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BACKGROUND AND PURPOSE: **The accurate identification of white matter injury in premature neonates is important for counseling parents and for targeting these high risk neonates for appropriate rehabilitation services. The objective of this study was to compare the diagnosis of white matter injury detected by serial MR imaging and ultrasonography of a contemporary cohort of premature neonates.**

METHODS: **Each of the 32 consecutively enrolled neonates was studied with MR imaging at a median postconceptional age of 31.9 weeks (range, 27.6–38.1 weeks) and again at a median postconceptional age of 36.5 weeks (range, 33.4–42.9 weeks) and with serial ultrasonography according to a clinical protocol. Because periventricular echogenicity shown on ultrasonograms evolves over time, both the highest grade of echogenicity and the grade of echogenicity shown on the last neonatal ultrasonogram were used in the analysis to determine the predictive values and correlation (Spearman's rho) of ultrasonography for predicting white matter abnormalities shown on MR images.**

RESULTS: **White matter abnormalities were diagnosed in 18 (56%) neonates based on MR imaging, consisting of foci of scattered T1 hyperintensity in the periventricular white matter, and in 22 (69%) neonates based on ultrasonography, consisting of abnormal periventricular echogenicity. The severity of white matter abnormalities shown by MR imaging was not correlated with the highest grade of white matter abnormalities detected with ultrasonography (rho = 0.18, $P = .3$) or with the grade of white matter abnormalities shown on the last ultrasonogram (rho = 0.16, $P = .4$).**

CONCLUSION: **Although ultrasonography is commonly used to screen premature neonates for white matter injury, it was not a sensitive predictor of the milder spectrum of MR imaging-defined white matter abnormalities.**

Of all premature survivors of the intensive care nursery, it is estimated that 5% to 10% exhibit major motor deficits and another 25% to 50% exhibit significant developmental and visual difficulties (1–7). These deficits are classically associated with neonatal evidence of white matter injury that is typically in the centrum semiovale, optic, and acoustic radiations (1, 3–7). The identification of white matter injury is important for accurately counseling parents of premature neonates and for targeting these high risk neonates for appropriate rehabilitation services.

Ultrasonography is the primary imaging technique for the evaluation of brain injury in premature neonates. It is noninvasive, inexpensive, and portable, allowing examinations to be performed without the need to move the infant. The anterior fontanel provides a convenient sonographic window, allowing excellent noninvasive imaging of the deep midline regions of the brain. Although this allows accurate detection of cystic periventricular white matter injury,

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germinal matrix hemorrhage, and hydrocephalus, the ability of ultrasonography to accurately diagnose non-cystic white matter injury remains controversial (8–10).

MR imaging provides high resolution, noninvasive imaging of brain parenchyma in neonates. Compared with ultrasonography, MR imaging may better define the site, extent, and type of non-cystic white matter abnormalities in premature neonates (11–13).

The goal of the present study was to determine the spectrum of white matter injury detected by serial MR imaging and ultrasonography of a contemporary cohort of premature neonates. A second goal of the study was to then determine the correlation of abnormalities shown by ultrasonography with white matter injury diagnosed based on MR imaging. We hypothesized that MR imaging is more sensitive for detecting small abnormalities of the periventricular white matter compared with ultrasonography, whereas MR imaging and ultrasonography are similarly sensitive for detecting more severe abnormalities, such as cystic white matter injury and ventriculomegaly.

Methods

All neonates <36 weeks gestational age born in or transferred to our institution's intensive care nursery were considered for enrollment in a prospective cohort study evaluating the detection of brain injury by MR imaging. This prospective cohort comprised a consecutive series of 32 neonates of <36 weeks gestational age who were enrolled in this study from September 2000 to March 2002 and who completed two MR imaging examinations. The inclusion criterion for this cohort was gestational age <36 weeks. Gestational age was calculated based on the last menstrual period or early sonography (<24 weeks); if the difference between the two methods was >7 days, the sonography date was used. Infants were excluded from enrollment if clinical evidence indicated a congenital malformation or syndrome, if congenital infection such as toxoplasmosis, rubella, cytomegalovirus infection, or herpes simplex infection was present; or if sonography showed evidence of large parenchymal hemorrhagic infarction (grade IV hemorrhage). Our institution's Committee on Human Research approved the protocol. Infants were studied only after voluntary informed consent was obtained from parents.

