

Neuroimaging and Neurodevelopmental Outcome of Premature Infants

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ABSTRACT

Preterm birth is associated with variable degrees of brain injury and adverse neurodevelopmental outcomes. Neuroimaging has been investigated as a predictor of outcome in this population. Head ultrasound allows for rapid bedside evaluation of the neonatal brain for early intraventricular hemorrhage surveillance and later detection of periventricular leukomalacia. Computed tomography can provide excellent views for bones, hemorrhage, extra-axial space, and the ventricles but is rarely used for prognostic purposes. Magnetic resonance imaging allows for high-resolution images of brain structures, differentiation of white and gray matter, visualization of the brain stem and posterior fossa, and getting additional physiological information with specialized sequences. Though controversial, the use of magnetic resonance imaging, at term equivalent, as a predictor of later outcome in preterm infants has been increasing and has been advocated by some as a standard practice. In this article, we review and contrast the use of these various imaging modalities in predicting neurodevelopmental outcome of premature infants.

KEYWORDS: MRI, head ultrasound, CT, brain injury, preterm

Neuroimaging has been extensively evaluated as a predictor of neurodevelopmental outcome in preterm infants. Major modalities used are head ultrasound (HUS), computed tomography (CT), and magnetic resonance imaging (MRI). HUS has been integrated into standard of care for early intraventricular hemorrhage (IVH) surveillance and later detection of periventricular leukomalacia (PVL). Cranial CT is rarely used for prognostic purposes but does have a role in specific clinical scenarios in the preterm infant. MRI is an emerging tool that is undergoing extensive research and improvements to increase its sensitivity and accuracy for detecting neurological abnormalities. In this article,

we review the use of these various imaging modalities in predicting neurodevelopmental outcome in premature infants.

HEAD ULTRASOUND

HUS via the cranial fontanels allows for rapid bedside evaluation of the neonatal brain. The standard views for HUS are the sagittal and coronal views through the anterior fontanel. Other views may be obtained by imaging via the mastoid or posterior fontanels. The mastoid fontanel allows better visualization of the posterior fossa and brain stem,^{1,2} and the posterior fontanel

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Table 1 Classification of IVH

Grade	Papile et al 1978 ⁴	Volpe 2008 ⁸ and Whitelaw 2001 ⁷
I	Subependymal hemorrhage	Hemorrhage apparently confined to GM, or minimum IVH (10% on parasagittal view) ⁸
II	IVH without dilatation	IVH clearly in ventricle, does not distend and <50% of the ventricles
III	IVH with dilatation	IVH >50%, usually distends lateral ventricles
IV	IVH with parenchymal involvement	Periventricular echodensity now termed "periventricular hemorrhagic infarction"

GM, germinal matrix; IVH, intraventricular hemorrhage.

allows for better visualization of the trigone and occipital horn of the lateral ventricles as well as the posterior fossa.³ Since its initial use in the late 1970s, numerous studies have reviewed the use of HUS in the detection of neonatal cranial abnormalities.

Abnormalities Detected by HUS

GERMINAL MATRIX IVH

The classic grading system of germinal matrix (GM) IVH was initially described by Papile et al,⁴ based on observations from CT scans performed on 46 very low-birth-weight (VLBW; <1500 g) infants. Findings were graded on a scale from I to IV (Table 1). Although this classification has been used in classic teaching and literature, it has its limitations both in nomenclature and significance.^{5,6} In grade I, there is no intraventricular element to justify calling it IVH. Grade III could be applied to either ventriculomegaly associated with IVH or more precisely large IVH distending the ventricles. Finally, neuropathological, Doppler blood flow, and MRI studies have determined that "grade IV" IVH is not a result of hemorrhage extending from the GM and ventricles to adjacent parenchymal tissue as previously believed. In contrast, it represents a distinct pathological entity caused by obstruction of blood flow in the terminal veins leading to venous infarction and hemorrhage into the surrounding tissue. Because of this, it is now more widely accepted to refer to grade IV hemorrhage as periventricular hemorrhagic infarction.^{7,8} Over the years, other classifications have evolved based on prognostic significance but have not been as popular.⁹ Although nowadays some authors call for totally abandoning such classification,⁵ others recommend continuing use of it with good understanding of its limitations.¹⁰ HUS findings in IVH are shown in Fig. 1.

VENTRICULOMEGALY

Ventriculomegaly is detected by HUS with excellent sensitivity.¹¹ Levene¹² described a ventricular index that is defined as the distance in millimeters between the midline and lateral border of the smaller lateral ventricle in the coronal plane at the level of the foramen of Monro. A curve showing the normal percentile at different gesta-

tional ages has been developed. Ventricular diameter >4 mm above the 97th percentile is considered severe and has been used as an inclusion criterion for different studies as a marker of progressive ventricular dilatation requiring intervention.¹³⁻¹⁵ Davies et al¹⁶ proposed a more detailed methodology that includes measuring different distances including anterior horn width, thalamo-occipital distance, third ventricle width, and fourth ventricle width and length. Reference measures ranges have been provided for preterm babies from 23 to 33 weeks postmenstrual age with good intra- and interobserver reliability. In our experience, we have proposed the use of simplified criteria to grade the severity of ventriculomegaly into mild (no third ventricular dilatation), moderate (third ventricle and temporal horn dilatation), and severe (with cortical thinning; Fig. 2).

WHITE MATTER INJURY (PERIVENTRICULAR LEUKOMALACIA)

White matter injury (WMI) appears on HUS as increased periventricular echogenicity that may or may not develop into cysts. De Vries et al¹⁷ has classified PVL by ultrasound into four grades. Grade I describes increased periventricular echogenicity that persists more than 7 days. Grade II describes the development of small periventricular cysts. Grade III describes the development of extensive periventricular cysts in the occipital and frontoparietal regions. Grade IV (rarely seen in premature infants) appears as echogenicity in deep white matter developing into extensive subcortical cysts. Cyst development is often not detectable by HUS until 4 to 6 weeks following injury as coagulation necrosis and cellular loss evolve over time.

CEREBELLAR HEMORRHAGE

Cerebellar hemorrhage has been recently recognized as an important complication of extreme prematurity and is associated with increased morbidity and mortality.^{18,19} At times, these lesions can be detected by ultrasound. However, the sensitivity and specificity are variable because the cerebellum is echogenic and often difficult to distinguish from infarctions and hemorrhages. Additionally, both the cerebellum and the posterior fossa are difficult to visualize on traditional anterior fontanelle views. With careful attention to asymmetry in echogenicity and the use of mastoid or

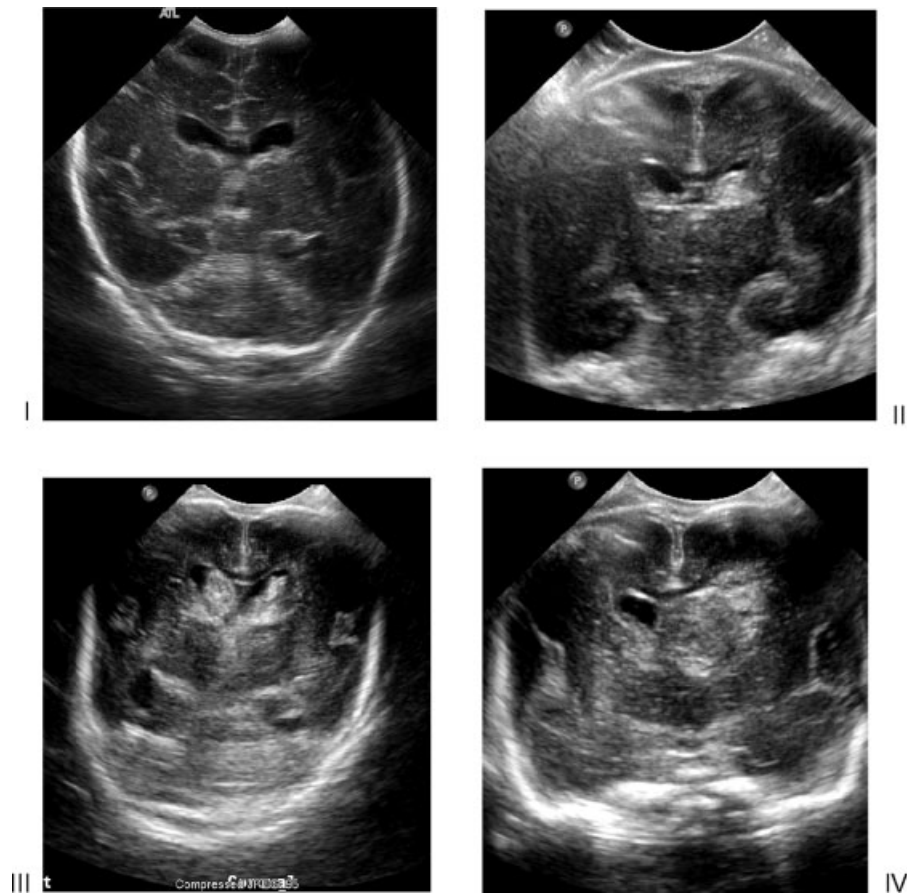


Figure 1 Grades of germinal matrix intraventricular hemorrhage (grades I to IV).

posterior fontanelle views, these lesions are more easily visualized (Fig. 3).^{19,20}

