Magnetic resonance imaging in neonatal hypoxic-ischemic brain injury

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Chapter 2

Hypoxic-ischemic encephalopathy: diagnostic value of conventional MR imaging pulse sequences in term-born neonates

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Purpose
To retrospectively compare different magnetic resonance (MR) imaging techniques and pulse sequences for the depiction of brain injury in neonatal hypoxic-ischemic encephalopathy.

Materials and methods
The institutional review board approved this retrospective study and waived informed consent. Term-born neonates underwent MR imaging within 10 days after birth because of perinatal asphyxia. Two investigators separately and retrospectively evaluated T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted, and T1-weighted contrast material-enhanced MR images for presence of hypoxic-ischemic injury patterns. Interobserver agreement between the raters for visualizing abnormalities on images obtained with the individual pulse sequences was analyzed. Individual assessments were compared with the consensus reading (reference standard) to determine which techniques were best for visualizing hypoxic-ischemic damage. Last, which combination of pulse sequences had the best performance for visualizing certain injury patterns was evaluated. All analyses were repeated for infants imaged within 4 days after birth and those imaged between 4 and 10 days after birth.

Results
Forty term-born neonates (22 boys; gestational age, 37 weeks to 42 weeks 2 days) were included. Interobserver agreement was moderate for all pulse sequences (intraclass correlation coefficient (ICC), 0.52 - 0.73). As compared with the reference standard, T1-weighted imaging performed best in both groups (infants imaged ≤ 4 days and those imaged > 4 days after birth) for lesions in the basal ganglia, thalamus, and posterior limb of internal capsule (ICC, 0.93), as well as for punctate white matter lesions (ICC, 0.88). For infarction, diffusion-weighted images were scored best in both groups (ICC, 0.86). For nonpunctate white matter lesions, T2-weighted images scored as good in both groups (ICC, 0.59). Adding FLAIR and contrast- enhanced imaging to the combination of T1- and T2-weighted imaging and diffusion-weighted imaging did not contribute to detection of hypoxic-ischemic brain damage.

Conclusion
The combination of T1- and T2-weighted MR imaging and diffusion-weighted imaging is best for detecting hypoxic-ischemic brain lesions in the early neonatal period in term-born infants.

Introduction

Magnetic resonance (MR) imaging findings of the brain in neonates with hypoxic-ischemic encephalopathy have been described by many authors (1-16). Different patterns of neonatal hypoxic-ischemic brain injury that depend on the severity and duration of the insult and the gestational age of the neonate have been described (2,12). The accuracy and reproducibility of conventional T1- and T2-weighted MR imaging after perinatal hypoxia-ischemia have been demonstrated (2,9-17). However, despite important brain injury, T1- and T2-weighted images may appear normal during the first days after the hypoxic-ischemic event or show only subtle findings that may be difficult to interpret or to distinguish from normal (maturational) phenomena in the neonatal brain (2-4,18). Assessment of conventional MR images can be hampered by the fact that in many patients, the precise timing of injury is not known (18).
Because of the high water content of the immature brain, fluid-attenuated inversion recovery (FLAIR) imaging is of less use in the first year after birth than in older children and adults (19,20). Contrast material- enhanced imaging shows temporal evolution in enhancement, depending on the time of imaging after the hypoxic-ischemic insult and the duration and nature of the incident (21). Thus, interpretation of contrast-enhanced images is also hampered by the fact that precise timing of injury is not known in many patients. In addition, contrast material administration may not be desirable in some infants, especially in sick newborns with hypoxic-ischemic renal failure and liver function disturbances.

MR imaging techniques such as diffusion-weighted imaging and spectroscopy are also used in neonatal hypoxic-ischemic encephalopathy (20,22-31). Diffusion-weighted imaging enables quantitative measurements of apparent diffusion coefficient (ADC) values in brain tissue (31-35). However, there are some pitfalls in diffusion-weighted imaging in neonatal hypoxic-ischemic encephalopathy. Some authors claim that findings on diffusion-weighted images are less conspicuous in young infants than in adults (22,28). Furthermore, the interpretation of diffusion-weighted imaging abnormalities in young infants may be more intricate due to the fact that the timing of the hypoxic-ischemic insult is often unknown and the time course of changes may be different from that in adults (28,29,31,36). In addition, in cases of global diffuse brain injury, diffusion-weighted images may be difficult to interpret because of the lack of normal brain tissue for comparison (20). Early pseudonormalization has been described in neonatal brain damage, with findings on diffusion-weighted images already appearing normal within 1 week after the insult (29,36). Although Rutherford et al. (31) found abnormal ADC values in severely abnormal white matter and deep grey matter, they found normal ADC values in moderate white matter and basal ganglia and thalamus lesions during the first week after the hypoxic-ischemic event. Normal ADC values thus do not exclude hypoxic-ischemic brain damage in neonates.
Most MR spectroscopy studies have dealt with the prediction of neurodevelopmental outcome after perinatal asphyxia, not with the ability to detect hypoxic-ischemic brain injury (18,22-26). In addition, MR spectroscopy takes longer to perform, and only certain regions of interest can be studied (37).

