Imaging Perinatal Brain Injury in Premature Infants

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The primary methods currently in use for imaging the infant brain are cranial ultrasound (CUS), computed tomography (CT) and magnetic resonance imaging (MRI). This review outlines the relative strengths and weaknesses of these modalities in relation to the premature infant, with specific focus on the correlations between imaging findings and neurodevelopmental outcome. Since MRI is undergoing rapid development at this time, the newer MRI methods of brain volume measurement and diffusion tensor imaging are reviewed in more detail. Current guidelines regarding the application of these neuroimaging methods to the premature infant are discussed.

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The three major neuroimaging modalities used in the evaluation of the premature infant brain are cranial ultrasound (CUS), computed tomography (CT) and magnetic resonance imaging (MRI)—each of which has relative strengths and weaknesses. In this review, we will compare and contrast these methods with specific regard to their clinical utility in the premature infant. A major focus of this review will be on MRI, since there have been many recent advances in the application of this methodology to the evaluation of the premature infant.

Due to the high incidence of neurodevelopmental disability in the premature infant, this patient population has a clear need for accurate and reliable neuroimaging. Imaging of the brain of the premature infant has at least two major aims: firstly, to accurately define the nature of cerebral injury in this population, and, secondly, to determine the imaging features that most accurately predict adverse neurodevelopmental outcome. In addition to defining cerebral injury, recent advances in neuroimaging techniques are now providing insight into alterations in structural brain development associated with prematurity.

Five to 15% of prematurely born children develop cerebral palsy, with an additional 30 to 50% displaying impaired academic achievement and/or behavioral disorders requiring additional educational resources. To understand and apply potentially beneficial neuroprotective strategies in the neonatal intensive care unit, it is necessary to first establish the nature, timing, and location of the cerebral lesions predisposing premature infants to long-term neurodevelopmental difficulties. In addition, accurate prognostic information before discharge from the hospital would be of high clinical utility by assisting in defining the need for continuing intervention strategies, such as physical therapy. With current conventional neuroimaging techniques, severely abnormal findings are moderately accurate for predicting an adverse outcome, particularly in relation to motor outcomes such as cerebral palsy (vide infra). However, there is little relationship between the findings of these conventional techniques and cognitive outcome in the premature infant, even when images are obtained later in life.

Newer MRI methods, including quantitative volumetric measurements and diffusion tensor imaging, may offer higher sensitivity to more subtle anatomic alterations. Thus, they have the potential to provide a better understanding of the anatomic substrate for the increased susceptibility for cognitive difficulties in this high-risk population.

With current neuroimaging technologies there are several well-defined forms of cerebral injury that are routinely detected in premature infants and have proven prognostic significance. The most common form of cerebral injury currently detected with conventional neuroimaging, particularly CUS, is intraventricular hemorrhage (IVH), with an incidence of approximately 20% for all grades of IVH. The complications associated with IVH include posthemorrhagic hydrocephalus, periventricular hemorrhagic infarction, and an increased incidence of periventricular leukomalacia (PVL). Another common neuropathology is that of PVL consisting of necrosis of white matter in a characteristic distribution, ie, dorsal and lateral to the external angles of the lateral ventricles, involving particularly the centrum semiovale (frontal horn and body), optic radiation (trigone and...
occipital horn), and acoustic radiation (temporal horn). The incidence of PVL varies in relation to its method of detection, which will be discussed further. In autopsy studies of premature infants it was found to differ between medical centers, ranging from 25 to 75%. Other major forms of neuropathology in the premature infant, less common than PVL, include selective neuronal injury and focal cerebral ischemic lesions.

Cranial Ultrasound

Background

Ultrasound relies on the reflection of ultrasound waves from tissue to provide images. Its greatest advantage lies in its portability, as it is possible to image infants without moving them from the intensive care unit. CUS images show the outline of the cerebral ventricles clearly, as the ventricles appear echolucent or dark as compared with adjacent white matter. CUS also has high sensitivity for detection of hemorrhage, which appears echogenic or bright. Thus, CUS is very useful for detection of intracranial hemorrhage and associated posthemorrhagic hydrocephalus. CUS is also used for detection of PVL, and a characteristic progression of imaging features has been described. During the first week following injury, there are echogenic foci in the periventricular white matter due to local necrosis with congestion and/or hemorrhage (Fig. 1). This is followed, during weeks one through three, by the appearance of echolucent cysts, which correlates with cyst formation due to tissue dissolution. By two to three months, ventriculomegaly appears, often with disappearance of the cysts. This is associated with deficient myelin formation and/or gliosis with collapse of the cysts.