CORPUS CALLOSUM GROWTH

The corpus callosum (CC) is one of the structures that can be easily identified, assessed, and measured in the sagittal midline view of HUS. When compared with the CC height, the CC length is more strongly correlated with gestational age with very good interobserver reliability. Because the CC is a major white matter pathway,

it was studied in correlation with WMI. Motor deficits were more prevalent in individuals with the slowest growth rates of CC between 2 and 6 weeks of age,²¹ as well as those with a shorter CC at term.²²

DOPPLER HUS

Doppler HUS has been used to measure cerebral blood flow in the major cerebral blood vessels. These measurements can be used to determine the resistance for blood flow. Normal flow velocities have been determined and

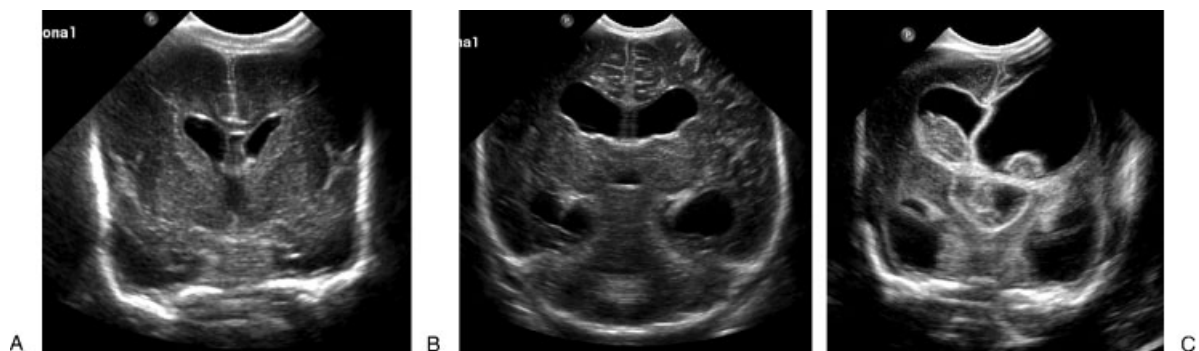


Figure 2 Grades of ventriculomegaly: (A) mild; (B) moderate; and (C) severe.

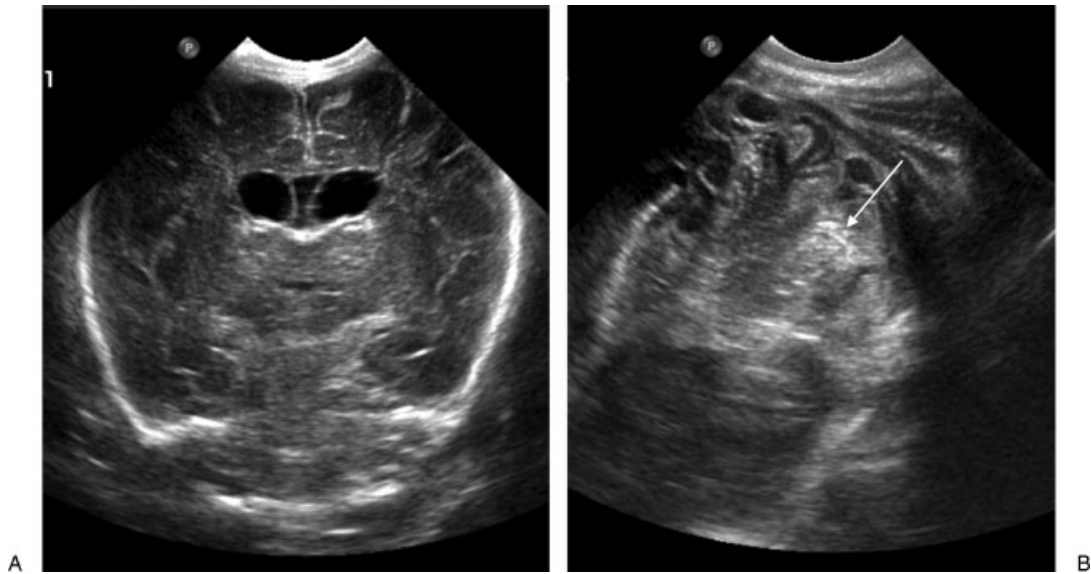


Figure 3 Mastoid view demonstrates posterior fossa abnormalities. (A) Image via the anterior fontanel does not demonstrate the posterior fossa hemorrhagic infarction, although (B) transmastoid images in same patient, same day, demonstrate the presence of a cerebellar hemorrhagic infarction (arrow).

were found to progressively increase with increasing birth weight²³ and gestational age.²⁴ Autoregulation in neonates can still be demonstrated even in extremely low-birth-weight (ELBW; <1000 g) infants.²⁵ However, it becomes impaired in the first few days of life after a hypoxic ischemic insult.²⁷ In preterm infants, fluctuation in cerebral blood flow velocity and absent end-diastolic flow was associated with development of GM IVH.^{26–28} In cases of established GM hemorrhage, absent flow in the terminal veins was associated with the development of periventricular hemorrhagic infarction.²⁹ Infants with posthemorrhagic ventricular dilatation had increased change in flow resistance with anterior fontanelle compression that was correlated with increased intracranial tension and was associated with the consequent need of surgical intervention.³⁰ Following cerebrospinal fluid (CSF) drainage, Doppler studies are useful in monitoring improving cerebral blood flow.³¹

Imaging Protocols

There is no universally accepted protocol for HUS screening in the preterm infant. The Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society states: “Routine screening cranial ultrasonography should be performed on all infants of 30 weeks’ gestation once between 7 and 14 days of age and should be optimally repeated between 36 and 40 weeks’ postmenstrual age.”³² Even with this recommendation, timing of HUS screening varies amongst U.S. centers due to physician practices and

availability of radiology staff and equipment. In Europe, HUS may be done more frequently. Some centers perform HUS as soon as possible after admission, at least once a week until discharge, and again at term equivalent during the first follow-up visit.³³ This variation in frequency and timing of imaging may affect the ability of HUS to detect abnormality and subsequently predict outcome. In our experience, performing at least three HUS in premature infants <1750 g, at 3 to 5 days, at 2 weeks, and at 4 to 6 weeks, is sufficient to identify early hemorrhage or late PVL.

Additionally, identification of abnormality depends on the imaging methodology used and the experience of the interpreter. As mentioned previously, posterior and mastoid views allow for detection of abnormalities in regions not well visualized through the anterior fontanel. Routine use of the posterior fontanel view increases the diagnostic rate of grade II IVH by 32%.³ Multiple studies have also shown that there is significant interobserver variability in interpreting HUS.^{34–38} This variability is more significant in low grade IVH (grades I and II) and PVL.³⁸ In our institute, we advocate including routine posterior and mastoid views in addition to Doppler interrogation of the major cerebral arteries in the routine HUS protocol for preterm infants.

Predictive Value of HUS

Many studies have investigated the predictive value of HUS in detecting either short- or long-term neurodevelopmental outcome.^{33,39–55} These studies include retrospective and prospective studies. When interpreting

predictive value calculations and conclusions regarding sensitivity and specificity of HUS in predicting future neurodevelopmental impairment, it should be noted that there is variation among studies regarding timing of HUS, imaging methodology and equipment utilized, study population examined, and outcome evaluated. Additionally, image interpretation interrater reliability is variable across centers, which may limit applicability of some study findings.

Despite these limitations, some generalizations regarding the utility of HUS in predicting neurodevelopmental outcome can be made. A summary of recent studies evaluating HUS as a predictor of intermediate and long-term developmental outcome is presented in Table 2. In general we can conclude that:

- Major abnormalities on HUS (including grade III IVH, periventricular hemorrhagic infarction, or cystic PVL) predict the development of cerebral palsy (CP) and neuromotor delay at variable ages of follow-up (odds ratio ranges between 5 and 10.5, sensitivity up to 0.86, and specificity up to 0.99).^{33,39,47,52,53,56}
- Major HUS abnormalities are also predictive of cognitive outcome,^{54,57} although this is less clear especially when controlling for the effects of significant motor delay on cognitive testing.^{47,53}

Prognostic conclusions about normal or mildly abnormal ultrasounds are more problematic. Many of those with normal HUS, especially those <1000 g, are still at risk for having CP, low Bayley's Mental Developmental Index (MDI), or neurological abnormality at the age of 2 years. Studies showed that one-third of the infants <32 weeks' gestational age who developed CP and 40% of ELBW infants with neurological abnormalities (CP, hypotonia, hypertonia, or shunt-dependent hydrocephalus) at 20 weeks' corrected age had normal HUS.^{39,48} Another study demonstrated that one-third of the ELBW infants with normal HUS will have either MDI <70 or CP at 18 to 22 months.⁵⁰

As explained earlier, Doppler US studies have been associated with different morbidities as GM IVH, periventricular hemorrhagic infarction, posthemorrhagic ventricular dilatation, and PVL. Few small studies examined the prognostic value of Doppler in the first few days of life in premature infants with conflicting results. In one study, children with major disability at 2 years of age had higher resistance index in the anterior cerebral artery compared with children with favorable outcome. This could be explained by increased peak systolic flow velocity, attributed to increased compliance of the vascular bed, with congestion and edema of the periventricular white matter.⁵⁸ In another study, adverse outcome at 1 year of age specifically in nonventilated preterm infants was associated with lowered cerebral blood

flow resistance as an indication of lower cerebral blood flow.⁵⁹

Although prognostic information derived from HUS can be used for parental counseling and planning of services required, its use as the sole criterion to suggest withholding or withdrawal of medical support is not justified.⁶⁰ Neuroimaging can provide information about structural damage but cannot provide an exact estimate of later dysfunction on an individual level. This is related to both limitations in the available techniques and also related to the plasticity of the premature brain. In a study that looked at survivors with periventricular hemorrhagic infarctions by HUS, more than two-thirds had preserved adaptive and communication skills and one-third did not have significant neuromotor or cognitive sequelae.⁶¹ Although statistics derived from various literature help in predicting neurodevelopmental outcome, its application to a specific infant is much more problematic especially when it comes to end-of-life decisions.