The purpose of our study was to retrospectively compare different MR imaging techniques and pulse sequences for the depiction of brain injury in neonatal hypoxic-ischemic encephalopathy.

Materials and methods

Patients and selection of MR imaging studies

The institutional review board approved our retrospective study and waived informed consent. Brain MR imaging studies in infants who were born between January 2001 and December 2003 at a gestational age of more than 37 weeks and who underwent MR imaging because of perinatal asphyxia were selected by one author (I.H.P.M.). All MR imaging examinations were performed within 10 days after birth. From the MR imaging studies of all infants who fulfilled all of the following criteria: a) signs of fetal distress before delivery (abnormal cardiotocograph recording such as decreased variability, late deceleration, baseline bradycardia), b) an Apgar score of less than 7 after 5 minutes, c) a cord blood pH level of less than 7.2, and d) clinical signs of hypoxic-ischemic encephalopathy (38), studies were used if the original report of the attending neuroradiologist mentioned hypoxic-ischemic brain injury. Normal MR imaging studies and MR imaging studies that showed nonacquired brain disease where thus excluded from the investigation.
Evaluation of the clinical history was performed by two authors (I.H.P.M. and G.v.W.M.), who were blinded to the results of the brain MR imaging examinations.

MR imaging

If necessary, the infants were sedated (with 75 mg oral chloral hydrate per kilogram of body weight) just before imaging. They were laid in a supine position and snugly swaddled in blankets during the imaging procedure. Ear protection was always used and consisted of commercially available neonatal ear muffs (MiniMuffs; Natus Medical, San Carlos, Calif) placed over the ear. The infant's head was immobilized by moulded foam, which was placed around the head during the imaging procedure. The temperature was maintained and heart rate and oxygen saturation were monitored throughout the procedure. A pediatrician experienced in resuscitation and MR imaging procedures was always present during imaging.

Images were obtained with superconducting magnets (Gyroscan ACS-NT 15, Philips Medical Systems, Best, the Netherlands) operating at a field-strength of 1.5 T. T1-weighted spin-echo sequences (repetition time msec/echo time msec, 550-560/14-20), T2-weighted spin-echo sequences (5406-6883/100-120), FLAIR sequences (6000-8000/110-120; inversion time, 2000 msec), T1-weighted gadolinium-enhanced spin-echo sequences (550-560/14-20), and diffusion-weighted imaging were performed. The gadolinium-enhanced spin-echo sequences were performed after the administration of 0.2 ml/kg (1 mmol gadolinium per kilogram) gadopentetate dimeglumine (Magnevist; Schering, Weesp, the Netherlands). Diffusion-weighted imaging was performed by using single-shot spin-echo echo-planar sequences (5132/74) with a b value of 1000 sec/mm^2 and

a section thickness of 6 mm. All sequences were performed in transverse planes, and section thickness (except for diffusion-weighted imaging) was 4 - 5 mm with an intersection gap of 0.4 - 0.5 mm.

MR imaging data collection

The MR images obtained in the infants were retrospectively evaluated by two investigators: a neonatologist (G.v.W.M., with 14 years of experience in neuroimaging (rater 1)) and a neuroradiologist (L.L., with 7 years of experience in neuroimaging (rater 2)) who were both experienced in neonatal neuroimaging. They were blinded to the infant's identity and thus to their clinical history. For correct assessment of cerebral development, they were aware of the gestational age and the age at the time of imaging of the infants. Global cerebral maturation was related to the postconceptional age of the infant (39).