Imaging Techniques

Each of the 32 neonates, with a median postconceptional age of 29 weeks (range, 24.7–32.4 weeks), was studied with MR imaging first at a median postconceptional age of 31.9 weeks (range, 27.6 –38.1 weeks) and again at a median postconceptional age of 36.5 weeks (range, 33.4–42.9 weeks). The first MR imaging session was performed as soon as the infants were stable enough to be transported to the MR imaging unit; the second MR imaging session was performed at term-equivalent age or just before discharge or transfer from the hospital. Each of the neonates was studied with ultrasonography of the head according to the clinical protocol of our intensive care nursery. For all except three of the neonates, this included at least one session of ultrasonography of the head performed during the first 3 days of life, then weekly ultrasonography sessions until 3 weeks of life, and one ultrasonography session before discharge at or near term-equivalent age. One neonate underwent the first ultrasonography session on the eighth day of life and then underwent weekly follow-up studies. Two neonates in the cohort each underwent only a single ultrasonography session coincident with MR imaging that had normal findings on the eighth day of life and the 32nd day of life, respectively; considering the normal MR imaging results, follow-up ultrasonography was not performed.

Cranial Ultrasonography

Cranial ultrasonography was performed according to a clinical protocol, acquiring images in the sagittal, parasagittal, and coronal planes via the anterior fontanel by using a multifrequency (5–8 MHz) transducer. A midline sagittal view image and five to 10 parasagittal planes of the white matter of the corticospinal tracts were obtained on each side. Ten to 20 images, including the area of the frontal horns through the posterior periventricular white matter, were obtained in coronal planes. Two or three axial view images, including the regions of the cerebellum, fourth ventricle, and cisterna magna, were obtained via the posterior fontanel. All ultrasonograms were reviewed initially by a clinical ultrasonologist and subsequently by a single ultrasonologist who was blinded to the neonate's clinical course, MR imaging findings, and findings of the clinical ultrasonologist. The sonographic images were reviewed for the diagnosis of intraventricular hemorrhage, ventricular enlargement, and white matter injury (14). Intraventricular hemorrhage was graded according to the system presented by Papile et al (15). Neonates were diagnosed with ventriculomegaly if the largest atrial ventricular diameter (obtained at the level of the glomus of the choroids plexus) measured >10 mm. A ventricular size of 8 to 10 mm was considered borderline. A grading system of white matter abnormalities was developed for both MR imaging and ultrasonography to determine whether even subtle ultrasonographic findings (those that might not be considered abnormal in general practice) might correlate with subtle MR imaging findings (Table 1). A score was developed to correspond to those abnormalities diagnosed by a clinical ultrasonologist, such that grades 0 to 1 would be diagnosed as normal, grades 2 to 4 would be diagnosed as abnormal periventricular echogenicity, and grade 5 would be diagnosed as macrocystic periventricular lesions. To determine the reliability of this score, the diagnosis of white matter abnormalities in the primary interpretation in the clinical record was compared with the interpretation of the ultrasonologist reviewing these cases for this study. For the diagnosis of abnormal periventricular echogenicity and periventricular cysts, the clinical and study ultrasonologists agreed in 87.5% of cases ($\kappa = 0.68$, $P < .00001$). Abnormal periventricular echogenicity was defined as *transient* if the abnormal echogenicity was present for <7 days, *persistent* if the abnormal echogenicity was present for ≥7 days, and *uncertain* if a follow-up examination was not performed within 7 days of the study with abnormal findings. Both the highest grade of periventricular echogenicity and the grade of periventricular echogenicity on the last neonatal sonogram by the study ultrasonologist were used in the analysis.