CT SCAN

CT can provide excellent views for bones, hemorrhage, extra-axial space, and the ventricles. It can differentiate white and gray matter. The cerebellum and brain stem are better visualized by CT as compared with US, but there is some limitation due to the effect of bone artifact at the skull base. CT was the tool initially used by Papile et al to describe the incidence and evolution of GM IVH in VLBW infants.⁴ However, due to the high radiation exposure to the infant and the high sensitivity of HUS in detection of cystic PVL, ventriculomegaly, and hemorrhage, CT is not routinely used in evaluating the newborn brain.

CT has been performed on ex-preterm children presenting with CP and can demonstrate a reduction in quantity of periventricular white matter with deep prominent sulci and ventriculomegaly with irregular margins.⁶² Few studies have correlated CT findings with late outcome. When evaluated in 145 VLBW infants with asphyxia or apnea, there was no relationship between outcome at 18 months and features on neonatal CT (done during the first 2 weeks of life).⁶³ However, when performed in ELBW infants at term equivalent, a wide ventricular diameter was predictive of learning disability at school age.⁶⁴

CT has several disadvantages. It is not a bedside tool and requires transporting the infant (who may be critically ill) to the scanner. Whereas ultrasound can adapt to patient movement and position, CT requires that the infant remain still, at times requiring sedation. The major disadvantage of CT is the exposure to ionizing radiation. Ionizing radiation has been associated with future development of malignancies^{65,66} and potential cognitive impairments.⁶⁷ These risks and the effective dose of radiation are particularly worrisome in

Table 2 Predictive Value of HUS

Study	No.	Inclusion Criteria	Follow-up Age	HUS Finding	Outcome
Hack et al ⁴⁸	241	<1000 g	20 mo	Grade 3 or 4 IVH, PVL, or persistent ventricular dilation	Neurological abnormality but not with poor cognitive outcome
NICHD ⁵⁶	3785	<32 wk GA	18–22 mo	Grade 3 or 4 IVH or c-PVL	Moderate to severe CP Independently associated with MDI score <70 (however, patients with severe neuromotor or neurosensory impairment were included in this group)
de Vries et al ³³	1929	<36 wk GA	2 y	Grade 3 and 4 IVH, c-PVL, subcortical leukomalacia, basal ganglia lesions, or focal infarction	<ul style="list-style-type: none"> • CP • With higher sensitivity and specificity in 32–36 wk GA
EPIPAGE study ³⁹	1954	<32 wk GA	24 mo	Intraparenchymal hemorrhage or cyst, PVL, or ventricular dilation	<ul style="list-style-type: none"> • CP in 24.4% • With cystic PVL: CP in 57% • With no HUS abnormalities: CP in just over 4%
EPIcure study ⁵³	283	<25 wk	30 mo	Parenchymal hemorrhage, cystic changes, or ventricular dilation	<ul style="list-style-type: none"> • CP • Severe motor disability • Not correlated with MDI score when motor disability was controlled for
Pinto-Martin et al ⁴⁷	658	<2000 g	2, 6, and 9 y	Parenchymal lesions or ventricular enlargement	<ul style="list-style-type: none"> • Poor motor abilities at 2, 6, and 9 y • Not cognitive ability, when motor disability was controlled for
Sherlock et al ⁵¹	270	<1000 g or <28 wk w GA	8 y	IVH	<ul style="list-style-type: none"> • Cerebral palsy, poor motor performance, and major neurosensory disability more prevalent with increasing severity of IVH • Cognitive functioning across domains worse with increasing severity of IVH
Taylor et al ⁵⁴	219	<1000 g	8 y	IVH	Decrement in scores on neuropsychological testing and academic achievement testing for infants with no abnormalities, grade 1 or 2 IVH, and grade 3 or 4, respectively
Stewart and Kirkbride ⁵⁷	1142	<33 wk	8 y	Periventricular hemorrhagic infarction and c-PVL	Disabling impairment; extraeducational provision; IQ <70
Patra et al ⁵⁵	362	<1000 g	20 mo	Grade I/II IVH	Higher rates of: <ul style="list-style-type: none"> • MDI <70 • Major neurological abnormality • Neurodevelopmental impairment

CP, cerebral palsy; c-PVL, cystic periventricular leukomalacia; GA, gestational age; HUS, head ultrasound; IVH, intraventricular hemorrhage; MDI, Bayley's Mental Developmental Index; PVL, periventricular leukomalacia.

the developing newborn brain.⁶⁸ In conclusion, CT is not recommended as a prognostic tool, and its use in the preterm infant should be limited to specific indications such as rapid evaluation following traumatic head injury to evaluate for potential neurosurgical intervention or other neurosurgical emergencies.⁶⁹

MAGNETIC RESONANCE IMAGING

MRI allows for high-resolution images of brain structure, differentiation of white and gray matter, visualization of the brain stem and posterior fossa, and acquisition of additional physiological information with specialized sequences (i.e., spectroscopy and functional MRI discussed below). Though controversial, the use of MRI at term equivalent as a predictor of later outcome in preterm infants has been increasing and has been advocated by some as a standard practice.

MRI General Principles and Sequences

Image contrast with MRI is based on properties of protons in water nuclei and take into account the proton density (water concentration), different relaxation times (T1 and T2) after excitation by magnetic pulse, and diffusion properties (Brownian movement of water molecules). Different image sequences prioritize or “weight” these properties differently to obtain desired image contrast.⁷⁰

T1 and T2 are tissue-specific characteristics that reflect the rate of relaxation. By varying the timing of the application of radiofrequency pulses (repetition time) and the timing of acquisition of the returning signal (echo time), an imaging sequence can accentuate either T1 or T2 characteristics. In T1 images, fat appears white or bright signal, and water (or CSF) appears dark. Alternatively, on T2 images, fat is dark, and blood, edema, and CSF appear white.⁷¹ Routine T1- and T2-weighted images are the most commonly used and allow for evaluation of anatomy, gray-white matter differentiation including presence of myelin, and evidence of subacute injury. Diffusion-weighted imaging or diffusion tensor imaging (DTI) allows for evaluation of acute injury. These sequences also have the advantage of allowing for quantitative measures with apparent diffusion coefficients (ADCs; reflecting degree of water diffusion) and fractional anisotropy (FA; reflecting directionality of water diffusion). In addition, special MRI-based techniques such as proton magnetic resonance spectroscopy (MRS) and functional MRI provide neurophysiological information. MRS is a technique that detects signals from certain metabolites in selected regions of the brain. Functional MRI is used for investigating the functional integrity of the brain by evaluation of activation patterns after stimulation such as passive forearm extension/flexion. Reports of MRI in

the preterm infant, particularly routine T1 and T2 image sequences, have been increasing in the past decade.

Abnormalities Detected by MRI

WHITE MATTER INJURY

WMI is easily detected by MRI. In addition to the cystic PVL that is easily detected by HUS, MRI is able to detect more subtle forms of WMI that are not well visualized by HUS. Diffuse excessive high-signal intensity was initially described by Maalouf et al as the high T2 signal in the periventricular and subcortical white matter that is believed to reflect diffuse WMI.⁷² MRI appearance of specific white matter tracts has been described. Presence or absence of myelination in the posterior limb of the internal capsule (PLIC), normally present in term newborns, and the volume of the CC can be better evaluated with MRI. Thinner CC has been noted in children and adults with a history of prematurity.⁷³

Volumetric analysis of the white matter and conversely ventricular volume reflecting white matter loss can be quantified with MRI. Decreased white matter volume was noted in preterm infants at term equivalent when compared with normal term infants.^{74,75} Similarly, preterm babies have increased ventricular size when compared with term infants when measured at either term equivalent,⁷⁵ childhood,⁷⁶ adolescence,⁷⁷ or adult life.⁷⁸

Diffusion sequences allow for quantitative measurements of white matter abnormality. ADC values in the central white matter are high at 28 weeks' gestation and decrease toward term. This is because of the decrease in extracellular water, axonal thickening, and myelination of axons limiting water molecules' free diffusion as the brain matures. In moderate WMI, ADC values may increase with age or at least fail to decline.⁷⁹ Conversely, FA normally increases as the white matter develops and water diffuses along myelinated axons.⁶⁹ In WMI, FA values are reduced by 20 to 25% in central white matter and internal capsule.^{79,80}

A qualitative scoring system for overall WMI on MRI was described (Table 3, Fig. 4). Scores in five domains (signal abnormality, white matter volume, presence of cystic abnormality, ventricular size, and appearance of the CC/myelination) are summated into an overall score to reflect degree of white matter abnormality. Scores are further classified as mild (score 7 to 9), moderate (score 10 to 12), or severe (score 13 to 15).^{81,82}

GRAY MATTER INJURY

Cortical gray matter can be evaluated for both morphology and volume on MRI. Cortical folding and surface area develop progressively toward term. MRI gray matter volumes in the cortex, subcortex, cerebellum, and

Table 3 Grades of White Matter Injury by MRI^{81,82}

	WM Injury		
	Grade 1	Grade 2	Grade 3
WM signal abnormality	Normal	Focal (one region only)	Extensive ≥ 2 regions (e.g., parieto-occipital)
Reduction in WM volumes	Normal	Mild–moderate loss	Diffuse loss
Cystic abnormality	Normal	Focal cystic change	Extensive WM cystic changes
Lateral ventricle size	Normal	Mild–moderate dilatation	Marked ventricular dilatation
CC and myelination	Normal or isolated partial thinning of CC	Marked thinning of CC	Marked thinning of CC and impaired PLIC myelination

CC, corpus callosum; MRI, magnetic resonance imaging; PLIC, posterior limb of the internal capsule; WM, white matter.

hippocampus have been evaluated and described in preterm infants.

