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Normal Fetal Brain Development: MR Imaging with a Half-Fourier Rapid Acquisition with Relaxation Enhancement Sequence[1]

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Abbreviation:
RARE = rapid acquisition with relaxation enhancement

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PURPOSE: To analyze normal maturation of the fetal brain with half-Fourier rapid acquisition with relaxation enhancement (RARE) magnetic resonance (MR) imaging.

MATERIALS AND METHODS: The normal brains of 25 fetuses of 12–38 weeks gestational age were examined in utero with half-Fourier RARE imaging. Gyrus maturation, gray and white matter differentiation, ventricle-to-brain diameter ratio, and subarachnoid space size were evaluated with respect to gestational age.

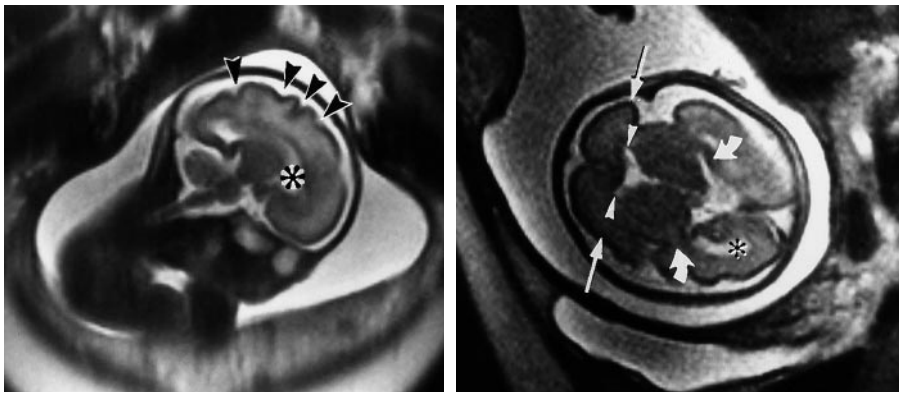
RESULTS: At 12–23 weeks, the brain had a smooth surface, and two or three layers were differentiated in the cerebral cortex. At 24–26 weeks, only a few shallow grooves were seen in the central sulcus, and three layers, including the immature cortex, intermediate zone, and germinal matrix, were differentiated in all fetuses. At 27–29 weeks, sulcus formation was observed in various regions of the brain parenchyma, and the germinal matrix became invisible. Sulcation was seen in the whole cerebral cortex from 30 weeks on. However, the cortex did not undergo infolding, and opercular formation was not seen before 33 weeks. At 23 weeks and earlier, the cerebral ventricles were large; thereafter, they gradually became smaller. The subarachnoid space overlying the cortical convexities was slightly dilated at all gestational ages, most markedly at 21–26 weeks.

CONCLUSION: Changes in brain maturation proceed through stages in an orderly and predictable fashion and can be evaluated reliably with half-Fourier RARE MR imaging.

Ultrasonography (US) has proved to be the method of choice for examination of the fetal brain in utero. However, it has known limitations in conditions such as maternal obesity and oligohydramnios (1–5). Magnetic resonance (MR) imaging may be the only complementary means available when US findings are inconclusive and inadequate. Fetal brain MR imaging findings have been reported; normal fetal brain appearance in utero has been observed in a few cases (1,2,4,6–16). However, the application of MR imaging in the fetus has been challenging because of fetal motion and altered fetal position.

