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MR Contrast Enhancement of the Normal Neonatal Brain

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PURPOSE: To determine the pattern of enhancement on contrast-enhanced MR studies of the brain in neonates. **METHODS:** Contrast-enhanced brain MR studies of 16 neonates were reviewed retrospectively. All infants had normal neonatal courses, normal noncontrast MR findings, and normal neurologic examinations at age 12 months. All enhancing regions within the brain, dura, calvaria, and orbits were recorded. An enhancement factor, $F = (Ic-Ip)/Ip$, was calculated from region-of-interest intensity measurements in five regions of each hemisphere (basal ganglia, thalami, and three hemispheric locations), where Ic was signal intensity after contrast administration and Ip was the noncontrast signal intensity for each region. **RESULTS:** Enhancement was detected in the choroid plexus, pituitary infundibula, pineal glands, dura, veins and venous sinuses, cranial sutures, and irises of the orbital globes. No enhancement of the brain parenchyma was detected by visual inspection, although some change in signal intensity of the cerebral parenchyma was detected by the region-of-interest intensity measurements, with enhancement factors ranging from 0 to 0.08 (mean, 0.04). No consistent regional variation in enhancement was detected. Because the degree of enhancement was identical to that in the normal adult brain, the slight enhancement detected was attributed to contrast material in capillaries and small venules. **CONCLUSION:** In addition to the expected findings of enhancement of the pituitary stalk, the pineal gland, the choroid plexus, the dura, and the cerebral veins, we detected enhancement of the calvarial sutures and ocular irises. No evidence of enhancement of the cerebral parenchyma was detected, suggesting that the blood-brain barrier to gadolinium chelates is intact in the neonatal brain.

Index terms: Brain, magnetic resonance; Infants, newborn; Magnetic resonance, in infants and children

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Although magnetic resonance (MR) imaging has been in clinical use for more than 13 years, and paramagnetic contrast material has been available for use in MR imaging for more than 7 years, little is known about the degree of enhancement of the neonatal brain. Knowledge of the normal enhancement pattern in neonates is of some importance, because scant information is available about the permeability of the blood-brain barrier in human neonates (1, 2). We report our findings of contrast-enhanced MR imaging of the brains of 16 healthy neonates; and, in so doing, assess the permeability of the neonatal blood-brain barrier to gadolinium chelates.

Materials and Methods

As part of an ongoing study of the utility of neonatal brain MR imaging in the assessment of brain damage in asphyxiated term neonates, 2241 consecutive term neonates born at or transferred to the intensive care nursery at our institution were screened for the following entry criteria: uterine artery pH less than 7.1, uterine artery base deficit greater than 10, and 5-minute Apgar score less than or equal to 5. Patients fulfilling any one of these criteria were considered eligible for this study. The criteria were intentionally formulated to include minimally affected infants who were unlikely to sustain brain damage and,