Preterm infants have reduced growth rate of cortical surface area.⁸³ At term equivalent, they have decreased volumes of cortical gray matter^{74,84} and smaller cortical surface,⁸⁵ which persist till adolescence.⁸⁶ Moreover, the volume of subcortical gray matter, especially the lentiform and thalamus, is smaller following preterm birth.^{87,88} Cortical folding has been the focus of recent research. Intrauterine growth-restricted preterm infants had a more pronounced reduction of surface in relation to the sulcation index compared with normal newborns, and these structural measurements were predictive of infants' outcome at term-equivalent age.⁸⁹

A scoring system for gray matter injury (Table 4, Fig. 5) that reflects cortical folding, signal abnormality, and brain volume (reflected by enlargement of the subarachnoid space) was also described. Gray matter injury is classified as normal (score 3 to 5) or abnormal (score 6 to 9).⁸¹

PHYSIOLOGICAL OR DEVELOPMENTAL ABNORMALITY

As mentioned previously, DTI FA has been used to evaluate progression of white matter myelination. Additionally, DTI allows for white matter tracking to further visualize development of neural pathways.

MRS measures brain biochemistry. N-acetylaspartate increases with advancing gestational age and

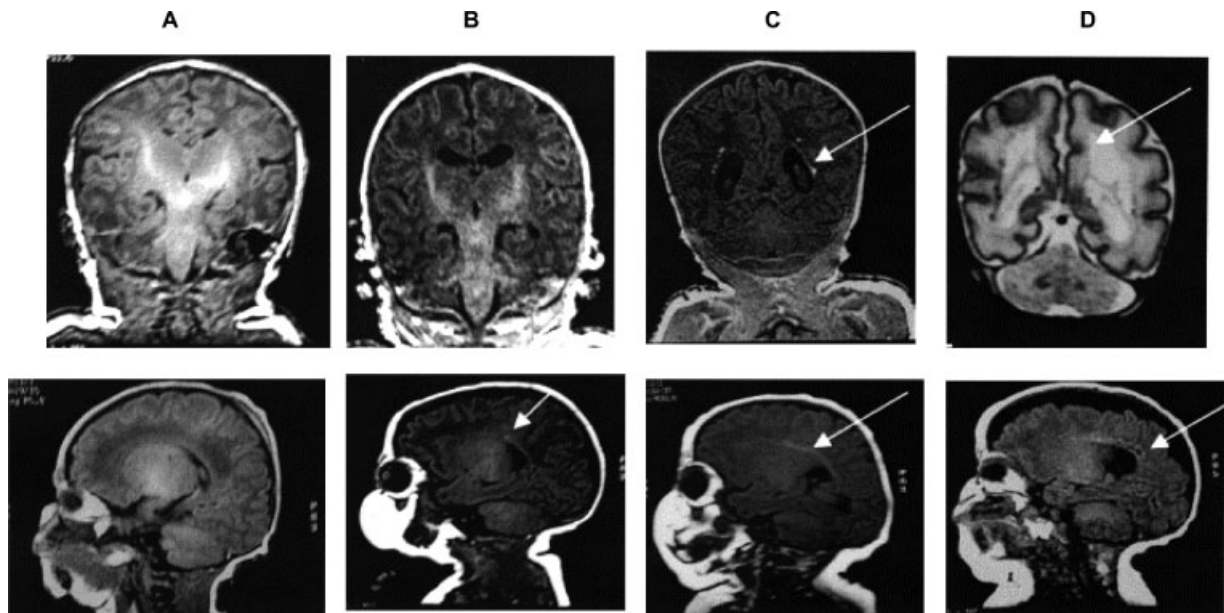


Figure 4 Representative magnetic resonance imaging (MRI; coronal images, top row, and sagittal T1 images, lower row) of the four grades of white matter abnormality in the premature infants on MRI at term: (A) normal; (B) mild white matter abnormality with ventricular dilatation, focal signal change (lower sagittal image, arrow), and thinning of the corpus callosum; (C) moderate white matter abnormality with more diffuse signal changes (upper and lower images, arrows); and (D) severe white matter abnormality (extensive cystic abnormality, upper T2 coronal image and lower sagittal T1 images, arrows). (Reprinted with permission from Inder TE, Wells SJ, Mogridge NB, Spencer C, Volpe JJ. Defining the nature of the cerebral abnormalities in the premature infant: a qualitative magnetic resonance imaging study. *J Pediatr* 2003;143:171–179.)

Table 4 Grades of Gray Matter Injury by MRI⁸¹

	Gray Matter Injury		
	Grade 1	Grade 2	Grade 3
Subarachnoid space	Normal	Mild enlargement	Moderate–severe enlargement
Cortical gray matter signal abnormality	Normal	Focal (one region only)	Extensive ≥ 2 regions (e.g., parieto-occipital)
Gyral maturation	Normal for age	Delay 2–4 wk	Delay >4 wk

MRI, magnetic resonance imaging.

maturity.⁹⁰ Presence of lactate, often seen as a sign of hypoxic ischemic injury in term newborns,⁹¹ can be seen in preterm infants even without other evidence of acute brain injury.⁹⁰

Most recently, functional MRI was evaluated a small number of preterm infants at term equivalent. After doing a unilateral passive forearm extension/flexion, a bilateral activation pattern was observed indicating a bilaterally distributed sensorimotor system. Failure to activate the sensorimotor cortex maturely may be an early indicator of abnormal development that needs to be further evaluated.⁹² Although the prognostic implications of these findings are unclear at this time, further research in these areas may expand the predictive abilities of MRI in preterm infants.

Predictive Value of MRI

Although there is an agreement that MRI gives a more detailed picture of brain structure and can recognize even minor abnormalities, its role as a predictive tool has been the area of active past and ongoing research. There have been several studies aimed to evaluate whether MRI performed at term-equivalent age is predictive of later neurodevelopmental outcome in preterm infants. The results of these investigations are summarized in Table 5.

WMI AND OUTCOME

1. Cystic periventricular WMI: Increased severity of cystic periventricular WMI and presence of cysts at term are associated with motor delay and CP,^{93,94} as well as worse cognitive function and object memory deficit at the age of 2 years.⁹⁵ However, at the age of 8 years, cystic periventricular WMI was still detected in 25% of preterm babies of normal outcome.⁹⁶

2. Diffuse periventricular WMI:

- Diffuse excessive high-signal intensity: After exclusion of infants with significant focal lesions, the presence and severity of diffuse excessive high-signal intensity were shown to be related to lower overall developmental quotient at 18 months' corrected age.⁹⁷
- T1 hyperintensity or cystic lesions in the corona radiata above the PLIC on an MRI coronal view by term were useful for predicting motor prognosis at 3 to 5 years. Sparing this area was associated with normal motor development, irrespective of findings of ventriculomegaly.⁹³
- Diffusion-weighted images: Higher white matter ADC values at term-equivalent age in preterm infants without overt lesions visible on other image sequences were associated with suboptimal developmental performance at the age of 2 years.⁹⁸

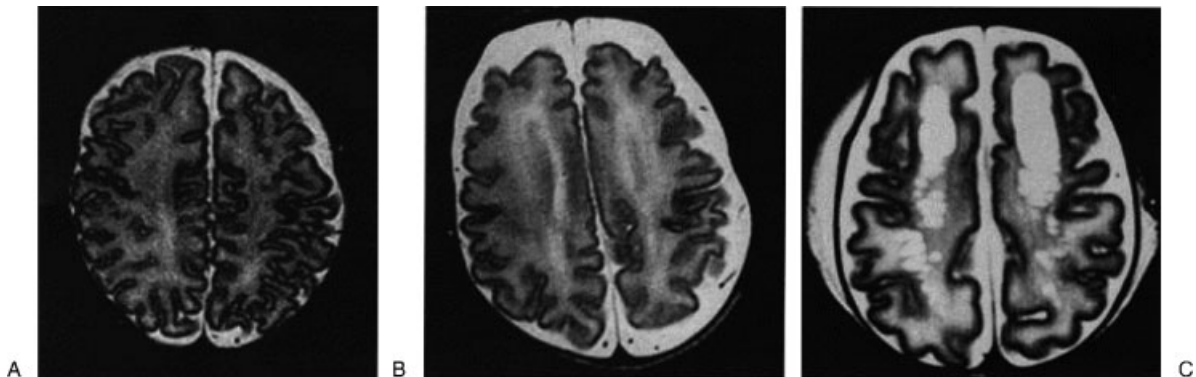


Figure 5 Representative magnetic resonance imaging (MRI) of the three grades of abnormality in gray matter gyral maturation in the premature infants on MRI at term: (A), grade 1, with normal gyral maturation at term; (B) grade 2, demonstrating a reduction in complex gyral folding but secondary gyri in the transverse sulci and gyri consistent with 36 to 37 weeks' gestational age; and (C) grade 3, demonstrating severe impairment in gyral development in all regions consistent with 34 weeks' gestational age. (Reprinted with permission from Inder TE, Wells SJ, Mogridge NB, Spencer C, Volpe JJ. Defining the nature of the cerebral abnormalities in the premature infant: a qualitative magnetic resonance imaging study. *J Pediatr* 2003;143:171–179.)