One of the disadvantages of CUS is that it provides relatively poor contrast for lesions of the brain parenchyma. Acute stroke, for example, can be difficult to detect with CUS as compared with CT and MRI. In addition, since CUS images are typically obtained through the anterior fontanel, there is a limited field of view which does not "see" the cerebral convexities. Further, image detail in the posterior fossa, which is relatively far from the transducer, is often poor. This can be overcome by imaging through the posterior fontanel, which should be encouraged as a standard of practice. Acquisition and interpretation of CUS images is also more operator-dependent than CT or MRI, and quality can vary markedly from medical center to medical center. Finally, assessment of increased echodensity is subjective, though this could potentially be overcome by comparing the echodensity of the region of possible abnormality with that of a standard structure, such as the choroid plexus.

Correlation of Image Findings with Outcome

CUS studies have been available for evaluation of premature infants for nearly 30 years. There is a relatively large literature describing associations between CUS findings and outcomes. Comparison of these studies is complicated by a variety of factors, some of the more prominent of which are differences in: (a) the timing and frequency of the HUS studies obtained, (b) the technical quality of the ultrasound equipment used, (c) the technical skills of the ultrasonographers, and (d) the duration of time for which subjects were in clinical follow up (more subtle neurodevelopmental abnormalities are not readily detected at younger ages). Nevertheless, the majority of studies suggest that 30 to 60% of premature infants who develop cerebral palsy (CP) had lesions on CUS during the perinatal period. A recently published study by deVries and coworkers suggests that CUS may be more sensitive than previously believed. In this study, preterm children underwent CUS studies weekly up to and including a scan at 40 weeks postmenstrual age (the latter scan was typically done

![Figure 1](image_url) Cranial ultrasound studies demonstrating PVL. The image on the left is a sagittal view. A, anterior; P, posterior. The lateral ventricle, which appears dark, is designated by the black arrow. A bright area of increased echodensity, corresponding to PVL, is designated by the white arrowhead. The image on the right is a coronal view of cystic PVL. L, lateral ventricles. The black arrowhead indicates a cyst present at the dorsolateral angle of the lateral ventricle.)
as an outpatient). Children were followed for two years and evaluated for CP and cognitive difficulties. Ninety-two percent of children with CP had abnormalities found on CUS studies. These abnormalities were major (IVH with ventricular dilation, hemorrhagic periventricular infarction, cystic PVL, subcortical leukomalacia, and basal ganglia lesions) in 83% and minor in 17%. Notably, CUS abnormalities were first detected after 28 days of life in 29% of infants with major abnormalities. Their data give a specificity of 95%, sensitivity of 76%, and positive predictive value of 48% for CUS detection of CP in infants ≤32 weeks gestational age (GA). Similar values were obtained for infants between 33 and 36 weeks GA. The high sensitivity for HUS in this study as compared with the rest of the literature may be related to the fact that infants were scanned more regularly and for a longer period of time than in typical CUS studies. It is also possible that a high level of technical competence contributed to the high sensitivity, as Wheeler and coworkers, performing weekly CUS studies and assessing children for CP at age 18 months, found CUS abnormalities in only 56% of children with CP.

While the studies described above address the detection of motor disability (CP), studies have also been done to evaluate the sensitivity of CUS to cognitive disabilities. In general, CUS seems relatively insensitive for predicting children who will go on to have cognitive difficulties, particularly subtle ones. It is also worth noting that recent studies indicate that MRI is more sensitive than CUS for the detection of diffuse PVL, though cystic PVL is readily detectable by both modalities.