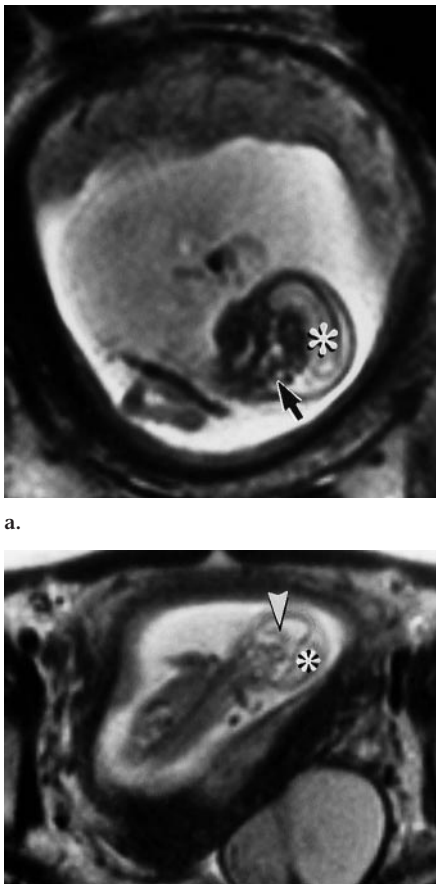
To decrease the influence of fetal movement on image quality, fast MR imaging with a half-Fourier rapid acquisition with relaxation enhancement (RARE) sequence has been applied. This sequence can be used to obtain information not only about central nervous system abnormalities but also about normal fetal brain development. Half-Fourier RARE allows T2-weighted MR images to be obtained in a few seconds. It also allows greater reduction of artifacts related to maternal and fetal motion (3) in comparison with conventional MR imaging sequences. However, to our knowledge, the usefulness of this imaging sequence for the depiction of normal fetal development has not been demonstrated.

The purpose of the present study was to analyze the developmental changes in normal fetal brain maturation with half-Fourier RARE MR imaging.



a. b.

Figure 1. MR images of a fetus at 28 weeks of gestation in a 32-year-old woman with leiomyomas. **(a)** Sagittal half-Fourier RARE image (∞/87 [repetition time msec/effective echo time msec]) reveals the formation of multiple sulci (arrowheads) in the central sulcal area but reveals no infolding of the cortex. ∗ = lateral ventricle. **(b)** Transverse half-Fourier RARE image (∞/87) also shows multiple sulci in the parietal lobe. The thalami (curved arrows) are shown to have low signal intensity. ∗ = ventricle. The size of the ventricular system at the level of the frontal horn angles and the midbody of the lateral ventricles was expressed as a fraction of the diameter of the brain at the same level (ventricle-to-brain ratio). Arrowheads point to the measured widths of the anterior horn of the lateral ventricle, and straight arrows indicate the diameter of the brain at the same level.



a.

b.

Figure 2. MR images in a fetus at 12 weeks gestation in a 25-year-old woman with a left ovarian chocolate cyst. **(a)** Sagittal and **(b)** coronal half-Fourier RARE images (∞/87) reveal the dilated ventricle, or so-called normal fetal hydrocephalus. The brainstem (arrow in **a**) and choroidal plexus (arrowhead in **b**) are noted. The cortex is shown to have a smooth surface. In **a** and **b**, ∗ = ventricle.

MATERIALS AND METHODS

The subjects were 25 fetuses whose brains were normal but whose mothers were suspected to have a maternal disease on the basis of US examination results and clinical manifestations. The stage of pregnancy at the time of MR imaging ranged from 12 to 38 weeks. Fetal age was estimated on the basis of the time of the last menstrual period compensated by the measurements of the crown-rump length on US images. All MR imaging was requested by the mothers' obstetricians as part of the clinical work-up for the various diseases. The parents' informed consent was obtained before MR imaging.

Maternal abnormalities included deep venous thrombosis in nine patients, uterine leiomyoma in six, ovarian tumor in five, ovarian vein syndrome complicated by hydronephrosis in two, femoral head necrosis in one, thin myometrium in one, and postuterine septal ectopia in one. In all fetuses, US images were normal. All mothers and neonates received at least 8 months of follow-up after delivery. All neonates showed normal development after birth.

The examinations were performed with a 1.5-T superconducting MR imaging unit (Magnetom Vision; Siemens, Erlangen, Germany) and a body phased-array coil. Half-Fourier RARE (HASTE; Siemens) imaging was performed, with an effective echo time of 87 msec, with one signal acquired, and with a 240 × 256 matrix. The echo train length was 128, and the echo space was 11.9 msec. Fat saturation suppressed the signal from peritoneal fat to increase the dynamic range of imaging. Each section was obtained in 2 seconds, and images were acquired sequentially. Therefore, total imaging time was determined by the number of sections obtained. We obtained nine sections, with a 5-mm thickness and with a 2-mm gap, in one breath hold (total acquisition time, 18 seconds). In all patients, pericoronal and/or oblique projections were acquired, depending on the position of the fetus.