To assess which MR imaging technique(s) was the best for the detection of different injury patterns, the following consecutive steps were taken:
The two investigators independently studied the hard copies of images obtained with all individual MR imaging pulse sequences randomly. This method was chosen because, by randomly mixing images obtained with all sequences for all patients, blindness of the investigators was better guaranteed than if only patient identities had been masked, because remembering patients by recognizing their MR images would be almost impossible and because possible influence on the assessment of one pulse sequence of the findings observed with another pulse sequence in the same patient was excluded.
During this first session, for each separate MR imaging pulse sequence, the presence of different injury patterns that can be encountered in hypoxic-ischemic encephalopathy was noted. These patterns include abnormal signal intensity of the basal ganglia, abnormal signal intensity of the thalamus, abnormal signal intensity of the posterior limb of the internal capsule, cortical highlighting on T1-weighted images, nonpunctate white matter lesions, border zone infarctions, arterial infarctions, punctate white matter lesions, diffuse edema, abnormal signal intensity of the brain stem, and abnormal signal intensity of the hippocampus (2,9-17). With a diagnostic confidence score, assigned by using a five-point scale as definitely abnormal, probably abnormal, equivocal, probably normal, or definitely normal, the confidence of the investigator for the detection of each of these abnormalities with each MR imaging pulse sequence was scored. All findings were noted on score forms, and the abnormalities detected were annotated on the hard copies of each of the MR images.
In the second session, which took place 4 weeks after the first session, all MR images were reexamined by the same two investigators. During this session, they assessed together and at the same time images obtained with all sequences of one complete MR imaging examination. They reached consensus in all cases. This consensus reading was considered to be the reference standard, indicating whether injury was present and which type of injury pattern was present in each infant.

Statistical analysis

All statistical analysis was performed in consensus by two authors (L.L. and A.v.d.B.H.). All statistical evaluations were performed with software (SPSS for Windows, version 11.5; SPSS, Chicago, Ill). The following analyses were performed:

1. Interobserver agreement analysis to obtain intraclass correlation coefficients (ICCs) was performed to study the agreement between the two observers in visualizing abnormalities with the separate MR imaging sequences. An ICC of less than 0.40 signified poor agreement; an ICC of 0.40-0.75, fair to good (moderate) agreement; and an ICC 0.76-1.00, excellent agreement (40). To investigate possible effects caused imaging at different times, we used a cutoff value of 4 days (the median time point at which the MR imaging examinations were performed in our study), and thus acquired two groups of equal size. This was also done because it is well known that hypoxic-ischemic injury may not be visualized with conventional T1- and T2- weighted sequences during the first days after the event and that, on the other hand, early pseudonormalization can appear at diffusion-weighted imaging (4,7,32,39). Therefore, in addition to analysis of the entire group, we performed a subanalysis of data in infants imaged less than 4 days after birth or on day 4 and infants imaged more than 4 days after birth.
2. To analyze the performance of the separate pulse sequences in showing the different injury patterns, correlation between the individual assessments and the reference standard was calculated, again using ICCs. Again, analyses were performed for the whole group and then separately for MR imaging studies performed within 4 days after birth and studies performed after 4 but within 10 days after birth. Because of small numbers of infants in some injury pattern categories, we grouped several injury patterns (eg, lesions in the basal ganglia and thalamus were grouped with lesions in the posterior limb of the internal capsule, arterial infarctions were grouped with border zone infarctions).
3. Because the performance of the *separate* pulse sequences does not necessarily reflect everyday practice, the best-performing pulse sequences were assessed in various combinations so that we could analyze the best *combination* of pulse sequences for visualizing hypoxic-ischemic injury patterns. These analyses, which involved obtaining k values, were performed for the whole group imaged within 10 days after birth. A k value < 0.40 signified poor agreement; a k value of 0.40-0.75, fair to good (moderate) agreement; and a k value of 0.76-1.00, excellent agreement (40). We evaluated the performance of combined pulse sequences relative to the reference standard by using the best-performing sequence as the first step, then adding the second-best-performing sequence, and so on.

Results

Forty infants were included in our study (Table 1). In three infants, FLAIR imaging was not performed. In four infants, contrast-enhanced imaging was not performed. In seven infants, diffusion-weighted imaging was not performed. In all four infants in whom contrast-enhanced imaging was not performed, diffusion-weighted imaging was also not performed. In the three infants in whom FLAIR imaging was not performed, it was the only pulse sequence that was not performed. According to the reference standard, no prevailing injury pattern was seen (Table 2).

Table 1 Demographic data for all infants.