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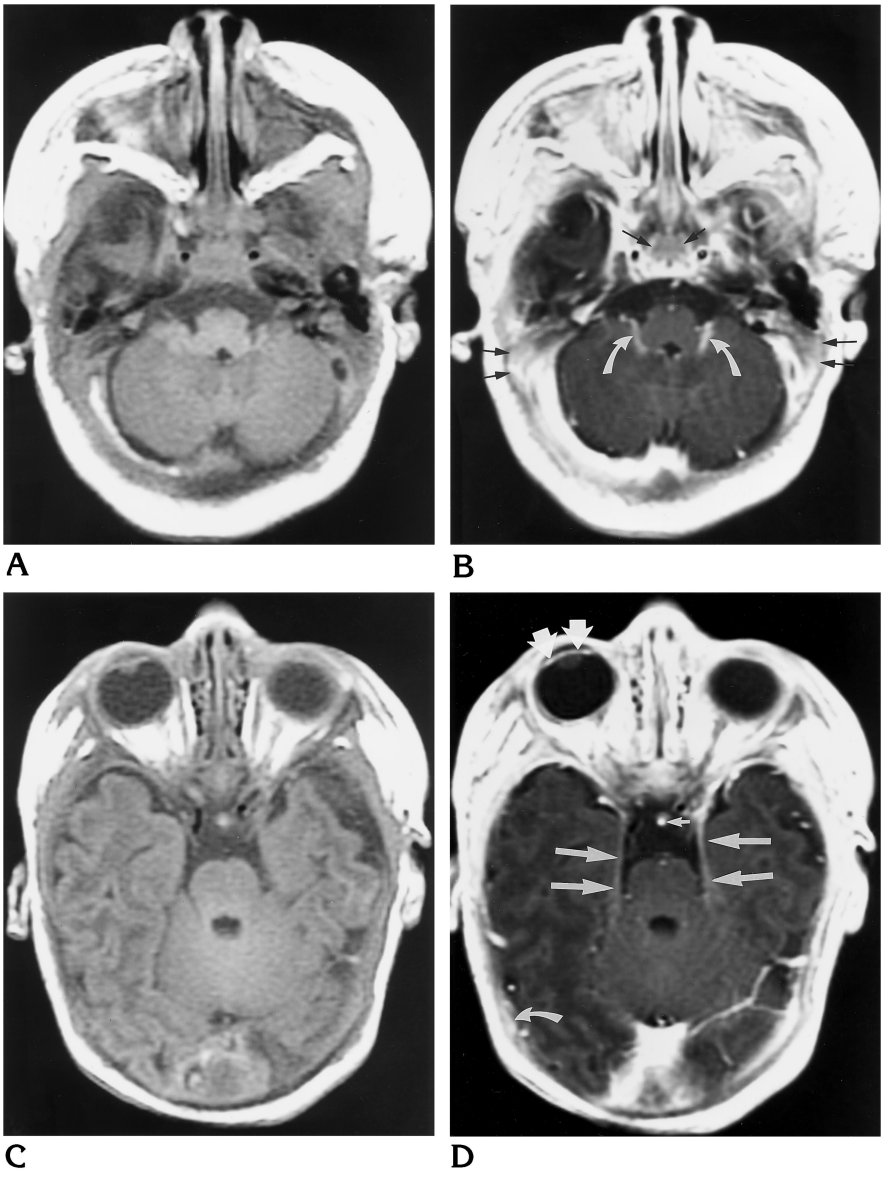

Fig 1. Typical contrast-enhanced neonatal brain MR findings.

Noncontrast (*A*) and contrast-enhanced (*B*) images show that the choroid plexus in the foramina of Luschka (*white arrows*) enhances. *Black arrows* point to enhancement in the diploë of the petrous portions of the temporal bones and the clivus.

Noncontrast (*C*) and contrast-enhanced (*D*) images at a higher level show enhancement of the iris (*short thick arrows*), pituitary infundibulum (*small straight arrow*), dura of the tentorium cerebelli (*large straight arrows*), and right lambdoid suture (*curved arrow*). The left lambdoid suture is difficult to distinguish from underlying venous structures at this level. *Figure continues.*

therefore, would constitute internal healthy control subjects. Patients with suspected or confirmed congenital malformations or congenital infections, and patients born before 36 weeks' gestational age, were excluded from the study. The protocol was approved by the Committee on Human Research at our institution. Participation in the study was voluntary; the infants were studied only after informed consent was obtained from their parents. Of the 2241 patients screened, 259 met the inclusion criteria. Of these, 47 were excluded on the basis of suspected or confirmed malformation or infection, 142 declined enrollment, and 10 refused the MR study after initially agreeing to participate. To date, 65 patients have been enrolled and studied by MR imaging. Of these, 16 patients met the criteria for inclusion in this assessment of brain enhancement in the healthy neonate: they had normal findings on noncontrast MR images, absence of neonatal encephalopathy, and normal developmental and neurologic examinations at age 12 months. These 16 patients included 10 males and six females, ranging in age from 35 to 42 postconceptional weeks at the time of the MR examination (mean, 40 weeks; median, 41 weeks).

