N, de Vries LS. Ultrasound diagnosis and neurodevelopmental outcome of localised and extensive cystic periventricular leucomalacia. Arch Dis Child Fetal Neonatal Ed 2001;84(3):F151–F156
33 Inder T, Huppi PS, Zientara GP, et al. Early detection of periventricular leukomalacia by diffusion-weighted magnetic resonance imaging techniques. J Pediatr 1999;134(5):631–634
34 Fu J, Xue X, Chen L, et al. Studies on the Value of Diffusion-Weighted MR Imaging in the Early Prediction of Periventricular Leukomalacia. J Neuroimaging 2009;19(1):13–18
35 Fazzi E, Orcesi S, Caffi L, et al. Neurodevelopmental outcome at 5-7 years in preterm infants with periventricular leukomalacia. Neuropediatrics 1994;25(3):134–139
36 Kersbergen KJ, de Vries LS, Groenendaal F, et al. Corticospinal tract injury precedes thalamic volume reduction in preterm infants with cystic periventricular leukomalacia (epub ahead of print). J Pediatr 2015; pii: S0022-3476(15)00493-X. doi: 10.1016/j.jpeds.2015.05.013
37 Back SA. Perinatal white matter injury: the changing spectrum of pathology and emerging insights into pathogenetic mechanisms. Ment Retard Dev Disabil Res Rev 2006;12(2):129–140
38 Volpe JJ. Systemic inflammation, oligodendroglial maturation, and the encephalopathy of prematurity. Ann Neurol 2011;70(4):525–529
39 Back SA, Miller SP. Brain injury in premature neonates: A primary cerebral dysmaturation disorder? Ann Neurol 2014;75(4): 469–486
40 André P, Thébaud B, Delavaucoupet J, et al. Late-onset cystic periventricular leukomalacia in premature infants: a threat until term. Am J Perinatol 2001;18(2):79–86
41 Verboon-Maciolek MA, Groenendaal F, Cowan F, Govaert P, van Loon AM, de Vries LS. White matter damage in neonatal enterovirus meningoencephalitis. Neurology 2006;66(8):1267–1269
42 Verboon-Maciolek MA, Groenendaal F, Hahn CD, et al. Human parechovirus causes encephalitis with white matter injury in neonates. Ann Neurol 2008;64(3):266–273
43 Verboon-Maciolek MA, Truttmann AC, Groenendaal F, et al. Development of cystic periventricular leukomalacia in newborn infants after rotavirus infection. J Pediatr 2012;160(1):165–8.e1
44 Yeom JS, Kim YS, Seo JH, et al. Distinctive pattern of white matter injury in neonates with rotavirus infection. Neurology 2015; 84(1):21–27
45 Hamrick SE, Miller SP, Leonard C, et al. Trends in severe brain injury and neurodevelopmental outcome in premature newborn infants: the role of cystic periventricular leukomalacia. J Pediatr 2004; 145(5):593–599
46 van Haastert IC, Groenendaal F, Uiterwaal CS, et al. Decreasing incidence and severity of cerebral palsy in prematurely born children. J Pediatr 2011;159(1):86–91.e1
47 Shankaran S, Langer JC, Kazzi SN, Laptook AR, Walsh M; National Institute of Child Health and Human Development Neonatal Research Network. Cumulative index of exposure to hypocarbia and hyperoxia as risk factors for periventricular leukomalacia in low birth weight infants. Pediatrics 2006;118(4):1654–1659
48 Counsell SJ, Allsop JM, Harrison MC, et al. Diffusion-weighted imaging of the brain in preterm infants with focal and diffuse white matter abnormality. Pediatrics 2003;112(1 Pt 1):1–7
49 Boardman JP, Craven C, Valappil S, et al. A common neonatal image phenotype predicts adverse neurodevelopmental outcome in children born preterm. Neuroimage 2010;52(2):409–414
50 de Bruïne FT, van den Berg-Huysmans AA, Leijser LM, et al. Clinical implications of MR imaging findings in the white matter in very preterm infants: a 2-year follow-up study. Radiology 2011;261(3): 899–906