Parameter	**All Infants** (n=40)	**Infants Imaged ≤ 4 Days after Birth** (n=17)	**Infants Imaged > 4 Days after Birth** (n=23)
No. of boys (%)	22 (55)	9 (53)	13 (57)
Mean gestational age in weeks^{+days} (range)	39^{+6} ($37\text{-}42^{+2}$)	39^{+6} ($37\text{-}42^{+2}$)	39^{+6} ($37^{+2}\text{-}42^{+2}$)
Mean time of imaging after birth in days (range)	5 (1-10)	2.5 (1-4)	6.7 (5-10)

Table 2 Categories of reference standard injury patterns and numbers of infants in each category.

Category	**No.of Infants**
Abnormal signal intensity in basal ganglia	16
Abnormal signal intensity in thalamus	15
Abnormal signal intensity in posterior limb of internal capsule (unilateral or bilateral)	10
Cortical highlighting (on T1-weighted images)	6
Nonpunctate white matter lesions	20
Border zone infarction	18
Arterial infarction	3
Punctate white matter lesions	12
Diffuse edema, cerebral swelling	3
Abnormal signal intensity in brain stem	0
Abnormal signal intensity in hippocampus	0

Note. -Because in some infants, more than one injury pattern was present, the total number of infants exceeds 40.

Interobserver agreement

Regarding the results of the interobserver agreement analysis between the two raters of the separate MR imaging sequences for the whole group and for infants examined before and those examined after 4 days (Table 3), for the entire group and for the two subgroups there was moderate to excellent interobserver agreement for all pulse sequences, except for contrast-enhanced imaging and T1-weighted imaging in the group imaged earlier. Except for diffusion-weighted imaging, agreement was better for the group imaged after 4 days than for the group imaged earlier; this was especially true for T1-weighted imaging.

Table 3 ICC values for interobserver agreement for individual pulse sequences.

Pulse Sequence	All Infants	Infants Imaged ≤ 4 Days after Birth	Infants Imaged > 4 Days after Birth
T1 weighted	0.52	0.28	0.79
T2 weighted	0.69	0.74	0.87
FLAIR	0.63	0.51	0.84
Contrast enhanced	0.54	0.21	0.38
Diffusion weighted	0.73	0.79	0.78

Type of injury

Regarding the ICCs of the individual assessments for the four most prevalent injury patterns in relation to the reference standard (Table 4), the type of hypoxic-ischemic brain injury had an influence on the performance of the different pulse sequences (Figures 1-4). For lesions in the basal ganglia, thalamus, and posterior limb of the internal capsule, T1-weighted imaging performed best in both subgroups (moderate to excellent agreement) (Table 4). However, performance was better in the group imaged later.

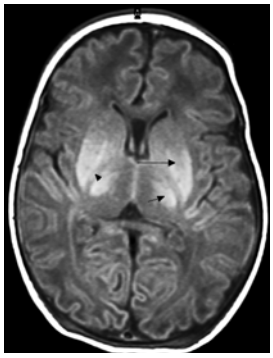

Figure 1

Figure 1 T1-weighted MR image (550/20; section thickness, 4 mm) at level of basal ganglia shows abnormally high signal intensity in basal ganglia (long arrow), thalamus (short arrow), and posterior limb of internal capsule (arrow head) in infant born at a gestational age of 37 weeks 5 days with severe perinatal asphyxia due to intertwined umbilical cord. Imaging was performed 6 days after birth at a postconceptional age of 38 weeks 4 days.

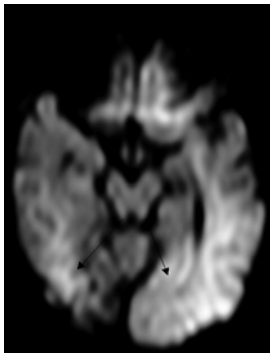

Figure 2a

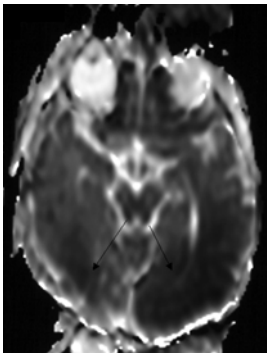

Figure 2b

Figure 2 Diffusion-weighted MR imaging (3447/74; section thickness, 6 mm) at level of occipital poles in infant born severely asphyxiated at a gestational age of 41 weeks 2 days by emergency caesarean section performed because of placenta previa and deterioration of fetal cardiotocographic results. **a**) Image obtained at b value of 1000 sec/mm² and **b**) ADC image show infarctions (arrows) in left and right occipital regions. Imaging was performed 3 days after birth at a postconceptional age of 41 weeks 5 days.