Guidelines for the Use of CUS

The frequency and duration of time for which CUS studies should be obtained in premature infants remains an area of controversy. It has been suggested that clinically-stable premature infants do not need repeat screening HUS if they have two normal studies ≥7 days apart, though infants <25 weeks GA require an additional HUS study at the time of discharge. The quality standards committee of the American Academy of Neurology and the practice committee of the Child Neurology Society recommend that infants be scanned at 7 to 14 days of age and again at 36 to 40 weeks postmenstrual age. In light of the findings of deVries and coworkers described above, which were not available at the time the practice parameter was developed, it seems likely that CUS is more sensitive for detecting injury if studies are obtained more frequently. Further, the window for the appearance of injury is longer than previously believed. As a result, it would be reasonable to obtain weekly HUS studies from birth to 32 weeks postmenstrual age, and finally at 36 to 40 weeks postmenstrual age. This guideline applies, of course, to clinically stable infants. Infants with clinical deterioration or alteration in neurological state may require more frequent imaging.

As noted above, CUS is also very useful for evaluating ventricular size. Posthemorrhagic ventricular dilation (PHVD) is a relatively common complication of IVH and should be carefully monitored for following the detection of Grade II or higher IVH. The incidence of adverse neurodevelopmental outcome following PHVD is high, and there is an increasing trend to earlier and more aggressive therapy for this condition to improve outcome. At present, CUS images are typically evaluated qualitatively for ventricular size. While this strategy has proven useful, it would appear more informative to evaluate ventricular size in a quantitative fashion, based on established norms. Further, the occipital horn is the first and the frontal horn is the last to enlarge following IVH. Thus, measurement of the thalamo-occipital dimension of the ventricle via the posterior fontanel, is the most sensitive indicator of ventriculomegaly. Frequent CUS monitoring of the ventricular dimensions, particularly in the acute period, may assist in assessing the infant’s course and determining the need for intervention with ventricular drainage. It may also guide the frequency and volume of CSF drainage necessary to decrease ventricular size.

Computed Tomography

Background

Computed tomography has been available for approximately 30 years. The method is based on passing an x-ray beam (ionizing radiation) through the sample at a series of different angles. Based on the attenuation of these beams, an image can be constructed using a method known as filtered back projection. Contrast in CT images is dependent on differing degrees of attenuation of x-rays by various structures. Bone, for example, causes a high degree of attenuation, and appears bright on CT images. CSF, on the other hand, causes a low degree of attenuation, appearing dark. CT provides excellent views of bone and is also very sensitive for the detection of hemorrhage, which appears bright. It allows differentiation of white and gray matter, though the contrast between these two types of tissue is relatively low in comparison with MRI. While it does not suffer the field of view difficulties associated with CUS, structures in the posterior fossa are relatively poorly demonstrated on CT because of nonuniform attenuation of x-ray energy by the bone at the base of the skull (beam hardening artifact). CT scans usually require that the infant be removed from the ICU, which is a disadvantage as compared with CUS. On the other hand, the scan time is shorter than that of a typical MRI study. Further, the infant is more readily accessible while in the scanner, in the event of an emergency, than for an MR scan, though there is a trend in MR magnet design toward more open magnet configurations which provide better patient access.

A further issue for CT is the exposure of the infant brain to ionizing radiation. There are two main areas of concern related to this exposure—firstly the risk of future malignancy and, secondly, cognitive impairment. The adverse impact of cranial irradiation on brain and cognitive development following radiation treatment of brain tumors has been clearly shown and is dose-related. However, the threshold value for the effect is not known. Recently, Hall and coworkers suggested that even low doses of ionizing radiation, similar to those delivered by CT scans, may adversely affect brain and...
cognitive performance in scores on tests for learning ability and cognitive reasoning for individuals who were exposed to >100 mGy ionizing radiation for the treatment of cutaneous hemangioma before age 18 months. In a study of 20,000 Israeli children treated with cranial irradiation for tinea capitis, Ron and coworkers found poorer cognitive performance in irradiated children as compared with controls.29 Currently, it is unclear what long-term effects, if any, low doses of cranial irradiation, such as those delivered during a cranial CT scan, may have when administered during infancy, a phase of rapid brain development. In relation to the risk of subsequent malignancy, a 0.1% risk of life long fatal malignancy from a head CT at age 12 months has been estimated.30 However, the risk of tumor may be significantly greater with exposure at a younger age. The risk of development of brain tumor was found to be 10-fold higher in infants exposed to cranial irradiation under 5 months of age in comparison to over seven months of age.31 While extrapolation of findings from cranial irradiation of children to head CT studies of premature infants must be regarded cautiously, the studies do raise concerns about exposure to ionizing radiation during infancy. Further research would be necessary to accurately define the nature of any risk associated with CT scanning of the infant brain. Until such data are available, it is reasonable to restrict the use of this neuro-imaging technique to selected settings in which the information obtained from the imaging study is clearly of benefit to the patient.