Table 5 Prognostic Value of MRI at Term Equivalent

CNS Structure	Abnormality	Association/Prognostic Value
White matter	Cystic lesions	Motor delay and CP at 1 y ⁹⁴ and 3–5 y of age ⁹³ Worse cognitive function at 2 y ⁹⁵
	Diffuse	
	• DEHSI	Decreased developmental quotient at 18 mo ⁹⁷
	• Corona radiata T1 hyperintensity	CP at 3–5 y ⁹³
	• Increased mean ADC on DWI	Decreased developmental quotient at 2 y ⁹⁸
	PLIC	
	• Asymmetric PLIC in cases with IVH and unilateral parenchymal lesion	Hemiplegia at age >1 y ^{100,101}
	• Bilateral abnormalities with c-PVL	Diplegia or quadriplegia ¹⁰¹
	• Lower FA	Poor neurological outcome including CP at 18–24 mo ¹⁰² and strong correlation with the severity of gait and motor deficits at 4 y ¹⁰³
	Corpus callosum	
• Lower FA in the splenium	Abnormal neurodevelopment at 18 mo ¹⁰⁴	
Volumetric measure		
• Decreased white matter volume	Especially sensorimotor and midtemporal regions, especially on the right, correlated strongly with measures of neurodevelopmental outcome at 18–20 mo, especially MDI ⁸⁴	
• Increased CSF volume	Associated with moderate to severe disability at 1 y of age ⁷⁴	
White matter abnormality score	At 2 y of age was associated with cognitive delay, motor delay, CP, neurosensory impairment ⁸²	
Gray matter	Decreased cortical and subcortical gray matter volume	Moderate to severe disability at 1 y of age ⁷⁴
	Gray matter abnormality score	Cognitive delay, motor delay, and CP at 2 y
Cerebellum	Decreased cerebellum volume	No significant correlation has been found between cerebellar volumes at term and outcome at 2 y of age ¹¹³
Total volumetric measure	Decreased volumes at dorsolateral prefrontal cortex, sensorimotor, parieto-occipital and premotor regions	Object working memory deficits at 2 y of age ⁹⁵

ADC, apparent diffusion coefficients; CNS, central nervous system; CP, cerebral palsy; c-PVL, cystic periventricular leukomalacia; CSF, cerebrospinal fluid; DEHSI, Diffuse excessive high signal intensity; DWI, Diffusion weighted imaging; FA, fractional anisotropy; IVH, intraventricular hemorrhage; MDI, Bayley's Mental Developmental Index; MRI, magnetic resonance imaging; PLIC, Posterior limb of internal capsule; PVL, periventricular leukomalacia.

- Diffusion tensor imaging: From DTI performed at 2 years of life in children born prematurely who develop CP, FA value of the motor tract is lower compared with those children with PVL who do not develop CP.⁹⁹

3. Appearance of PLIC: In infants with IVH and unilateral parenchymal involvement, symmetrical signal intensity of the PLIC was strongly associated with normal outcome, and asymmetrical PLIC was found to be an early predictor of future hemiplegia. To a lesser extent, PLIC abnormalities were predictors of diplegia or quadriplegia in infants with bilateral cystic PVL.^{100,101} Using DTI, FA values in the PLIC were lower in neonates who subsequently developed CP.^{102–104}

4. Appearance of CC: Similar to findings of US evaluation of the CC, abnormal appearance of the CC on MRI

was seen in infants with adverse neurodevelopmental outcome. Thinner CC on MRI is a common finding in children with CP.^{105,106} In adolescents who were born preterm, verbal IQ and verbal fluency scores were positively associated with total midsagittal CC size.¹⁰⁷ Additionally, on MRI performed at term-equivalent age, FA values of the splenium of CC were lower in those who had abnormal outcome at 18 months' corrected age.¹⁰⁴ At 2 years of age, linear relation could be detected between the following: developmental quotient and FA values in parts of the CC; performance subscores and FA values in the CC and right cingulum; and eye-hand coordination subscores and FA values in the cingulum, fornix, anterior commissure, CC, and right uncinate fasciculus.¹⁰⁸

5. Optic radiation fiber tracking: With advances in MRI and DTI, qualitative fiber tracking analysis

has been performed for the optic radiation in premature infants.^{109,110} FA of the optic radiation was found to be increased with GA and correlated significantly with scores from the visual fixation tracking assessment.¹⁰⁹ At term equivalent, the visual assessment score was independently correlated with FA values but not gestational age at birth, postmenstrual age at scan, or the presence of lesions on conventional MRI.¹¹⁰

6. Volumetric measurements:

- **Cerebral white matter:** In a small study that included 10 preterm infants, white matter volumes in the sensorimotor and midtemporal regions, especially on the right, correlated strongly with measures of neurodevelopmental outcome (especially mental developmental index) at 18 to 20 months' corrected age.⁸⁴
- **CSF and ventricular size/volume:** Increased CSF volume (including ventricular and extra-axial CSF) demonstrated on term-equivalent MRI was correlated with moderate to severe disability at 1 year of age.⁷⁴ However, in a large study, only posthemorrhagic ventricular dilatation was associated with reduced developmental quotient at 18 months' corrected age. Ventricular dilatation not in the context of IVH was not associated with later developmental impairment.⁹⁷ In older infants, abnormally dilated occipital horns seen with MRI were correlated with CP and low scores on the Denver and the Bayley tests at the age of 1 year.¹¹¹

GRAY MATTER INJURY AND OUTCOME

1. **Cortical gray matter:** Smaller volumes of cortical and deep gray matter is associated with moderate to severe disability at 1 year of age (defined as moderate to severe motor spasticity/weakness and developmental delay >4 months using parent report and Denver Developmental Screening tool).⁷⁴ When measured in adolescents, reduced gray matter volume was associated with a decreased IQ.¹¹²
2. **Subcortical gray matter:** At term equivalent, subcortical gray matter volume was reduced in association with IVH, cystic periventricular white matter, or periventricular hemorrhagic infarction⁸⁸ and was associated with moderate to severe disability at 1 year of age.⁷⁴

OTHER CENTRAL NERVOUS SYSTEM STRUCTURES AND OUTCOME

1. **Cerebellum**
 - **Volume:** Preterm infants do not have decreased cerebellar volumes unless white matter damage is present.¹¹³⁻¹¹⁵ No significant correlation has been found between cerebellar volumes at term and outcome at 2 years of age.¹¹³

- **Hemorrhage:** In one study, neurological abnormalities were present in two-thirds of the isolated cerebellar hemorrhagic injuries at the age of 32 months (diagnosed by US and confirmed by late MRI). These infants had significantly lower mean scores on all tested measures, including severe motor disabilities, expressive language, delayed receptive language, cognitive deficits, and severe functional limitations in day-to-day activities. They also had a higher risk for autism and internalizing behavioral problems. Deficits were more common and profound in preterm infants with injury to the vermis.¹⁹

2. **Hippocampus:** The importance of hippocampal size and injury as predictor of outcome is controversial. Some studies did not find reduction of volume in adults born prematurely⁷⁸ and did not correlate injury to IQ in childhood.¹¹⁶ However, other studies showed significantly smaller hippocampal volumes in infants with moderate to severe WMI¹¹⁷ and adolescents born prematurely.¹¹⁸ Reduction of hippocampal volume was independently associated with lower MDI at 2 years and in adolescence was associated with specific deficits in certain aspects of everyday memory, lower freedom from distractibility, and lower arithmetic scores.¹¹⁸

MRS AND OUTCOME

In one study using MRS, age affected many metabolites, and neuronal maturation was associated with an increase in N-acetylaspartate. However, absolute brain metabolite content in premature infants at term was not different from that in full-term infants.⁹⁰ When compared between appropriate-for-gestational-age and small-for-gestational-age premature infants, MRS showed no significant differences.¹¹⁹ Finally, when specifically tested as a predictor of outcome in VLBW infants, metabolite ratios from near-term MRS were not predictive of Bayley scores at 18 to 24 months' corrected age.¹²⁰