MR Imaging

The premature neonates were studied longitudinally. The first MR imaging session was performed as soon after birth as the neonate was stable enough to be transported safely to the MR imaging unit and imaging time was available, and the second MR imaging session was performed just before discharge or transfer from the hospital. Twenty-three neonates did not require mechanical ventilatory support, were fed before the MR imaging examination, and needed no pharmacologic sedation. Five neonates required sedation with IV administered Nembutal for both studies. Four neonates required sedation for only one MR imaging session. All studies were performed by using a 1.5-T Signa EchoSpeed system (GE Medical Systems) with an MR-compatible isolette that was developed for these studies. A neonatologist in the MR imaging suite monitored the neonates during imaging and hand-ventilated the intubated neonates. The same MR imaging techniques were used for the entire cohort. MR images of the brain

TABLE 1: Grading of white matter abnormalities based on ultrasonography and MR imaging

	Description of White Matter Abnormalities
Ultrasonography	
Grade 1	Small foci of abnormal echogenicity less echogenic than choroid plexus
Grade 2	Diffuse foci of increased echogenicity less than the choroid plexus or irregularity of the lateral borders of the periventricular white matter (junction of the normal halo and surrounding cortex)
Grade 3	Focal areas of abnormal echogenicity greater than or equal to the echogenicity of the choroid plexus
Grade 4	Diffuse increased echogenicity greater than or equal to the echogenicity of the choroid plexus
Grade 5	Periventricular cysts (cavitation) defined as anechoic regions with increased through transmission
MR imaging	
Normal	No periventricular white matter abnormalities
Minimal white matter abnormality	Three or fewer areas of T1 signal abnormalities measuring <2 mm
Moderate white matter abnormality	Three areas of T1 signal abnormalities or areas measuring >2 mm but <5% of the hemisphere involved*
Severe white matter abnormality	T1 signal abnormalities involving >5% of the hemisphere

* Percent of hemisphere involved estimated by visual inspection.

included the following for all neonates: 1) T1-weighted sagittal and axial view spin-echo images; 500/11/1 (TR/TE/number of excitations); section thickness, 4 mm; flip angle, 90 degrees; acquisition matrix, 192 × 256; 2) T2-weighted spin-echo images; 3000/60, 120; section thickness, 4 mm; flip angle, 90 degrees; acquisition matrix, 192 × 256; 3) coronal view spoiled gradient recall images; 36/2 (TR/number of excitations); partition size, 1.5 mm; TE = 9 ms; flip angle, 35 degrees; field of view, 18 cm.

Two pediatric neuroradiologists interpreted each of the MR imaging studies blinded to the patients' clinical conditions and ultrasonographic findings. Discrepancies were resolved by discussion and consensus.

The white matter abnormalities detected included foci of abnormal T1 hyperintensity in the absence of marked T2 hypointensity in the periventricular white matter and foci of low intensity on T1-weighted images. The constellation of T1 hyperintensity, in the absence of marked T2 hypointensity, most likely represented areas of gliosis, which have been seen pathologically in similar patient populations in other pathologic studies, whereas areas of low intensity on T1-weighted images likely represented cavitation (11, 16). Areas of T1 hyperintensity and significant T2 hypointensity ("blooming" on the 120 TE images more than on the 60 TE images) were interpreted as foci of hemorrhage. Based on the severity of white matter abnormalities shown by MR imaging, neonates were classified as having normal, minimal, moderate, or severe white matter abnormalities (Table 1). In developing this grading system of white matter abnormalities, two pediatric neuroradiologists independently interpreted 38 MR imaging studies blinded to the patients' clinical conditions and achieved agreement in 89.5% of cases ($\kappa = 0.84$, $P < .00001$).

Neonates were diagnosed with ventriculomegaly if the largest atrial ventricular diameter (at the level of the glomus of the choroid plexus) measured >10 mm and were diagnosed as borderline if it measured 8 to 10 mm. Intraventricular hemorrhage was graded by using the same scale as that used for the ultrasonography. The presence of other brain abnormalities was noted separately.

Statistical Analysis

Statistical analysis was conducted by using Stata (Stata Corporation, College Station, TX). Clinical variables were compared between the groups with and without white matter injury by using the Kruskal Wallis test or the Fisher exact test for categorical variables. The severity of white matter abnormalities shown by MR imaging was correlated with the severity of white matter abnormalities shown by ultrasonography by using the Spearman Rank Correlation for categorical data. The relative risk associated with white matter abnormalities shown by MR imaging was determined for the presence of abnormal periventricular echogenicity. To determine the clinical value of abnormal periventricular echogenicity on ultrasonograms as a predictor of white matter abnormalities shown by MR imaging, the sensitivity, specificity, and predictive values were calculated. The analyses considering the severity of abnormal periventricular echogenicity were repeated for both the highest grade of periventricular echogenicity and the grade of periventricular echogenicity on the last neonatal ultrasonogram. Because these statistical analyses compared the diagnosis of white matter abnormalities shown by MR imaging and ultrasonography *within* an individual neonate, potential confounding variables, such as the severity of intraventricular hemorrhage, were accounted for in these univariate analyses.