CT scanning of the premature infant has been employed for detection of both hemorrhage and PVL. Although it is likely no more sensitive than CUS for detecting cystic PVL during the perinatal period, findings of reduced volume of periventricular white matter and ventriculomegaly with irregular outline of the lateral ventricles have been described in older children with clinical findings consistent with PVL (ie, spastic diplegia).32 CT can also be used to detect stroke, though image contrast for nonhomorrhagic stroke is weak,33 particularly in comparison with MR.

**Correlation of Image Findings with Outcome**

There are relatively few studies correlating CT findings with outcome, and the majority of them are from the mid 1980s. In general, the correlations have not been especially strong. For example, there was no relationship found between neonatal CT and clinical outcome at age 18 months in a study of 145 children.34 However, in a series of 45 infants imaged at 40 weeks postmenstrual age, the finding of ventriculomegaly correlated with the presence of learning disabilities at school age.35

**Guidelines for the Use of CT**

CT scanning has not been demonstrated to contribute significantly to the evaluation of the brain of the premature infant. Correlations between CT findings and outcome are weak, and similar information can be gleaned from CUS studies. In addition, the concerns regarding exposure to ionizing radiation must be considered. CT has a role in the rapid evaluation of the newborn infant with traumatic head injury following delivery in consideration of urgent neurosurgical intervention, but this situation is rarely encountered in preterm infants.

**Magnetic Resonance Imaging**

**Background**

The signal from which magnetic resonance images are derived arises from the $^1$H atoms of water ($^1$H$_2$O). The concentration of $^1$H in water is on the order of 100 mol/L. This high concentration provides a strong signal from which to obtain images. Other nuclei, such as $^{23}$Na and $^{31}$P, also provide MR signal, but their concentrations in the brain are on the order of tens of mM—roughly 10,000 times less than that of $^1$H in water. While signals from these nuclei are detectable by MR spectroscopy, for which signal is obtained from a relatively large volume of brain, they are not strong enough to be used to obtain images of high spatial resolution. Though MR spectroscopy has been applied to evaluation of the neonate brain and has proven to have prognostic value,36,37 this review is focused on MR imaging.

**Conventional MR Imaging**

Image contrast obtained in MR images is primarily the result of the different MR properties for the $^1$H atoms of water residing in different parts of the brain. Depending on the image acquisition conditions (or acquisition parameters), images with a variety of contrasts can be obtained. Two common forms of contrast are based on the T1 and T2 MR imaging characteristics of water. (T1 and T2 represent different MR relaxation time constants, which will simply be referred to as “T1” and “T2” for this discussion.) The T1 and T2 characteristics of water differ between the tissue types of CSF, white matter, and gray matter providing contrast for the images. For example, water in CSF has a relatively long T1, and thus appears dark on T1-weighted images while in T2 images, water in CSF looks bright relative to brain tissue. It can sometimes be difficult to distinguish injured brain from adjacent CSF-containing spaces on T2-weighted images. This is because both injured tissue and CSF appear bright. One means of compensating for this is the use of fluid-attenuated inversion recovery (FLAIR) imaging. In this case, an additional RF pulse is applied during image acquisition, serving to eliminate signal from CSF, making it appear dark on an otherwise T2-weighted image. In current clinical practice, T1-weighted, T2-weighted, and FLAIR images are usually obtained. In addition, Gd-based contrast agents are often injected into the intravascular space. These agents, when in contact with water, shorten the T1 so that the water appears bright on T1-weighted images. T1-weighted images following injection of intravenous contrast appear bright in areas which are highly vascular or for which contrast agent has extravasated into the extravascular space due to disruption of the blood brain barrier.
Diffusion MR Imaging