CLINICAL UTILITY OF NEUROIMAGING AS A PREDICTOR OF OUTCOME

Each neuroimaging technique has its own advantages and disadvantages, which we summarized in Table 6. Although CT can sometimes provide more data than HUS, it cannot be recommended as a routine for prediction of outcome. HUS, being an easily performed bedside study, has been the most attractive screening tool commonly used in the NICU. The technical difficulties of performing an MRI in a preterm infant has improved with the development of MRI-compatible incubators, monitoring devices, ventilators, and immobilizing devices that decrease the need for sedation.^{82,121,122} Although MRI provides more detailed images of the brain, its superiority as compared with HUS as a

Table 6 Neuroimaging Techniques and Neurodevelopmental Outcome of Premature Infants

	Advantages	Disadvantages	Prognostic Value
Head ultrasound	Bedside test No sedation required Can adequately characterize germinal matrix intraventricular hemorrhage, periventricular hemorrhagic infarction, and ventricular dilatation	Operator dependent Variable in technique and timing protocols Unable to visualize the details of gray and white matter, the posterior fossa, and not accurate for volumetric measurements	Can adequately predict cerebral palsy Less clear correlation with cognitive outcomes
Computed tomography	Good visualization for bones, hemorrhage, extra-axial space, and the ventricles Can differentiate white and gray matter and has limited visualization of cerebellum and brain stem	Exposure to ionizing radiation Requires transport	Not recommended for this indication
Magnetic resonance imaging	The best quality in assessing gray and white matter, the posterior fossa, and volumetric data Functional imaging and new techniques are being progressively developed	Expensive Needs transport May require sedation	Has promising predictive value in both motor and cognitive outcomes

predictor of outcome is not absolute. In fact, available data suggest that HUS may have similar sensitivity and specificity for predicting subsequent CP. In a study that included 1460 premature infants <34 weeks' gestational age, major HUS abnormalities (grade III and IV hemorrhage, cystic PVL and subcortical leukomalacia, basal ganglia lesions, and focal infarction) predicted CP with sensitivity of 76%, and specificity of 95%.³³ In comparison, moderate to severe MRI abnormalities predicted CP with a sensitivity of 65% and specificity of 84%.⁸² However, MRI appears to have a role in prediction of later cognitive delay and neurosensory impairment, where the role of HUS is less clear.^{47,53,82} Neither study has adequate negative predictive value to reduce the need for developmental follow-up of these high-risk infants. Thirty-two percent of babies without any WMI on MRI had either an MDI or a psychomotor developmental index score less than 70, CP, or neurosensory impairment at the age of 2 years.⁸² Similarly, 30% of ELBW infants with normal HUS had either MDI score below 70 or CP at the age of 18 to 22 months' corrected age.⁵⁰ Thus, although predischarge neuroimaging provides useful prognostic information, it is not an adequate surrogate for long-term neurodevelopmental follow-up.

CONCLUSION

The major neuroimaging tools used to predict neurodevelopmental outcome of preterm infants currently include HUS and MRI. Both modalities provide complementary information, with HUS useful in the acute setting and MRI perhaps more useful for long-term

outcome assessment. Whether MRI is cost-effective as a screening tool for all preterm babies remains to be determined.

REFERENCES

- Buckley KM, Taylor GA, Estroff JA, Barnewolt CE, Share JC, Paltiel HJ. Use of the mastoid fontanelle for improved sonographic visualization of the neonatal midbrain and posterior fossa. *AJR Am J Roentgenol* 1997;168:1021-1025
- Luna JA, Goldstein RB. Sonographic visualization of neonatal posterior fossa abnormalities through the posterolateral fontanelle. *AJR Am J Roentgenol* 2000;174:561-567
- Correa F, Enríquez G, Rosselló J, et al. Posterior fontanelle sonography: an acoustic window into the neonatal brain. *AJNR Am J Neuroradiol* 2004;25:1274-1282
- Papile L-A, 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;92:529-534
- Leviton A, Kuban K, Paneth N. Intraventricular haemorrhage grading scheme: time to abandon? *Acta Paediatr* 2007;96:1254-1256
- Paneth N. Classifying brain damage in preterm infants. *J Pediatr* 1999;134:527-529
- Whitelaw A. Intraventricular haemorrhage and posthaemorrhagic hydrocephalus: pathogenesis, prevention and future interventions. *Semin Neonatol* 2001;6:135-146
- Volpe JJ. *Neurology of the Newborn*. 5th ed. Philadelphia: Saunders/Elsevier; 2008:xiv
- Stewart AL, Reynolds EO, Hope PL, et al. Probability of neurodevelopmental disorders estimated from ultrasound appearance of brains of very preterm infants. *Dev Med Child Neurol* 1987;29:3-11

10. Whitelaw A. A different view: there is value in grading intraventricular hemorrhage. *Acta Paediatr* 2007;96:1257–1258
11. Leijser LM, Srinivasan L, Rutherford MA, Counsell SJ, Allsop JM, Cowan FM. Structural linear measurements in the newborn brain: accuracy of cranial ultrasound compared to MRI. *Pediatr Radiol* 2007;37:640–648
12. Levene MI. Measurement of the growth of the lateral ventricles in preterm infants with real-time ultrasound. *Arch Dis Child* 1981;56:900–904
13. 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
14. Maertzdorf WJ, Vles JS, Beuls E, Mulder AL, Blanco CE. Intracranial pressure and cerebral blood flow velocity in preterm infants with posthaemorrhagic ventricular dilatation. *Arch Dis Child Fetal Neonatal Ed* 2002;87:F185–F188
15. Whitelaw A, Pople I, Cherian S, Evans D, Thoresen M. Phase 1 trial of prevention of hydrocephalus after intraventricular hemorrhage in newborn infants by drainage, irrigation, and fibrinolytic therapy. *Pediatrics* 2003;111(4 Pt 1):759–765
16. 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–F223
17. de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. *Behav Brain Res* 1992;49:1–6
18. Limperopoulos C, Benson CB, Bassan H, et al. Cerebellar hemorrhage in the preterm infant: ultrasonographic findings and risk factors. *Pediatrics* 2005;116:717–724
19. 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;120:584–593
20. Merrill JD, Piecuch RE, Fell SC, Barkovich AJ, Goldstein RB. A new pattern of cerebellar hemorrhages in preterm infants. *Pediatrics* 1998;102:E62
21. Anderson NG, Laurent I, Cook N, Woodward L, Inder TE. Growth rate of corpus callosum in very premature infants. *AJNR Am J Neuroradiol* 2005;26:2685–2690
22. Anderson NG, Laurent I, Woodward LJ, Inder TE. Detection of impaired growth of the corpus callosum in premature infants. *Pediatrics* 2006;118:951–960
23. Bode H, Wais U. Age dependence of flow velocities in basal cerebral arteries. *Arch Dis Child* 1988;63:606–611
24. Kehrer M, Krägeloh-Mann I, Goelz R, Schöning M. The development of cerebral perfusion in healthy preterm and term neonates. *Neuropediatrics* 2003;34:281–286
25. Lightburn MH, Gauss CH, Williams DK, Kaiser JR. Cerebral blood flow velocities in extremely low birth weight infants with hypotension and infants with normal blood pressure. *J Pediatr* 2009;154:824–828
26. Blankenberg FG, Loh NN, Norbash AM, et al. Impaired cerebrovascular autoregulation after hypoxic-ischemic injury in extremely low-birth-weight neonates: detection with power and pulsed wave Doppler US. *Radiology* 1997;205:563–568
27. Perlman JM, McMennamin JB, Volpe JJ. Fluctuating cerebral blood-flow velocity in respiratory-distress syndrome. Relation to the development of intraventricular hemorrhage. *N Engl J Med* 1983;309:204–209
28. Julkunen M, Parviainen T, Janas M, Tammela O. End-diastolic block in cerebral circulation may predict intraventricular hemorrhage in hypotensive extremely-low-birth-weight infants. *Ultrasound Med Biol* 2008;34:538–545
29. Taylor GA. Effect of germinal matrix hemorrhage on terminal vein position and patency. *Pediatr Radiol* 1995;25(Suppl 1):S37–S40
30. Taylor GA, Madsen JR. Neonatal hydrocephalus: hemodynamic response to fontanelle compression—correlation with intracranial pressure and need for shunt placement. *Radiology* 1996;201:685–689
31. van Alfen-van der Velden AA, Hopman JC, Klaessens JH, Feuth T, Sengers RC, Liem KD. Cerebral hemodynamics and oxygenation after serial CSF drainage in infants with PHVD. *Brain Dev* 2007;29:623–629
32. Ment LR, Bada HS, Barnes P, et al. Practice parameter: neuroimaging of the neonate: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2002;58:1726–1738
33. De Vries LS, Van Haastert ILC, Rademaker KJ, Koopman C, Groenendaal F. Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. *J Pediatr* 2004;144:815–820
34. Pinto J, Paneth N, Kazam E, et al. Interobserver variability in neonatal cranial ultrasonography. *Paediatr Perinat Epidemiol* 1988;2:43–58
35. Corbett SS, Rosenfeld CR, Luptook AR, et al. Intraobserver and interobserver reliability in assessment of neonatal cranial ultrasounds. *Early Hum Dev* 1991;27:9–17
36. Corah NL, Anthony EJ, Painter P, Stern JA, Thurston DL. Effects of perinatal anoxia after seven years. *Psychol Monogr* 1965;79(Suppl 3):1–34
37. O'Shea TM, Volberg F, Dillard RG. Reliability of interpretation of cranial ultrasound examinations of very low-birthweight neonates. *Dev Med Child Neurol* 1993;35:97–101
38. Hintz SR, Slovis T, Bulas D, et al; NICHD Neonatal Research Network. Interobserver reliability and accuracy of cranial ultrasound scanning interpretation in premature infants. *J Pediatr* 2007;150:592–596, e1–e5
39. Ancel PY, Livinec F, Larroque B, et al; EPIPAGE Study Group. Cerebral palsy among very preterm children in relation to gestational age and neonatal ultrasound abnormalities: the EPIPAGE cohort study. *Pediatrics* 2006;117:828–835
40. Stewart AL, Thorburn RJ, Hope PL, Goldsmith M, Lipscomb AP, Reynolds EO. Ultrasound appearance of the brain in very preterm infants and neurodevelopmental outcome at 18 months of age. *Arch Dis Child* 1983;58:598–604
41. Costello AM, Hamilton PA, Baudin J, et al. Prediction of neurodevelopmental impairment at four years from brain ultrasound appearance of very preterm infants. *Dev Med Child Neurol* 1988;30:711–722
42. Roth SC, Baudin J, McCormick DC, et al. Relation between ultrasound appearance of the brain of very preterm infants and neurodevelopmental impairment at eight years. *Dev Med Child Neurol* 1993;35:755–768
43. Aziz K, Vickar DB, Sauve RS, Etches PC, Pain KS, Robertson CM. Province-based study of neurologic disability