Neither sedation nor oxygen inhalation was used in any patient. The typical total examination time was 15 minutes, which included patient preparation and image acquisition. The peak specific absorption rate for radio-frequency exposure at the maternal skin was measured in all patients.

The MR images were analyzed by two observers (L.M.L. and Y.Y.) in consensus, without knowledge of the fetuses' gestational ages, in accordance with the *Atlas of Normal Fetal Brain Morphology* [in French] by Feess-Higgins and Larroche (17). The observers evaluated the gyrus maturation, the differentiation of gray and white matter, the ventricle-to-brain diameter ratio, and the size of the subarachnoid space.

The fetuses' cerebral parenchymal layering state was correlated with their gestational ages. By using the signal intensity on half-Fourier RARE images, we determined the number of layers. Because the myelination could not be determined confidently on half-Fourier RARE images (see Discussion), this was not considered for the evaluation of the cerebral parenchymal layering.

The development of fetal sulci or fissures was correlated with gestational age. Because the identification of small sulci was difficult, the grading of cortical development and maturation was based on the major landmarks (fissures and sulci), which included the central sulci, the interparietal sulci, and the superior temporal sulci.

The size of the ventricles at the level of the frontal horn angles relative to the midbody of the lateral ventricles was cal-

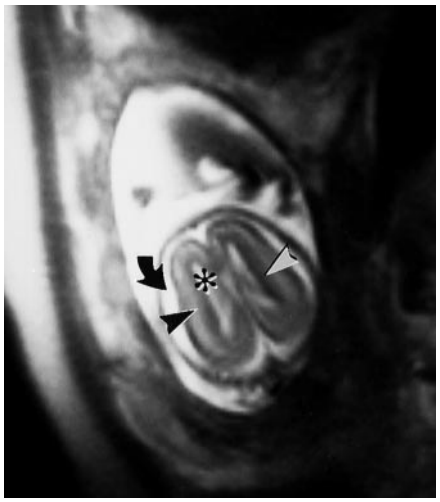


Figure 3. Transverse half-Fourier RARE MR image (∞/87) of a fetus at 20 weeks gestation in a 32-year-old woman with deep venous thrombosis reveals the dilated ventricle (*) and the subarachnoid space (arrow). The cortex still shows absent sulcation. The cerebral cortex has three layers. The innermost layer is of low signal intensity (arrowheads) and corresponds to the germinal matrix .

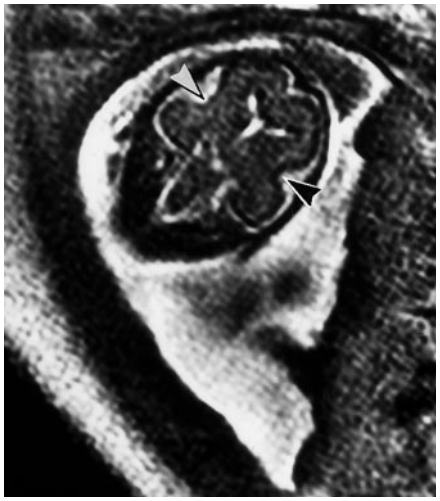


Figure 4. Coronal half-Fourier RARE MR image (∞/87) of a fetus at 22 weeks gestation in a 35-year-old woman with leiomyomas reveals the sylvian fissure (arrowheads). The ventricle was slightly dilated but is not apparent in this section.

culated as a ratio (ventricle-to-brain ratio) of the diameter of the ventricles to the diameter of the brain (Fig 1b). This method of determining the ventricular size has been used previously (18). The ventricle-to-brain ratio was not determined at the level of the occipital horns because of the variability in their appearance.

The widths of the subarachnoid space were measured at various points on the transverse images. These widths were determined for the anterolateral and posterolateral parts of the subarachnoid space at the levels of the centrum semiovale, the midbody of the lateral ventricles, and the thalamus and the width of the part of the subarachnoid space anterior to the temporal lobes. The means of these figures were divided by the distance between the right and left inner tables. The subarachnoid space anterior to the frontal lobes was noted but was not measured, since this space tends to widen when the patient is lying in a supine position (18).