Noncontrast MR studies included sagittal 4-mm (1-mm gap) spin-echo (500/16/0.75 [repetition time/echo time/excitations]) sequences, axial 4-mm (2-mm gap) spin-echo (3000/60,120/1) sequences, and axial 4-mm (1-mm gap) spin-echo (500/11/2) sequences. The postcontrast sequence consisted of axial 4-mm (1-mm gap) spin-echo (500/11/2) images, identical to the precontrast T1-weighted axial sequence. Paramagnetic contrast material was administered intravenously in a dose of 0.1 mmol/kg.

The contrast-enhanced images were compared with the noncontrast images by visual inspection to determine

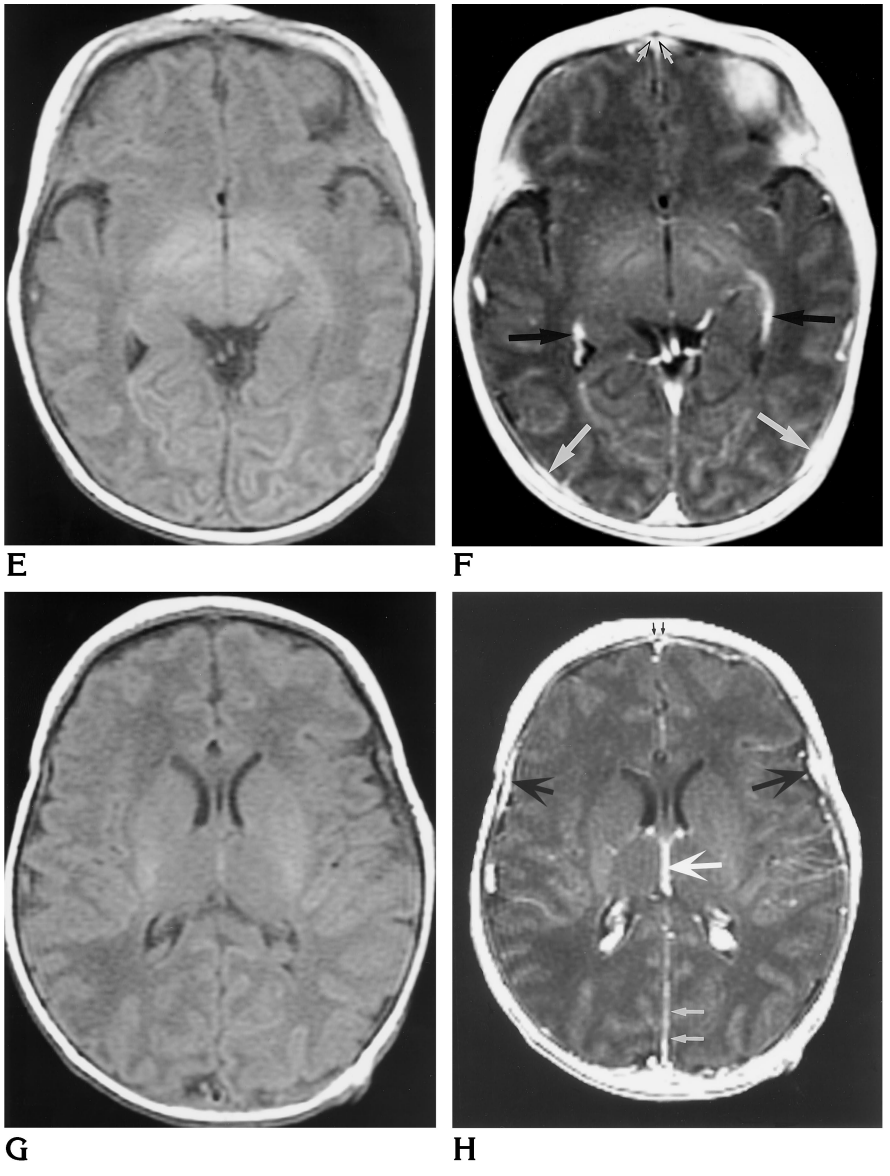

Fig 1, *continued.*

Noncontrast (*E*) and contrast-enhanced (*F*) images at the level of the third ventricle show enhancement of the metopic (*small arrows*) and lambdoid (*large white arrows*) sutures and the choroid plexus of the temporal horns of the lateral ventricles (*large black arrows*).