- of children weighing 500 through 1249 grams at birth in relation to neonatal cerebral ultrasound findings. *Pediatrics* 1995;95:837-844
44. Chaudhari S, Kinare AS, Kumar R, Pandit AN, Deshpande M. Ultrasonography of the brain in preterm infants and its correlation with neurodevelopmental outcome. *Indian Pediatr* 1995;32:735-742
 45. Ong LC, Boo NY, Chandran V, et al. Neurodevelopmental outcome of Malaysian very low birth weight infants: predictive value of cranial ultrasound appearances. *Singapore Med J* 1997;38:108-111
 46. Ment LR, Vohr B, Allan W, et al. The etiology and outcome of cerebral ventriculomegaly at term in very low birth weight preterm infants. *Pediatrics* 1999;104(2 Pt 1): 243-248
 47. Pinto-Martin JA, Whitaker AH, Feldman JF, Van Rossem R, Paneth N. Relation of cranial ultrasound abnormalities in low-birthweight infants to motor or cognitive performance at ages 2, 6, and 9 years. *Dev Med Child Neurol* 1999;41: 826-833
 48. Hack M, Wilson-Costello D, Friedman H, Taylor GH, Schluchter M, Fanaroff AA. Neurodevelopment and predictors of outcomes of children with birth weights of less than 1000 g: 1992-1995. *Arch Pediatr Adolesc Med* 2000;154:725-731
 49. Vollmer B, Roth S, Baudin J, Stewart AL, Neville BG, Wyatt JS. Predictors of long-term outcome in very preterm infants: gestational age versus neonatal cranial ultrasound. *Pediatrics* 2003;112:1108-1114
 50. Laptook AR, O'Shea TM, Shankaran S, Bhaskaran B; NICHD Neonatal Network. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics* 2005;115:673-680
 51. Sherlock RL, Anderson PJ, Doyle LW; Victorian Infant Collaborative Study Group. Neurodevelopmental sequelae of intraventricular haemorrhage at 8 years of age in a regional cohort of ELBW/very preterm infants. *Early Hum Dev* 2005;81:909-916
 52. Vohr BR, Msall ME, Wilson D, Wright LL, McDonald S, Poole WK. Spectrum of gross motor function in extremely low birth weight children with cerebral palsy at 18 months of age. *Pediatrics* 2005;116:123-129
 53. Wood NS, Costeloe K, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR; EPICure Study Group. The EPICure study: associations and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth. *Arch Dis Child Fetal Neonatal Ed* 2005;90:F134-F140
 54. Taylor HG, Klein N, Drotar D, Schluchter M, Hack M. Consequences and risks of <1000-g birth weight for neuropsychological skills, achievement, and adaptive functioning. *J Dev Behav Pediatr* 2006;27:459-469
 55. Patra K, Wilson-Costello D, Taylor HG, Mercuri-Minich N, Hack M. Grades I-II intraventricular hemorrhage in extremely low birth weight infants: effects on neurodevelopment. *J Pediatr* 2006;149:169-173
 56. Vohr BR, Wright LL, Poole WK, McDonald SA. Neurodevelopmental outcomes of extremely low birth weight infants <32 weeks' gestation between 1993 and 1998. *Pediatrics* 2005;116:635-643
 57. Stewart A, Kirkbride V. Very preterm infants at fourteen years: relationship with neonatal ultrasound brain scans and neurodevelopmental status at one year. *Acta Paediatr Suppl* 1996;416:44-47
 58. van Bel F, den Ouden L, van de Bor M, Stijnen T, Baan J, Ruys JH. Cerebral blood-flow velocity during the first week of life of preterm infants and neurodevelopment at two years. *Dev Med Child Neurol* 1989;31:320-328
 59. Ojala T, Käätä P, Helenius H, et al. Low cerebral blood flow resistance in nonventilated preterm infants predicts poor neurologic outcome. *Pediatr Crit Care Med* 2004;5: 264-268
 60. Stevenson DK, Goldworth A. Ethical considerations in neuroimaging and its impact on decision-making for neonates. *Brain Cogn* 2002;50:449-454
 61. Bassan H, Limperopoulos C, Visconti K, et al. Neurodevelopmental outcome in survivors of periventricular hemorrhagic infarction. *Pediatrics* 2007;120:785-792
 62. Flodmark O, Roland E, Hill A, Whitfield M. Radiologic diagnosis of periventricular leukomalacia. *Acta Radiol Suppl* 1986;369:664-666
 63. Fitzhardinge PM, Flodmark O, Fitz CR, Ashby S. The prognostic value of computed tomography of the brain in asphyxiated premature infants. *J Pediatr* 1982;100: 476-481
 64. Ishida A, Nakajima W, Arai H, et al. Cranial computed tomography scans of premature babies predict their eventual learning disabilities. *Pediatr Neurol* 1997;16:319-322
 65. Karlsson P, Holmberg E, Lundell M, Mattsson A, Holm LE, Wallgren A. Intracranial tumors after exposure to ionizing radiation during infancy: a pooled analysis of two Swedish cohorts of 28,008 infants with skin hemangioma. *Radiat Res* 1998;150:357-364
 66. Brenner DJ, Doll R, Goodhead DT, et al. Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. *Proc Natl Acad Sci U S A* 2003;100:13761-13766
 67. Hall P, Adami HO, Trichopoulos D, et al. Effect of low doses of ionising radiation in infancy on cognitive function in adulthood: Swedish population based cohort study. *BMJ* 2004;328:19
 68. Stein SC, Hurst RW, Sonnad SS. Meta-analysis of cranial CT scans in children. A mathematical model to predict radiation-induced tumors. *Pediatr Neurosurg* 2008;44: 448-457
 69. Neil JJ, Inder TE. Imaging perinatal brain injury in premature infants. *Semin Perinatol* 2004;28:433-443
 70. Mori S, Zhang J. Principles of diffusion tensor imaging and its applications to basic neuroscience research. *Neuron* 2006; 51:527-539
 71. Mettler FA. *Essentials of Radiology*. 2nd ed. Philadelphia: Elsevier Saunders; 2005:xi
 72. Maalouf EF, Duggan PJ, Rutherford MA, et al. Magnetic resonance imaging of the brain in a cohort of extremely preterm infants. *J Pediatr* 1999;135:351-357
 73. Fearon I, Kisilevsky BS, Hains SM, Muir DW, Tranmer J. Swaddling after heel lance: age-specific effects on behavioral recovery in preterm infants. *J Dev Behav Pediatr* 1997;18: 222-232
 74. Inder TE, Warfield SK, Wang H, Hüppi PS, Volpe JJ. Abnormal cerebral structure is present at term in premature infants. *Pediatrics* 2005;115:286-294
 75. Thompson DK, Warfield SK, Carlin JB, et al. Perinatal risk factors altering regional brain structure in the preterm infant. *Brain* 2007;130(Pt 3):667-677