RESULTS

Sulcation

In vivo fetal gyral formation was clearly visualized on T2-weighted half-Fourier RARE images, and development was well correlated with gestational age (Fig 2).

At 12–23 weeks gestational age, images of the brain showed a smooth surface, except for the interhemispheric fissure, in all six fetuses (Figs 2, 3) in this age group. However, sylvian fissures were visualized as early as 15 weeks gestational age (Fig 4).

From 24 to 26 weeks of gestation, the cerebral cortex had a mostly smooth surface, with a few shallow grooves in the central sulcus, in the interparietal sulci, or in the superior temporal sulci in three of the four fetuses in this age group. The cerebral cortex of one fetus had a completely smooth surface.

In all three fetuses of 27–29 weeks gestational age, sulcus formation was observed in various brain parenchyma, especially in the occipital lobe and the area around the central sulcus (Fig 1).

In three of the four fetuses of 30–32 weeks gestational age, deep sulcation was seen in the whole cerebral cortex. However, the cortex had not undergone infolding, and opercular formation (Fig 5) had not yet occurred. The remaining fetus had the same appearance as that described for fetuses of 27–29 weeks gestational age.

As early as 33 weeks gestational age, sulcation was completed and appeared similar to that in an adult (Fig 6).

At 36–38 weeks of gestation, mature sulcation was seen in all four fetuses in this age group.

Cerebral Parenchymal Layering Pattern

The layering structure of the cerebral parenchyma was evident after 16 weeks of gestation. Different layering patterns were observed, depending on the age of the fetus (Fig 7). At 12–23 weeks of gestation, two or three layers were differentiated in the cerebral cortex (Figs 2, 3).

The inner layer had low signal intensity on T2-weighted half-Fourier RARE images and corresponded to the germinal matrix. This layer was not observed in two fetuses in the 12–23-week group.

The intermediate layer showed relatively high signal intensity on T2-weighted half-Fourier RARE images and corresponded to the intermediate zone, which was composed of sparse neuroglial cells.

The outer layer had a relatively low signal intensity on T2-weighted half-Fourier RARE images and corresponded to the immature cortex, which was composed of a molecular layer and the subplate zone.

From 24 to 26 weeks of gestation, three layers typically were differentiated in all four fetuses in this group. At 27 weeks of gestation and later, the germinal matrix typically became invisible (Fig 5), which typically resulted in the differentiation of only two layers: the internal layer, which had relatively high signal intensity on T2-weighted half-Fourier RARE images and which corresponded to the white matter, and the outer layer, which had low signal intensity on T2-weighted half-Fourier RARE images and which corresponded to the cortex. Basal ganglia showed low signal intensity, which became evident after 26 weeks of gestation.

Ventricular Size

The ventricle-to-brain ratio results are shown in Figure 8. In the fetuses of 12–23 weeks gestational age ($n = 6$), the cerebral ventricles were large, which corresponded to the relatively normal fetal hydrocephalus (Figs 2, 3). In five of the 10 fetuses of 12–26 weeks gestational age, marked dilatation of the ventricles was noted. The ventricles gradually became smaller and in fetuses of 33–38 weeks gestational age or later ($n = 8$) had become almost invisible in four (Figs 5, 6).

Subarachnoid Space

The subarachnoid space along the lateral aspect of the convexities appeared as a thin, high-signal-intensity rim of cerebrospinal fluid on heavily T2-weighted half-Fourier RARE images. The width of the subarachnoid space in the middle fossa anterior to the temporal lobe was

greater than that in the cisterns and in the dependent portions of the subarachnoid space. The width of the subarachnoid space relative to the distance between the right and left inner tables is shown in Figure 9. The subarachnoid space overlying the convexities was slightly dilated at all gestational ages (Figs 1, 3). Marked dilatation was seen frequently from 21 to 26 weeks of gestation.

DISCUSSION

MR imaging has been used for the examination of the fetus in the second and third trimesters (1,2,4,6–16). US is still regarded as the imaging modality of choice in the evaluation of fetal abnormalities because of its accuracy and safety in addition to its easy access, low cost, and real-time capability. Since the introduction of MR imaging for clinical applications, the results of fetal studies have shown that MR imaging may be complementary to US in difficult cases (3,5).