Noncontrast (*G*) and contrast-enhanced (*H*) images at the level of the frontal horns of the lateral ventricles show enhancement of the internal cerebral veins (*large white arrow*), falx cerebri (*small white arrows*), and lambdoid (*small black arrows*) and coronal (*large black arrows*) sutures. Note that no enhancement of the brain parenchyma is noticeable at any level.

which cranial and intracranial structures enhanced. In addition, region-of-interest intensity measurements were obtained from the precontrast and postcontrast T1-weighted images in 10 regions of the brain (bilateral basal ganglia, bilateral thalami, bilateral anterior, middle, and posterior cerebral hemispheres). From these measurements, an enhancement factor, $F = (Ic-Ip)/Ip$, was calculated, where Ic was signal intensity after contrast administration and Ip was the precontrast signal intensity for each region.

Results

No enhancement was evident in the cerebral or cerebellar cortex or white matter, the basal nuclei, the brain stem, or the leptomeninges in any patient. Enhancement was noted in the pituitary infundibulum, the pineal gland, the dura, all large veins and venous sinuses, and the choroid plexus of the lateral, third, and fourth ventricles (Fig 1B, D, F, and H) in all patients. Of interest, and somewhat unexpected, was the finding of enhancement in the cranial sutures (Fig 1D, F, and H). Enhancement of the metopic and coronal sutures was detected in all patients, whereas enhancement of the lambdoid sutures could only be detected in four patients. The lambdoid suture, in particular, was often difficult to separate from underlying veins (Fig 1D). The sagittal suture was not well evaluated because the high signal intensity of the subcu-

taneous fat was averaged in with the suture on the axial images; we suspect that distinguishing the sagittal suture from the underlying sagittal sinus may have been difficult as well. Additional curvilinear enhancement was noted surrounding the lens in the anterior chambers of the ocular globes (Fig 1D) that was believed to correspond to the iris. The diploë of the bones of the skull base, believed to represent red marrow, showed enhancement also. No relationship between the location of enhancement and the postconceptional age of the patient was appreciated.

The calculated enhancement factors varied from 0 to 0.08 (mean, 0.04; SD, 0.02) in the regions measured. No significant consistent difference in enhancement factor was noted among the different regions of the brain in which the measurements were obtained. No deleterious effects were noted in any of the patients as a result of contrast administration.

Discussion

Although most pediatricians and radiologists try to avoid the use of intravenous contrast material in neonates, sometimes the presence or absence of contrast enhancement can be useful in identifying disease (ie, metastatic neuroblastoma) or specifying a diagnosis (such as congenital/neonatal brain tumor). As a consequence of an ongoing study of MR imaging in the assessment of perinatal asphyxia, we have had the opportunity to study the appearance of contrast-enhanced MR images in healthy neonates. The present study was designed so that neonates with minimal biochemical or neurologic derangements would be included as internal healthy control subjects. We believe that our patients, who had normal noncontrast MR findings, no evidence of neonatal encephalopathy, and normal developmental and neurologic examinations at age 12 months, qualify as healthy and are suitable subjects for this study.