MR images can also be obtained in which contrast is dependent on water displacement (diffusion-weighted imaging or DWI). With this method, water displacements on the order of 10 μm can be detected. The physical constant characterizing this water motion is called the “apparent” diffusion coefficient (ADC) in recognition of the fact that water displacements in tissue are influenced by factors other than simple Brownian motion, such as restrictions due to cell membranes. While one might not expect tissue water displacements to be especially useful for image contrast, diffusion-based MR imaging provides remarkably rich information about cerebral structure and its disruption. For example, water ADC values decrease within minutes after a variety of forms of tissue injury, including stroke. As a result, diffusion-based MR imaging provides one of the earliest indicators of tissue injury, showing changes many hours to days before abnormalities are detectable with other forms of imaging.

There are a variety of ways of obtaining and displaying diffusion images, and this has lead to confusion in the interpretation of diffusion-based MR studies. It is possible to obtain a conventional, diffusion-weighted MR image as a single scan. This permits fast image acquisition and processing. However, image contrast with this single-scan method of diffusion imaging is influenced by both water ADC and T2. As a result, a region may appear bright either because of a low water ADC or a long T2. During the subacute phase of stroke, water ADC values are decreased and T2 constants increased. Both changes make the region of abnormality bright, providing reinforcing contrast. Unfortunately, these two forms of contrast may interfere with, or even cancel, one another under other circumstances. The finding of an area of increased signal intensity on a diffusion-weighted image in which the ADC is normal but the T2 is long is referred to as “T2 shine through.” One means of avoiding this admixture of contrasts is to obtain images both with and without diffusion weighting. These images can be combined to eliminate the effect of T2 weighting, providing quantitative values for water ADC (in units of μm²/ms). The resulting data are shown as parametric maps in which image intensity is directly related to quantitative ADC values. Image acquisition time for parametric maps is slightly longer, as it requires at least two, and typically four, acquisitions, but parametric maps provide more easily interpreted, quantitative diffusion information. Diffusion sequences that correct for T2 relaxation are available on most commercial MR scanners, and their use should be encouraged as a standard of clinical practice. It is worth noting that parametric maps and diffusion-weighted images have opposite image intensity conventions—areas of low ADC values appear dark on parametric maps, but bright on diffusion-weighted images.

Another form of contrast available with diffusion imaging is based on diffusion anisotropy. Anisotropy refers to the condition in which water ADC values differ depending on the direction along which they are measured. In myelinated white matter, for example, water molecular displacements are smaller perpendicular to fibers than parallel to them because motion perpendicular to fibers requires passing through or around layers of myelin membrane, whereas motion parallel to them does not. Thus, water apparent diffusion in mature white matter is highly anisotropic. In this manner, diffusion imaging characterizes tissue microstructure. Two parameters related to diffusion anisotropy are particularly useful for microstructural characterization: the degree of anisotropy of water motion (eg, relative anisotropy or RA) and the direction along which water apparent diffusion is greatest (the direction of the major eigenvector of the diffusion tensor). RA values approach zero for CSF, for which diffusion is isotropic and ADC values are equal in all directions. RA values are highly positive for myelinated white matter, for which ADC values are on the order of three times smaller for diffusion perpendicular to fibers as compared with parallel to them. For white matter, the direction along which water ADC values are greatest represents the primary orientation of myelinated fibers within an image fiber with voxel (remember that water displacements are greatest parallel to fibers). This information can be used for a form of “tract tracing” in which neural connections can be inferred. For gray matter, the direction along which water ADC values are greatest reflects the radial organization of developing cortex (Fig. 2).