We believe that MR imaging is more accurate than US in evaluating ventricular walls and subarachnoid spaces and particularly in demonstrating intraparenchymal tissue organization because of its excellent contrast resolution. In addition, lesions such as atrophy and porencephaly are very difficult to depict with US; in such cases, MR imaging may be helpful (19). However, because of fetal movement and the relatively long imaging time, blurring of MR images may occur. Although fetal details have been revealed occasionally, to our knowledge reliable measurement has not been possible.

Several fast pulse sequences have been applied in fetal imaging. The echo-planar technique is used for snapshot imaging (20). However, in our experience, its image resolution was not sufficient. Gradient-echo or fast spin-echo imaging requires more than 10 seconds to obtain a sufficient signal-to-noise ratio. In vivo, T2-weighted half-Fourier RARE MR imaging is of special interest, since fast spin-echo imaging with a short acquisition time is unaffected by fetal motion, can afford numerous sections per acquisition, and can provide a better signal-to-noise ratio than can spin-echo or gradient-echo, T1-weighted imaging (3,5).

The development of the central nervous system during intrauterine life is the result of morphologic changes and maturation, which include histogenesis and myelination (19). The results of our examination of 25 cases showed the morphologic changes in the fetal brain and the change in signal intensity between gray and white matter. Investigators in several studies already have described MR images of the fetal brain (1,2,4,6–16); however, few were concerned with the normal fetal brain (12,13,16). Our results show that sequential changes in the normal fetal brain in relation to the stage of the pregnancy can be demonstrated clearly on T2-weighted half-Fourier RARE images.

Sulcation

The in vivo evaluation of gyrus formation has been difficult with US or conventional MR imaging. We found that half-Fourier RARE imaging very clearly shows gyrus formation in vivo.

During the early weeks of gestation, the surfaces of the cerebral hemispheres are smooth. The interhemispheric fissure and primitive sylvian fissure appear during the 5th gestational month. At 12–23 weeks of gestation, the brain surfaces viewed on half-Fourier RARE MR images essentially are smooth. This stage is followed by the appearance of central, interparietal, and superior temporal sulci at 24–26 weeks of gestation. Half-Fourier RARE images obtained in this stage showed a few shallow sulci. From 30 weeks of gestation, the cortex begins to undergo infolding, which is first apparent in the occipital lobe, particularly medially, in the region of the calcarine fissure. By 36 weeks of gestation, the cortex is extensively and compactly folded. Because normal fetal brain maturation follows a predictable course and because half-Fourier RARE MR imaging can accurately depict these sequential changes, the maturation of the fetal brain can be evaluated by assessing the pattern of sulcation.

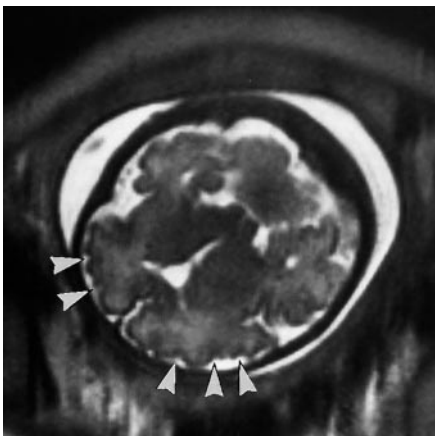


Figure 5. Transverse half-Fourier RARE MR image (∞/87) of a fetus at 34 weeks gestation in a 39-year-old woman with deep venous thrombosis reveals the formation of multiple sulci (arrowheads), but opercular formation has not yet occurred.

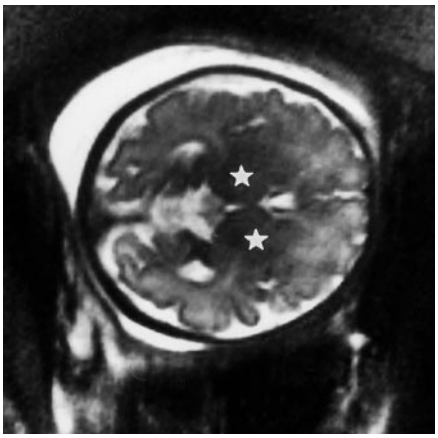


Figure 6. Transverse half-Fourier RARE MR image (∞/87) of a fetus at 37 weeks gestation in a 32-year-old woman with leiomyomas shows that brain sulcation in the fetus is similar to that in the adult. The basal ganglia (★) show low signal intensity. Ventricular dilatation is not seen.