Results

White Matter Abnormalities

White matter abnormalities were diagnosed in 18 (56%) of the 32 neonates based on MR imaging; they were minimal in 10, moderate in seven, and severe in one (Figs 1 and 2). Because only one neonate had severe white matter abnormalities, this patient was included with the moderate group (all $P > .1$). The timing of the MR imaging and ultrasonography studies did not significantly differ across the groups. Male neonates were significantly more likely to have white matter abnormalities shown by MR imaging ($P = .02$). In other respects, the clinical characteristics of the groups with and without white matter abnormalities did not differ meaningfully (Table 2).

The most common white matter abnormalities observed were foci of T1 hyperintensity that were seen throughout the white matter, more commonly within 1 to 2 cm of the ventricles. These foci of T1 hyperintensity were occasionally associated with small areas

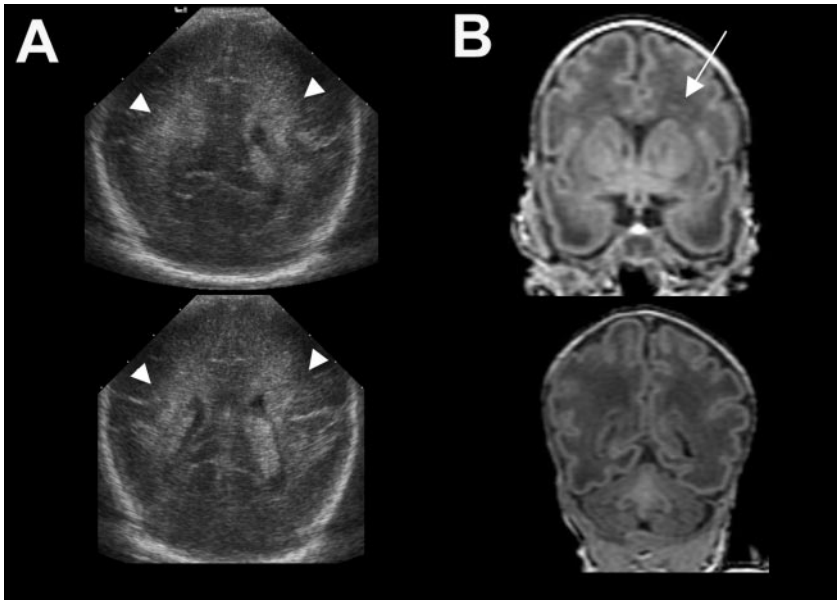

FIG 1. Minimal white matter injury shown on ultrasonograms and MR images of premature neonate born 31.1 weeks after conception and studied at 32.9 weeks postconceptional age.

A, Coronal view transfontanel ultrasonograms show diffuse foci of mildly increased echogenicity (less than that of the choroid plexus) in addition to irregularity of the lateral borders of the periventricular white matter (*arrowheads*).

B, Corresponding MR images (spoiled gradient-echo volumetric images) show a few small foci of T1 hyperintensity in the absence of marked T2 hypointensity, which were thought to represent astrogliosis in the periventricular white matter without cavitation (*arrow*). The abnormalities shown by MR imaging and ultrasonography are not anatomically concordant, although both were graded as minimal white matter abnormalities.