Despite the enormous amount of research that has been performed on the blood-brain barrier in mature animals (for a review, see Sage and Wilson [3]), the relative maturity of the blood-brain barrier in the human neonate is controversial; authorities disagree as to the status of the blood-brain barrier in the neonate. Textbooks commonly issue general statements describing cerebral capillaries with increased permeability at birth, with gradual development of the blood-brain barrier during the early years of life (4). This concept has evolved primarily from the observation that protein concentration in cerebrospinal fluid (CSF) is higher in the premature than in the term neonate and higher in the term neonate than in older children and adults (1, 2). The concentration of normal CSF protein diminishes as the fetus approaches 40 weeks' postconceptional age, reaching adult levels by the end of the first year of life (2). In support of the concept of late maturity of the blood-brain barrier in humans, some authors have reported relatively late blood-brain barrier formation in a rat model (5). However, work by Møllgård and Saunders suggests that mature tight junctions and an intact blood-brain barrier to endogenous proteins is present from the earliest stages of vascularization in a broad range of species (6–10). Møllgård and Saunders believe that those proteins found in the CSF of neonates are less a manifestation of immaturity of the blood-brain barrier and blood-CSF barrier than of "developmental specialization"; they believe that the proteins found in neonatal CSF are likely to play an important role in development. Obviously, the present study cannot solve this dispute. Nonetheless, the fact that we saw no significant parenchymal enhancement in any of our patients combined with the fact that the measured increase in intensity after administration of contrast material is identical to that in healthy adults (11), in whom the blood-brain barrier is unquestionably intact, indicates that a blood-brain barrier to gadolinium chelates is present in the healthy neonate within the limits of the sensitivity of MR imaging to detect it. The small amount of enhancement detected on the region-of-interest measurements and reflected in the calculated enhancement factors most likely represents the presence of contrast material in capillaries and small venules that run through the brain substance.

A consistent pattern of enhancement was seen in all the patients in our study. Enhancement was seen in the choroid plexus of the lateral ventricles, third ventricle, and fourth ventricle, in the parenchymal veins, in the dura, in the calvarial sutures, and in the anterior chambers of the ocular globes around the lenses (Fig 1A–D). The enhancement of the pineal gland, pituitary infundibulum, choroid plexus, veins, and dura was expected. These are structures that lack a blood-tissue barrier and enhance in healthy adults (12). Of greater interest is the

enhancement seen in the cranial sutures and the anterior globes, which was not anticipated in either area.

Enhancement was seen along the metopic and coronal sutures in all patients (Fig 1C and D) and along the lambdoid sutures in four patients. Although this observation was initially surprising, a review of the anatomy of calvarial sutures in the neonate reveals that the stroma in the suture is quite vascular (13–15). As there are no tight junctions in the capillary epithelium in this region, significant enhancement is the natural consequence. The less frequent enhancement along the lambdoid sutures is probably due to the fact that the infants were scanned while supine; thus, the subcutaneous tissues in the occipital regions were compressed, and it is more difficult to differentiate the enhancing tissue from overlying fat of the scalp. No fat-suppressed sequences were obtained; however, we postulate that the use of such sequences to negate the signal of the overlying fat may have made the sutures visible more often. If normal intrasutural stroma enhances, it may be of interest to investigate the potential utility of contrast-enhanced MR imaging in infants with suspected craniosynostosis.

The curvilinear region of enhancing tissue seen surrounding the lens in the anterior region of the globe almost certainly represents the iris. That the iris enhances is not surprising, as it is composed primarily of blood vessels with loose connective tissue between them (16). Presumably, the intense enhancement results from diffusion of contrast material from the blood vessels into the extensive extracellular spaces. Although the retina most likely enhances as well, it was not observed in this study, probably because of the high signal intensity of the adjacent orbital fat on the T1-weighted images.

In summary, we have reported the pattern of contrast enhancement on brain MR studies of healthy neonates. In addition to the expected findings of enhancement of the pituitary stalk, the pineal gland, the choroid plexus, the dura, and the cerebral veins, we found enhancement of the calvarial sutures and ocular irises. No evidence of significant enhancement of the cerebral parenchyma was detected, suggesting that the blood-brain barrier to gadolinium chelates is intact in the neonatal brain.

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