Layering and Myelination

Our findings with in vivo half-Fourier RARE imaging of the fetal brain show that the changes in cerebral parenchymal layering and myelination proceed through stages in an orderly and predictable manner. Gray matter and white matter differentiation and myelination are not synonymous terms (21). In neonates, the former is related to the hydration state of the white matter, while the latter describes the laying down of myelin, most of which occurs beyond the immediate neonatal period (19,22).

Microscopic myelination is already detectable at 20 weeks of gestation in the medial longitudinal fasciculus of the medulla and pons (23). Findings of studies in which T2-weighted imaging was used showed the myelination proper, which appeared as an area of low signal intensity (21,24). In this study, we did not evaluate myelination because decrease in signal intensity on T2-weighted images, including those obtained with a half-Fourier RARE sequence, may indicate changes in either cellular density or myelination. When the size of the brain is sufficient to allow good spatial discrimination on MR images (after 19 weeks of gestation), accurate distinction between

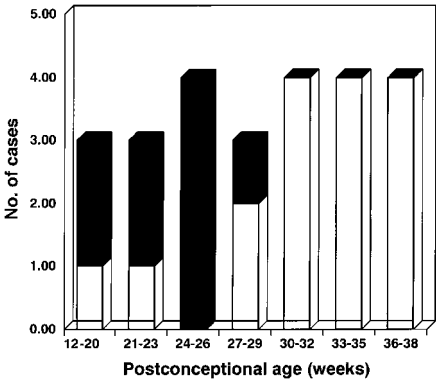


Figure 7. Graph shows the cerebral parenchymal layering pattern in 25 fetal brains in relation to gestational age. The three-layer pattern includes a low-signal-intensity inner layer that corresponds to the germinal matrix, a relatively high-signal-intensity intermediate layer that corresponds to the intermediate zone, and a relatively low-signal-intensity outer layer that corresponds to the immature cortex. The two-layer pattern includes an internal layer and an outer layer. Black bars = three-layer pattern, white bars = two-layer pattern.

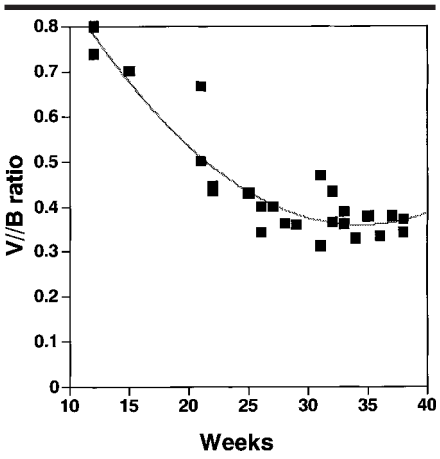


Figure 8. Graph shows ventricular size in relation to gestational age. Each square represents one fetal brain (N = 25). The size of the ventricular system at the level of the frontal horn angles and of the midbody of the lateral ventricles was expressed as a fraction of the diameter of the brain (ventricle-to-brain ratio [*V/B*]). The ventricles gradually became smaller with gestational age.

these changes may be difficult on half-Fourier RARE images.

Before 16 weeks of gestation, the spatial resolution did not permit us to separate the matrix from the migrating cells. At 19 weeks of gestation, the layer of migrating cells probably was so close to the matrix that the deep intermediate zone could not be differentiated. At 22 weeks of gestation, the migrating cells are adjacent to the matrix; thus, the inner