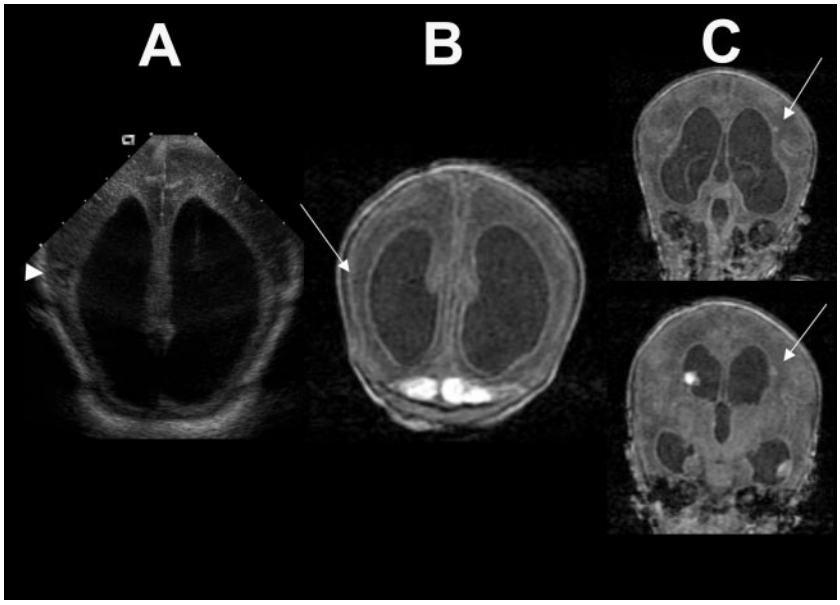

FIG 2. Images show moderate to severe white matter injury in a premature neonate born 29.1 weeks after conception and studied at 32 weeks postconceptional age

A, Coronal view transfontanel ultrasonogram shows small areas of hypoechogenicity in the periventricular white matter, indicating small areas of cavitation, in addition to pronounced ventriculomegaly (*arrowhead*).

B and *C*, Corresponding MR images (spoiled gradient-echo volumetric images) show small areas of T1 hypointensity, indicating cavitation in the periventricular white matter (*B*, *arrow*), in addition to multiple small foci of T1 hyperintensity in the absence of marked T2 hypointensity, which were thought to represent astrogliosis in the periventricular white matter (*C*, *arrow*). The degree of ventriculomegaly is similar on the ultrasonogram and MR images. Note that the areas of T1 hyperintensity are more extensive than the small cystic lesions evident on the ultrasonogram or MR images.

(<2 mm) of T1 hypointensity, which were interpreted as cavitation. Of note, both the cavitary and noncavitary areas were detected better on the T1-weighted images than on the T2-weighted images. The white matter abnormalities were present on the first MR images of all neonates and remained unchanged on the second MR images, except for one neonate who had minimal abnormalities shown by the first MR imaging session and moderate abnormalities shown by the second; this neonate was classified as having moderate abnormalities. In this one neonate, white matter abnormalities progressed from minimal to moderate severity; in the other cases, however, the T1 hyperintensity became less conspicuous over time. Large cystic lesions were not observed in this cohort. Areas of white matter T1 hyperintensity and T2 hypointensity consistent with foci of hemorrhage were not observed.

Abnormal periventricular echogenicities were commonly observed on the ultrasonograms of all three MR imaging-classified groups and were present for 22 (69%) of the 32 neonates (Table 3). However, five neonates with moderate white matter abnormalities shown by MR imaging (62% of the moderate group) did not have significant periventricular echogenicity on the ultrasonograms. The single neonate with periventricular cysts (grade 5) shown by ultrasonography had severe white matter abnormalities shown by MR imaging with extensive foci of T1 hyperintensity, small areas of white matter cavitation (T1 hypointensity), and marked volume loss of white matter. The duration of the abnormal periventricular sonographic echodensity among the patients in the three MR imaging-defined groups was similar. The severity of white matter abnormalities shown by MR imaging was not correlated with the greater severity of white

TABLE 2: Clinical characteristics of the MR imaging defined white matter abnormality groups

	Normal n (%)	Minimal WMA n (%)	Moderate WMA n (%)	*P*
No.	14	10	8	
Postconceptional age at birth				.9
>24–26 weeks	3 (21)	1 (10)	1 (13)	
>26–28 weeks	3 (21)	2 (20)	2 (25)	
>28–30 weeks	6 (43)	4 (40)	2 (25)	
>30 weeks	2 (14)	3 (30)	3 (37)	
Male gender	3 (21)	7 (70)	6 (75)	.02
Birth weight [median (range)]	1187 (485–1615)	1102 (650–1600)	1075 (630–1830)	.9
Assisted delivery*	6 (43)	3 (30)	5 (63)	.4
5-min Apgar score [median (range)]	7 (1–9)	7 (1–10)	4.5 (0–7)	.3
Prenatal betamethasone	10 (71)	5 (50)	6 (75)	.5
Chorioamnionitis	1 (7)	0	0	1.0
Chronic lung disease	7 (50)	3 (30)	3 (38)	.9

Note.—WMA indicates white matter abnormality.