51 Hart A, Whitby E, Wilkinson S, Alladi S, Paley M, Smith M. Neurodevelopmental outcome at 18 months in premature infants with diffuse excessive high signal intensity on MR imaging of the brain. Pediatr Radiol 2011;41(10):1284–1292
52 Kidokoro H, Anderson PJ, Doyle LW, Neil JJ, Inder TE. High signal intensity on T2-weighted MR imaging at term-equivalent age in preterm infants does not predict 2-year neurodevelopmental outcomes. AJNR Am J Neuroradiol 2011;32(11):2005–2010
53 Jeon TY, Kim JH, Yoo SY, et al. Neurodevelopmental outcomes in preterm infants: comparison of infants with and without diffuse excessive high signal intensity on MR images at near-term-equivalent age. Radiology 2012;263(2):518–526
54 Skiöld B, Vollmer B, Böhm B, et al. Neonatal magnetic resonance imaging and outcome at age 30 months in extremely preterm infants. J Pediatr 2012;160(4):559–566.e1
55 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(7):685–694
56 Woodward LJ, Clark CA, Bora S, Inder TE. Neonatal white matter abnormalities an important predictor of neurocognitive outcome for very preterm children. PLoS ONE 2012;7(12):e51879
57 Bassi L, Chew A, Merchant N, et al. Diffusion tensor imaging in preterm infants with punctate white matter lesions. Pediatr Res 2011;69(6):561–566
58 Leijser LM, de Bruïne FT, van der Grond J, Steggerda SJ, Walther FJ, van Wezel-Meijler G. Is sequential cranial ultrasound reliable for detection of white matter injury in very preterm infants? Neuroradiology 2010;52(5):397–406
59 Kersbergen KJ, Benders MJ, Groenendaal F, et al. Different patterns of punctate white matter lesions in serially scanned preterm infants. PLoS ONE 2014;9(10):e108904
60 Benders MJ, Groenendaal F, Uiterwaal CS, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the preterm infant. Stroke 2007;38(6):1759–1765
61 Ecury-Goossen GM, Raets MM, Lequin M, Feijen-Roon M, Govaert P, Dudink J. Risk factors, clinical presentation, and neuroimaging findings of neonatal perforator stroke. Stroke 2013;44(8): 2115–2120
62 Barkovich AJ, Sargent SK. Profound asphyxia in the premature infant: imaging findings. AJNR Am J Neuroradiol 1995;16(9): 1837–1846
63 Logitharajah P, Rutherford MA, Cowan FM. Hypoxic-ischemic encephalopathy in preterm infants: antecedent factors, brain imaging, and outcome. Pediatr Res 2009;66(2):222–229
64 Eicke M, Briner J, Willi U, Uehlinger J, Boltshauser E. Symmetrical thalamic lesions in infants. Arch Dis Child 1992;67(1 Spec No): 15–19
65 Buldini B, Drigo P, Via LD, Calderone M, Laverda AM. Symmetrical thalamic calcifications in a monozygotic twin: case report and literature review. Brain Dev 2005;27(1):66–69

66 Pearce R, Baardsnes J. Term MRI for small preterm babies: do parents really want to know and why has nobody asked them? Acta Paediatr 2012;101(10):1013–1015
67 Ment LR, Hirtz D, Hüppi PS. Imaging biomarkers of outcome in the developing preterm brain. Lancet Neurol 2009;8(11): 1042–1055
68 van den Heuvel MP, Kersbergen KJ, de Reus MA, et al. The Neonatal Connectome During Preterm Brain Development. Cereb Cortex 2014:bhu095 (e-pub ahead of print)
69 van Kooij BJ, de Vries LS, Ball G, et al. Neonatal tract-based spatial statistics findings and outcome in preterm infants. AJNR Am J Neuroradiol 2012;33(1):188–194
70 Ball G, Pazderova L, Chew A, et al. Thalamocortical Connectivity Predicts Cognition in Children Born Preterm. Cereb Cortex 2015: bhu331 [Epub ahead of print]
71 Moore T, Hennessy EM, Myles J, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. BMJ 2012;345:e7961