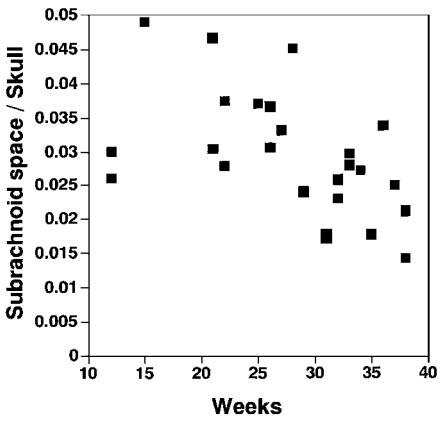


Figure 9. Graph shows the subarachnoid space in relation to the gestational age. The extracerebral space was measured on the transverse images. The widths of the subarachnoid space were measured at various points. Extracerebral space widths were determined for the following regions: the anterolateral and posterolateral dimensions of the subarachnoid space at the levels of the centrum semiovale, lateral ventricles, and thalamus and the part of the subarachnoid space anterior to the temporal lobes. The means of these figures were divided by the distance between the right and left inner tables. The subarachnoid space tends to become smaller with gestational age.

layer on MR imaging sections corresponded to the matrix and to the deeper part of the layer of migrating cells. At 27 weeks of gestation, some migrating cells are also included in the inner layer. Thus, three layers were found at 20–26 weeks of gestation.

Our results agree with those of Mintz et al (16), Hansen et al (15), and Brisse et al (25), who described a three-layer pattern at 17, 18, and 24 weeks of gestation. Our observations also correspond to the appearance in the Feess-Higgins and Larroche atlas (17). Girard et al (12,19) and Chong et al (26) described a five-layer pattern between 23 and 28 weeks of gestation. These investigators interpreted the layers as representing the germinal matrix, the deep white matter, the intermediate migrant cell zone, the subcortical white matter, and the cortical plate.

We have no definitive explanation to account for the signal intensities of the different layers. Investigators in a histologic study excluded the hypothesis of a difference in myelination state (27). Like Girard et al (12,19), we surmise that a good correspondence exists between signal intensity and cellular density. The germinal matrix and the cortical plate, which have high cellular densities, exhibit low-intensity signals on T2-weighted half-Fourier RARE images. However, the relationship between the relaxation times and the cellular density remains unclear. McArdle et al (21) suggested that the higher interstitial water content in the immature brain could explain the long T1 and T2 of white matter.

Ventricular Size

Ventricular size can be evaluated confidently not only by using US but also by using half-Fourier RARE MR imaging. Our results agree with those of US studies (18,28) of ventricular size in neonates. In one report, the diameter of a single lateral ventricle ranged from 0.8–1.0 cm (mean, 0.9 cm) at 29 postmenstrual weeks to 1.1–1.4 cm (mean, 1.3 cm) at 42 postmenstrual weeks (28). Investigators in another study (29) reported a range of 0.5–1.3 cm (mean, 1.0 cm) in premature neonates and a range of 0.9–1.3 cm (mean, 1.1 cm) in term neonates.

The ventricle-to-brain ratio percentages in preterm neonates were slightly larger (range, 24%–34%; mean, 31%) than those in term neonates (range, 29%–30%; mean, 28%) (29). A similar decrease in the ventricle-to-brain ratio with gestational age has been reported by investigators in US studies (30) and in previous neurohistologic observations (17). Although we could not perform a statistical evaluation, the previously reported data appear to correspond well with our measurements with half-Fourier RARE imaging.

Subarachnoid Space

The subarachnoid space has been extremely difficult to evaluate in vivo with US. The space is beyond the field of view of many transducers placed over the anterior fontanel. In premature neonates, in whom the space is most pronounced, it is difficult to distinguish between the low-signal-intensity white matter and the isointense cerebrospinal fluid, since the cortex is not well delineated with spin-echo or fast spin-echo imaging sequences. In full-term neonates with more large white matter, the subarachnoid space is better seen but is neither as large nor as frequently encountered. This space may be due to the incomplete growth of the parietal lobes.

Use of the half-Fourier RARE sequence allows clear imaging of the subarachnoid space and ventricles. According to a postnatal study of premature neonates (18), the subarachnoid space posterior to the parietal lobes can be prominent in both

premature and mature neonates, particularly in premature neonates. Similar findings were obtained with half-Fourier RARE MR imaging in the present study.

In conclusion, MR imaging with a half-Fourier RARE sequence appears to be a valuable, safe, and reliable method for examining the fetal brain. Changes in brain maturation proceed through stages in an orderly and predictable fashion and can be evaluated reliably with half-Fourier RARE MR imaging. The sequence allows the depiction of the morphologic and signal intensity changes that correspond to the evolving processes of maturation.

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