* Cesarean section or vacuum extraction.

TABLE 3: Highest grade of periventricular echogenicity and the grade of periventricular echogenicity shown on the last neonatal sonogram in the MR imaging-defined white matter abnormality groups

	Normal (n = 14) n (%)		Minimal WMA (n = 10) n (%)		Moderate WMA (n = 8) n (%)	
	Highest Grade	Last Study	Highest Grade	Last Study	Highest Grade	Last Study
Grade periventricular Echogenicity						
None	4 (29)	13 (93)	5 (50)	6 (60)	1 (13)	7 (87)
Grade 1	3 (21)	1 (7)	2 (20)	3 (30)	2 (25)	0
Grade 2	7 (50)	0	2 (20)	1 (10)	2 (25)	0
Grade 3	0	0	1 (10)	0	2 (25)	1 (13)
Grade 5	0	0	0	0	1 (13)	0
Duration periventricular Echogenicity (if present)						
Transient	3 (30)		0		2 (29)	
Persistent	6 (60)		3 (60)		5 (71)	
Uncertain	1 (10)		2 (40)		0	

Note.—WMA indicates white matter abnormality.

matter abnormalities detected with ultrasonography (rho = 0.18, $P = .3$) or with the severity of white matter abnormalities on the last ultrasonograms (rho = 0.16, $P = .4$).

Intraventricular Hemorrhage and Ventriculomegaly

The diagnoses of intraventricular hemorrhage and ventriculomegaly were similar based on ultrasonography and MR imaging (Table 4). Of neonates with moderate white matter abnormalities, only four (50%) had associated ventriculomegaly; this was associated with grade 3 intraventricular hemorrhage in three.

Other Injury

One neonate had thalamostriate vasculopathy (branching curvilinear hyperechogenicity in the deep gray cerebral nuclei) shown by ultrasonography, although no thalamic or striatal abnormalities were evident based on MR imaging. Ultrasonographically abnormal thalamic echogenicity for two neonates and abnormal echogenicity in the tegmentum of the mesencephalon of another neonate did not correspond to thalamic or brain stem abnormalities shown by MR imaging.

Sonogram Predictors of MR Imaging-defined White Matter Abnormalities

The presence of significant periventricular echogenicity on ultrasonograms (grades 3–5) or definite ventriculomegaly had a high specificity and positive predictive value for white matter abnormalities shown by MR imaging (Table 5). These features, however, had a low sensitivity and only moderate negative predictive values for predicting minimal or moderate white matter abnormalities based on MR imaging.

TABLE 4: Highest grade of intraventricular hemorrhage, ventriculomegaly, and thalamic echogenicity in the MR imaging-defined white matter abnormality groups

	Normal (n = 14)		Minimal WMA (n = 10)		Moderate WMA (n = 8)		*P*
	US	MR imaging	US	MR imaging	US	MR imaging	
Intraventricular Hemorrhage							.2
Grade 1	6 (43%)	5 (36%)	4 (40%)	2 (20%)	1 (13%)	1 (13%)	
Grade 2	1 (7%)	0	0	0	2 (25%)	1 (13%)	
Grade 3	0	0	1 (10%)	1 (10%)	2 (25%)	3 (38%)	
Ventriculomegaly							.02
Borderline (8–10 mm)	1 (7%)	0	1 (10%)	1 (10%)	0	0	
Definite (>10 mm)	0	0	1 (10%)	0	4 (50%)	4 (50%)	
Thalamic echogenicity	1 (7%)	0	1 (10%)	0	0	0	1.0

Note.—WMA indicates white matter abnormality; US, ultrasonography.

TABLE 5: Periventricular echogenicity and ventriculomegaly shown on sonograms as predictors of MR imaging-defined white matter abnormalities*

	Relative Risk of WMA (95% CI)	Sensitivity %	Specificity %	Positive Predictive Value %	Negative Predictive Value %
Minimal to moderate WMA					
Periventricular echogenicity Grade 2–5 on any sonogram	0.9 (0.5–1.7)	44	50	53	41
P value	.8				
Periventricular echogenicity Grade 3–5 on any sonogram	2.0 (1.4–2.9)	22	100	100	50
P value	.06				
Moderate WMA only					
Periventricular echogenicity Grade 2–5 on any sonogram	.9 (0.3–3.0)	38	58	23	74
P value	.8				
Periventricular echogenicity Grade 3–5 on any sonogram	4.2 (1.6–11.1)	38	96	75	82
P value	.04				
Definite ventriculomegaly on any sonogram	2.1 (1.4–3.1)	28	100	100	52
P value	.05				

* Ultrasonography is compared with MR imaging in the absence of an in vivo gold standard of brain injury in the newborn.