76. Skranes JS, Vik T, Nilsen G, Smevik O, Andersson HW, Brubakk AM. Cerebral magnetic resonance imaging and mental and motor function of very low birth weight children at six years of age. *Neuropediatrics* 1997;28:149–154
77. Cooke RW, Abernethy LJ. Cranial magnetic resonance imaging and school performance in very low birth weight infants in adolescence. *Arch Dis Child Fetal Neonatal Ed* 1999;81:F116–F121
78. Fearon P, O'Connell P, Frangou S, et al. Brain volumes in adult survivors of very low birth weight: a sibling-controlled study. *Pediatrics* 2004;114:367–371
79. 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;16:621–632
80. Hüppi PS, Murphy B, Maier SE, et al. Microstructural brain development after perinatal cerebral white matter injury assessed by diffusion tensor magnetic resonance imaging. *Pediatrics* 2001;107:455–460
81. Inder TE, Wells SJ, Mogridge NB, Spencer C, Volpe JJ. Defining the nature of the cerebral abnormalities in the premature infant: a qualitative magnetic resonance imaging study. *J Pediatr* 2003;143:171–179
82. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *N Engl J Med* 2006;355:685–694
83. Kapellou O, Counsell SJ, Kennea N, et al. Abnormal cortical development after premature birth shown by altered allometric scaling of brain growth. *PLoS Med* 2006;3:e265
84. Peterson BS, Anderson AW, Ehrenkranz R, et al. Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants. *Pediatrics* 2003;111(5 Pt 1): 939–948
85. Ajayi-Obe M, Saeed N, Cowan FM, Rutherford MA, Edwards AD. Reduced development of cerebral cortex in extremely preterm infants. *Lancet* 2000;356:1162–1163
86. Nosarti C, Al-Asady MHS, Frangou S, Stewart AL, Rifkin L, Murray RM. Adolescents who were born very preterm have decreased brain volumes. *Brain* 2002;125(Pt 7):1616–1623
87. Boardman JP, Counsell SJ, Rueckert D, et al. Abnormal deep grey matter development following preterm birth detected using deformation-based morphometry. *Neuroimage* 2006;32:70–78
88. Srinivasan L, Dutta R, Counsell SJ, et al. Quantification of deep gray matter in preterm infants at term-equivalent age using manual volumetry of 3-tesla magnetic resonance images. *Pediatrics* 2007;119:759–765
89. Dubois J, Benders M, Borradori-Tolsa C, et al. Primary cortical folding in the human newborn: an early marker of later functional development. *Brain* 2008;131(Pt 8):2028–2041
90. Kreis R, Hofmann L, Kuhlmann B, Boesch C, Bossi E, Hüppi PS. Brain metabolite composition during early human brain development as measured by quantitative in vivo 1H magnetic resonance spectroscopy. *Magn Reson Med* 2002;48:949–958
91. Miller SP, Newton N, Ferriero DM, et al. Predictors of 30-month outcome after perinatal depression: role of proton MRS and socioeconomic factors. *Pediatr Res* 2002;52:71–77
92. Heep A, Scheef L, Jankowski J, et al. Functional magnetic resonance imaging of the sensorimotor system in preterm infants. *Pediatrics* 2009;123:294–300
93. Nanba Y, Matsui K, Aida N, et al. Magnetic resonance imaging regional T1 abnormalities at term accurately predict motor outcome in preterm infants. *Pediatrics* 2007;120:e10–e19
94. Aida N, Nishimura G, Hachiya Y, Matsui K, Takeuchi M, Itani Y. MR imaging of perinatal brain damage: comparison of clinical outcome with initial and follow-up MR findings. *AJNR Am J Neuroradiol* 1998;19:1909–1921
95. Woodward LJ, Edgin JO, Thompson D, Inder TE. Object working memory deficits predicted by early brain injury and development in the preterm infant. *Brain* 2005;128(Pt 11):2578–2587
96. Olsén P, Pääkkö E, Vainionpää L, Pyhtinen J, Järvelin MR. Magnetic resonance imaging of periventricular leukomalacia and its clinical correlation in children. *Ann Neurol* 1997; 41:754–761
97. Dyet LE, Kennea N, Counsell SJ, et al. Natural history of brain lesions in extremely preterm infants studied with serial magnetic resonance imaging from birth and neurodevelopmental assessment. *Pediatrics* 2006;118: 536–548
98. Krishnan ML, Dyet LE, Boardman JP, et al. Relationship between white matter apparent diffusion coefficients in preterm infants at term-equivalent age and developmental outcome at 2 years. *Pediatrics* 2007;120:e604–e609
99. Murakami A, Morimoto M, Yamada K, et al. Fiber-tracking techniques can predict the degree of neurologic impairment for periventricular leukomalacia. *Pediatrics* 2008;122:500–506
100. De Vries LS, Groenendaal F, van Haastert IC, Eken P, Rademaker KJ, Meiners LC. Asymmetrical myelination of the posterior limb of the internal capsule in infants with periventricular haemorrhagic infarction: an early predictor of hemiplegia. *Neuropediatrics* 1999;30:314–319
101. Roelants-van Rijn AM, Groenendaal F, Beek FJ, Eken P, van Haastert IC, de Vries LS. Parenchymal brain injury in the preterm infant: comparison of cranial ultrasound, MRI and neurodevelopmental outcome. *Neuropediatrics* 2001;32: 80–89
102. Arzoumanian Y, Mirmiran M, Barnes PD, et al. Diffusion tensor brain imaging findings at term-equivalent age may predict neurologic abnormalities in low birth weight preterm infants. *AJNR Am J Neuroradiol* 2003;24:1646–1653
103. Rose J, Mirmiran M, Butler EE, et al. Neonatal microstructural development of the internal capsule on diffusion tensor imaging correlates with severity of gait and motor deficits. *Dev Med Child Neurol* 2007;49:745–750
104. Rose J, Butler EE, Lamont LE, Barnes PD, Atlas SW, Stevenson DK. Neonatal brain structure on MRI and diffusion tensor imaging, sex, and neurodevelopment in very-low-birthweight preterm children. *Dev Med Child Neurol* 2009;51:526–535
105. Rademaker KJ, Lam JNGP, Van Haastert IC, et al. Larger corpus callosum size with better motor performance in prematurely born children. *Semin Perinatol* 2004;28:279–287
106. Iai M, Tanabe Y, Goto M, Sugita K, Niimi H. A comparative magnetic resonance imaging study of the corpus callosum in neurologically normal children and children with spastic diplegia. *Acta Paediatr* 1994;83:1086–1090
107. Nosarti C, Rushe TM, Woodruff PWR, Stewart AL, Rifkin L, Murray RM. Corpus callosum size and very preterm birth: relationship to neuropsychological outcome. *Brain* 2004;127(Pt 9):2080–2089

108. Counsell SJ, Edwards AD, Chew AT, et al. Specific relations between neurodevelopmental abilities and white matter microstructure in children born preterm. *Brain* 2008;131(Pt 12):3201–3208
109. Berman JI, Glass HC, Miller SP, et al. Quantitative fiber tracking analysis of the optic radiation correlated with visual performance in premature newborns. *AJNR Am J Neuro-radiol* 2009;30:120–124
110. Bassi L, Ricci D, Volzone A, et al. Probabilistic diffusion tractography of the optic radiations and visual function in preterm infants at term equivalent age. *Brain* 2008;131(Pt 2):573–582
111. Skranes JS, Vik T, Nilsen G, et al. Cerebral magnetic resonance imaging (MRI) and mental and motor function of very low birth weight infants at one year of corrected age. *Neuropediatrics* 1993;24:256–262
112. Martinussen M, Fischl B, Larsson HB, et al. Cerebral cortex thickness in 15-year-old adolescents with low birth weight measured by an automated MRI-based method. *Brain* 2005;128(Pt 11):2588–2596
113. Shah DK, Anderson PJ, Carlin JB, et al. Reduction in cerebellar volumes in preterm infants: relationship to white matter injury and neurodevelopment at two years of age. *Pediatr Res* 2006;60:97–102
114. Limperopoulos C, Soul JS, Gauvreau K, et al. Late gestation cerebellar growth is rapid and impeded by premature birth. *Pediatrics* 2005;115:688–695
115. Srinivasan L, Allsop J, Counsell SJ, Boardman JP, Edwards AD, Rutherford M. Smaller cerebellar volumes in very preterm infants at term-equivalent age are associated with the presence of supratentorial lesions. *AJNR Am J Neuro-radiol* 2006;27:573–579
116. Abernethy LJ, Klafkowski G, Foulder-Hughes L, Cooke RWI. Magnetic resonance imaging and T2 relaxometry of cerebral white matter and hippocampus in children born preterm. *Pediatr Res* 2003;54:868–874
117. Thompson DK, Wood SJ, Doyle LW, et al. Neonate hippocampal volumes: prematurity, perinatal predictors, and 2-year outcome. *Ann Neurol* 2008;63:642–651
118. Isaacs EB, Lucas A, Chong WK, et al. Hippocampal volume and everyday memory in children of very low birth weight. *Pediatr Res* 2000;47:713–720
119. Roelants-van Rijn AM, van der Grond J, Stigter RH, de Vries LS, Groenendaal F. Cerebral structure and metabolism and long-term outcome in small-for-gestational-age preterm neonates. *Pediatr Res* 2004;56:285–290
120. Augustine EM, Spielman DM, Barnes PD, et al. Can magnetic resonance spectroscopy predict neurodevelopmental outcome in very low birth weight preterm infants?. *J Perinatol* 2008;28:611–618
121. Dumoulin CL, Rohling KW, Piel JE, et al. Magnetic resonance imaging compatible neonate incubator. *Concepts Magn Reson Part B* 2002;15:117–128
122. Blüml S, Friedlich P, Erberich S, Wood JC, Seri I, Nelson MD Jr. MR imaging of newborns by using an MR-compatible incubator with integrated radiofrequency coils: initial experience. *Radiology* 2004;231:594–601