Volumetric Measurements through MR

MR images can be used to measure cerebral volumes. Images of different contrasts, such as T1, T2, and proton-density weighted, are analyzed to classify tissue as CSF, gray matter or white matter in a process referred to as “segmentation” (Fig. 3). The number of image elements, or voxels, corresponding to each class can be summed to compute volumes in units of cm³. There is not yet a consensus as to the optimal means of assessing and comparing these volumes. While it has proven useful to measure total intracranial volumes for tissue types, it is also desirable to evaluate volumes on a regional basis because injuries affecting cerebral volumes may preferentially affect some brain areas. One approach is to apply arbitrary boundaries for regions, similar to lines for latitude and longitude on a map. Though this approach is fairly simple and relatively straightforward to implement, it tends to group brain regions of disparate function and physiology, such as brainstem and temporal lobe, in the same volume. It also may miss volume abnormalities that involve small brain regions that cross the border of adjacent areas chosen for analysis. A more sophisticated approach consists of applying statistical methods to compare the volume of the brain of interest to that of a “standard” brain on a voxel-by-voxel basis. This method provides parametric maps of the regions for which volumes are statistically different, similar to the maps generated for functional MRI studies. There is also no agreement on how these volumes should be normalized. For example, should gray matter be expressed as an absolute volume (ml), as a percentage of total brain volume, or as a percentage of intracranial volume? It might also be useful to express brain volumes in relation to postconceptional age. Though the uncritical application of the volumetric approach has been unfavorably likened to phrenology, identification of areas of volume abnormality is an important step in iden-
tifying the anatomic substrate of brain injury in premature infants.

Overall, MR has the disadvantage that it typically requires that the infant be transported from the NICU to the scanner for study. The risk to the infant associated with transport out of the ICU has been ameliorated by the availability of MR-compatible, purpose-built transport isolettes. These devices include support equipment for the infant as well as the RF coil necessary for MR studies. The isollette holding the infant can be placed in the MR scanner for imaging. Once placed in such an isollette in the ICU, an infant can be taken to the scanner and left undisturbed until he/she returns to the ICU after the scan. These isolettes are now commercially available. MRI is also relatively expensive, requiring equipment costing millions of dollars and involving careful and sometimes costly preparation of the site at which the scanner is housed. MRI has several advantages. Unlike CT, it does not involve ionizing radiation, making it relatively safer. It also offers a rich variety of tissue contrasts, providing tissue characterization superior to both CT and CUS. Preliminary studies suggest that MR is more sensitive to subtle tissue injury than either CT or CUS.

Correlation of Image Findings with Outcome

MR imaging of premature infant brain has been available for approximately 20 years and remains an area of active research. The earliest studies used conventional MR imaging and focused on studies obtained after discharge from the hospital on patients for whom PVL had been diagnosed by CUS during the perinatal period. Areas of abnormal signal intensity in periventricular white matter, ventriculomegaly, varying degrees of cerebral atrophy, thinning of the corpus callosum, and delayed myelination have been described in children as old as five years.45-47 These findings are common in prematurely born children48,49 and suggest that MR can be used to detect the sequelae of PVL in older children. However, MR abnormalities consistent with PVL detected in prematurely born children at ages 850 and 15 to 17 years7 show only moderate correlation with cognitive and motor deficits. In contrast, abnormalities of visual pathways detected on MR...
images obtained in late infancy show strong correlation with visual impairment.51

Conventional MR studies obtained at term equivalent, near the time of discharge of the premature infant from the hospital, have prognostic significance. The presence of parenchymal lesions gave a sensitivity of 100% and specificity of 79% for motor abnormality in a study of 51 infants, 11 of whom had neurologic deficit at follow up.52 The parenchymal lesions consisted of hemorrhage, changes consistent with PVL, infarction, and reduction in white matter volume. In a study of 15 premature infants, 13 of whom had neurologic deficits at follow up, findings of changes consistent with PVL and widespread infarction were associated with adverse neurologic outcome at age 1 year.53

There has been focus on abnormalities of the posterior limb of the internal capsule (PLIC) and outcome. Abnormal signal intensity in the PLIC in term infants following hypoxic–ischemic injury correlates with adverse neurodevelopmental outcome.54 In preterm infants with intraventricular hemorrhage and unilateral hemorrhagic parenchymal involvement, signal abnormalities in the PLIC on MR studies obtained at term equivalent strongly predicted future hemiplegia.55 Abnormalities of diffusion parameters of the PLIC also correlate with outcome. In term infants with hypoxic ischemic encephalopathy, low values for ADC56 predict poor outcome. For preterm infants imaged at term equivalent, low values for diffusion anisotropy57 correlate with adverse outcome at age 1 year.53