Note.—WMA indicates white matter abnormality; CI, confidence interval.

Discussion

Spectrum of White Matter Injury

We found cystic periventricular leukomalacia based on ultrasonograms for only one (3%) neonate. Although the presence of cystic periventricular changes shown by ultrasonography is *specific* for the diagnosis of periventricular leukomalacia (10) and correlates well with the development of motor and visual disabilities of affected children (1, 3–7, 17, 18), this type of lesion was distinctly uncommon in our cohort. Instead, we found scattered foci of predominantly noncavitary white matter abnormalities. The MR imaging characteristics of these lesions, with T1 hyperintensity in the absence of T2 hypointensity, are most consistent with increased focal cellularity secondary to astrogliosis, as shown by previous pathologic studies (11, 15). Such subtle white matter abnormalities have been associated with widespread impairment of cerebral development (19). Specifically, one study that used diffusion tensor imaging revealed that although anisotropy increased with age in all white matter regions in normal participants, it did not increase in frontal white matter in those with minimal white matter injury and in widespread white matter areas in those with moderate white matter injury (19). Another study that used volumetric MR imaging techniques showed that neonates with white matter abnormalities revealed by MR imaging, including those with diffuse rather than cystic abnormalities, had significantly lower volumes of cortical gray matter and myelinated white matter at term compared with control term infants (20). These results indicate that non-cystic white matter injury is

associated with widespread impairments in cerebral development. Furthermore, the white matter abnormalities evident in our cohort present early in life and persist through the neonatal period. Therefore, this mild spectrum of white matter abnormalities detected only by MR imaging likely reflects an early and persistent form of white matter injury.

The finding that cystic periventricular leukomalacia is distinctly uncommon is consistent with other descriptions of MR imaging findings in recent cohorts of premature neonates (13, 21). Our findings, however, contrast with these other descriptions of white matter injury in that we did not observe hemorrhagic lesions or abnormal diffuse excessive high T2 signal intensity in the periventricular white matter (10, 13, 21). Several potential reasons might explain these discrepancies. In contrast with our cohort studied by using a 1.5-T MR imaging unit, other groups have studied premature neonates by using a 1.0-T unit. Other groups have selected neonates with abnormalities shown by sonography (10, 13, 21), whereas we recruited all neonates without brain anomalies, congenital infections, or catastrophic hemorrhages. Despite the discrepancies, these studies all indicated that MR imaging is a sensitive technique with which to detect white matter injury in premature neonates early in life.

Correspondence of Ultrasonography and MR Imaging for White Matter Abnormalities

Several groups have shown that macro-cystic lesions of the periventricular white matter (grade IV hemorrhage) in premature neonates, classic periventricular leukomalacia, and ventriculomegaly are associated with adverse neurodevelopmental outcomes (1, 3, 5, 6, 18, 22–24). In our cohort, these more severe sonographic abnormalities of the periventricular white matter were *specific* indicators of white matter abnormalities shown by MR imaging. Although the positive predictive value of these abnormalities shown by ultrasonography for predicting white matter abnormalities shown by MR imaging was high, the sensitivity of these findings was low. This is consistent with previous observations in which the correspondence between periventricular white matter abnormalities shown by sonography and MR imaging was best for neonates with cystic changes shown by sonography (8–10).

Because mild to moderate white matter injury may not cavitate, changes may not be detected by sonography of all premature neonates with periventricular white matter injury. This has been confirmed in some sonography-pathology correlation studies (6, 8, 25). Further, some cysts (<3 mm) may elude sonographic detection. This is consistent with the observation in this cohort that ultrasonography did not detect the small cavitations (<2 mm) observed with MR imaging in the periventricular white matter. These findings suggest that only periventricular cysts of sufficient size and severity are detected by sonography. In contrast with sonography, the extent and localization of MR imaging abnormalities in the white matter correspond closely to histopathologic changes found by postmortem examination (8, 11, 16, 25). However, in contrast to macro-cystic white matter injury, the neurodevelopmental consequences of the scattered foci of noncavitary or small cavitary abnormalities in the periventricular white matter are not yet defined.