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Abnormalities in ADC are associated with MR evidence of white matter injury. Abnormally high ADC values have been found for white matter in subjects with diffuse signal abnormalities on T2-weighted images67 and focal white matter signal abnormalities on T1- and T2-weighted images.68 In a study of twelve term infants with hypoxic ischemic encephalopathy, the presence of white matter abnormalities on diffusion imaging correlated with adverse outcome in infants followed for up to 11 months.69

While evaluation of ADC values is proving useful for detecting injury, measures of diffusion anisotropy have the potential to provide additional information regarding tissue microstructure. As noted above, diffusion anisotropy is present in both white and gray matter. For white matter, anisotropy values are relatively low until myelination takes place.70,71 For gray matter, diffusion anisotropy values are highest during early development, due to the radial organization of developing cortex, and decrease steadily up to term.41 Thus, anisotropy values change with development for both tissues. To date, there have been relatively few studies of anisotropy in injured premature brain. However, alterations in white
matter anisotropy values and organization have been described in infants with PVL. Further, using diffusion anisotropy for white matter “tract tracing,” abnormalities in sensory cortex pathways have been demonstrated in two children with spastic cerebral palsy. These methods show tremendous potential for evaluation of premature infant brain, but more studies are necessary to fully define their clinical role.

MR images can also be evaluated for tissue volumes. In general, prematurity and white matter injury are associated with reduced brain tissue and increased cerebrospinal fluid volumes. Studies of former premature infants when they reach adolescence show reductions in overall brain volume and gray matter volume with an increase in lateral ventricular volume. The presence of signal abnormalities in white matter of former premature infants evaluated at the age of 15 years is associated with reduced white matter volume. Further, prematurity and white matter injury are associated with reduced brain tissue and increased cerebrospinal fluid volumes. Studies of former premature infants when they reach adolescence show reductions in overall brain volume and gray matter volume with an increase in lateral ventricular volume. The presence of signal abnormalities in white matter of former premature infants evaluated at the age of 15 years is associated with reduced white matter volume.
ther, increased lateral ventricular size in this population is associated with cognitive and motor deficits.\textsuperscript{76} Volumes of sensorimotor and midtemporal cortices are associated positively with full-scale, verbal, and performance IQ scores.\textsuperscript{42} Thus, alterations in cerebral volumes have a significant clinical correlate.

Fewer studies have been obtained in which volumes are reported for premature infants imaged near the time of discharge at term equivalent, and there are not yet any published studies that include clinical follow up. Nevertheless, a variety of MR abnormalities have been described. In infants with prior evidence of PVL by either CUS or MR, there is a marked reduction in cerebral cortical gray matter as compared with either preterm infants without PVL or term infants. This change is associated with a significant decrease in total brain myelinated white matter and an apparent compensatory increase in total cerebrospinal fluid volume.\textsuperscript{77} Further, studies indicate that gyral development is markedly immature in infants with evidence of white matter injury\textsuperscript{78} (Fig. 5). Thus, while there has been a strong focus on white matter injury in premature infants, these studies provide evidence for cortical gray matter injury as well. It is not yet known whether these gray matter changes are a consequence of white matter injury, or occur independently.

**Guidelines for the Use of MRI**

The use of MRI to evaluate the brain of premature infants represents a moving target, as the more advanced MR diffusion and volumetric methods are still under active investigation. However, MRI clearly has a role to play in evaluating premature infants. It is important to note that brain water content is higher for infant brain than for older children, and T1 and T2 relaxation time constants are consequently greater. This, in association with other changes related to brain maturation, causes the gray/white contrast on T1- and T2-weighted images of infants to be exactly opposite that of children greater than one year of age. Thus, it is critically important that the image acquisition parameters be optimized for newborn infants. In general, it would be useful to obtain T1-weighted, T2-weighted, T2*-weighted (sensitive to hemorrhage) and diffusion images around term equivalent to evaluate myelinization through the posterior limb of the internal capsula. In addition, if there is any evidence of acute cerebral ischemia, then diffusion MR imaging may define the full extent of the cerebral injury early. If undertaken as an acute or subacute evaluation, the diffusion images should be obtained in a way that allows compensation for T2 shine through and permits calculation of ADC maps. Such sequences are widely available on commercial MR imaging systems.

**References**