No accepted in vivo measure of white matter injury in the premature neonate is currently available. Considering the strong association of MR imaging abnormalities in the white matter with injury evident on histopathology in other studies, we chose to compare the predictive value of white matter abnormalities shown by ultrasonography for those detected by MR imaging. In making this comparison, in the absence of an in vivo gold standard with which to compare both tests, the relatively poor sensitivity of ultrasonography for white matter abnormalities may have been exaggerated. However, the finding that sonography is relatively insensitive for the detection of mild white matter abnormalities detected by MR imaging is consistent with observations in other cohorts (8, 13, 21). Some investigators have reported that the duration of increased periventricular echogenicity, and not the degree of echogenicity, is the important predictive factor. It has been found that increased periventricular echogenicity persisting longer than 1 week significantly increases the risk of adverse outcome, whereas those lasting <1 week may be a normal finding (26, 27). Still others have suggested that rather than the duration of abnormal periventricular echogenicity, it is the timing of abnormal echogenicity after the first week of life or the degree of increased abnormal echogenicity that improves the predictive value of this finding for white matter injury shown by MR imaging (13, 27). In this cohort, no meaningful difference was observed in the duration of abnormal periventricular echogenicity on ultrasonograms among the MR imaging-defined white matter injury groups.

A limitation of this study was that all neonates in the cohort were not studied with ultrasonography and MR imaging on the same day. Although this would seem to limit our ability to compare these imaging techniques, the timing of the most severe abnormalities shown by ultrasonography was variable, with a marked tendency for ultrasonographically detected white matter abnormalities to resolve. This is an inherent problem in the diagnosis of white matter injury with ultrasonography and is in contrast to MR imaging, with which abnormalities in the white matter are stable over a period of weeks to several months. Therefore, calculating the predictive value of ultrasonography findings for MR imaging findings by using the most severe grade of echogenicity shown on the ultrasonograms would have biased our findings toward exaggerating the sensitivity of the ultrasonography. Because ultrsonography had limited sensitivity and high specificity for diagnosing MR imaging-detectable white matter injury, it is unlikely that the timing of the ultrasonograms studied in relation to the MR images substantially biased the comparison of the most severe abnormalities shown by ultra-

sonography with the MR imaging findings. Furthermore, consistent with previous observations, neither the periventricular echogenicities shown on the ultrasonograms nor the white matter injury detected by MR imaging progressed to macro-cystic periventricular white matter injury or classic periventricular leukomalacia (27).

The impact of the white matter lesions detected by MR imaging on neurodevelopmental outcome needs to be determined to understand the true importance of these MR imaging findings. Neurodevelopmental outcome after neonatal brain injury likely reflects both the severity of the brain injury measured by neuroimaging in addition to other genetic and environmental factors such as socioeconomic status (5, 28). However, because a substantial number of premature neonates with abnormal neurodevelopmental outcomes have normal ultrasonography findings during the neonatal period (23, 29), it will be important to determine whether these neonates have MR imaging-detectable white matter injury.

Other Lesions

Unlike the findings in the cerebral white matter, ultrasonography and MR imaging corresponded well regarding intraventricular hemorrhage and ventriculomegaly. Although ventriculomegaly was a highly specific sign for moderate white matter injury (and, when present, had a high predictive value), it was not a sensitive sign.

Conclusion

This study supports the previous observations that cystic periventricular leukomalacia is becoming distinctly uncommon (13, 21). Instead, the premature neonates in this study commonly had scattered foci of abnormalities in the periventricular white matter. This white matter injury was detected *early* in life by using MR imaging and persisted through the neonatal period. Although ultrasonography offers many advantages for screening premature neonates for white matter injury (noninvasive, inexpensive, and portable), it was not a sensitive predictor of the *milder* spectrum of MR imaging-defined white matter abnormalities. Better MR imaging techniques (such as diffusion-tensor MR imaging) and proton MR spectroscopy may offer the potential for even earlier diagnosis of this form of brain injury (30, 31). The neurodevelopmental consequences of the milder spectrum of white matter injury detected by MR imaging are not yet known and are currently being prospectively determined.

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