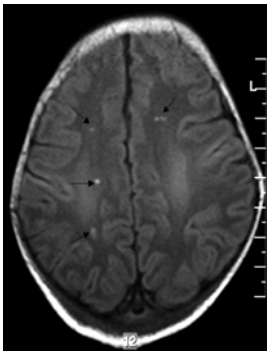

Figure 3

Figure 3 T1-weighted MR image (550/16; section thickness, 4 mm) at level of centrum semiovale in infant born at a gestational age of 41 weeks 2 days shows punctate white matter lesions in centrum semiovale (arrows). This infant experienced repetitive intrauterine insults due to umbilical cord problems; meconium aspiration syndrome was also present. Imaging was performed 8 days after birth at a postconceptional age of 42 weeks 3 days.

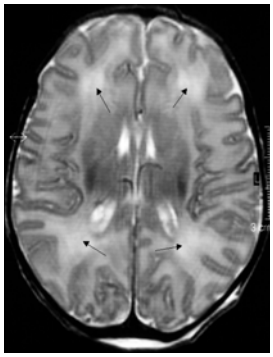

Figure 4

Figure 4 T2-weighted MR image (5406/120; section thickness, 4 mm) at level of body of lateral ventricles in infant born asphyxiated at a gestational age of 39 weeks 1 day shows nonpunctate white matter injury appearing as abnormal high signal intensity (arrows). Imaging was performed 1 day after birth at a postconceptional age of 39 weeks 2 days. Movement artifacts are visible.

Table 4 Agreement between individual assessments and the reference standard and agreement between the two raters for the most prevalent injury patterns.

	All Cases			≤ 4 Days after Birth			> 4 Days after Birth		
Lesions and Imaging Method	**Rater 1**	**Rater 2**	**ICC**	**Rater 1**	**Rater 2**	**ICC**	**Rater 1**	**Rater 2**	**ICC**
Basal ganglia, thalamus, and PLIC (n=20)									
T1 weighted	**0.66**	**0.59**	**0.93**	**0.4**	**0.41**	**0.98**	**0.77**	**0.77**	**0.72**
T2 weighted	0.26	0.61	0.47	0	0.36	0	0.48	0.68	0.52
FLAIR	0.45	0.42	0.85	0.24	0	0	0.58	0.63	0.79
Contrast enhanced	0.44	0.51	0.97	0	0	0	0.35	0.59	0.74
Diffusion weighted	0.15	0.70	0.39	0	0.71	0.28	0.23	0.71	0.52
Infarctions (n=19)									
T1 weighted	0.55	0.71	0.82	0.66	0.68	0.83	0.48	0.73	0.82
T2 weighted	0.69	0.83	0.89	0.58	0.80	0.80	**0.79**	**0.84**	**0.98**
FLAIR	0.18	0.25	0.38	0	0.30	0	0.41	0.25	0.45
Contrast enhanced	0.26	0.60	0.60	0	0.35	0	0.41	0.72	0.60
Diffusion weighted	**0.81**	**0.97**	**0.86**	**0.87**	**0.94**	**0.93**	**0.73**	**1.00**	**0.75**
Punctate white matter lesions (n=12)									
T1 weighted	**0.79**	**0.86**	**0.88**	**0.76**	**0.76**	**1**	**0.80**	**0.85**	**0.32**
T2 weighted	0.54	0.60	0.79	0.53	0	0.57	0.55	0.77	0.47
FLAIR	0.71	0.76	0.85	0.71	0.42	0.76	**0.71**	**0.84**	**0.66**
Contrast enhanced	0	0.43	0	0	0	0	0	0.57	0
Diffusion weighted	0.32	0.15	0.76	0	0	0	0.42	0.34	0
Nonpunctate white matter lesions (n=20)									
T1 weighted	0	0	0	0	0	0	0	0	0
T2 weighted	0.63	0.83	0.59	0.66	0.83	0.74	**0.62**	**0.80**	**0.24**
FLAIR	0	0	0	0	0	0	0	0	0
Contrast enhanced	0	0	0	0	0	0	0	0	0
Diffusion weighted	0	0	0	0	0	0	0	0	0

Note.- Numbers in first two columns under each subgroup are the agreements between the two separate assessments by the raters and the reference standard; number in the third column is the agreement between the two raters. All data are ICC values; 0 indicates a very low value. Best performing sequences and best agreement values are in boldface type. PLIC= posterior limb of internal capsule.

For the detection of infarction, diffusion-weighted imaging scored best in both groups (moderate to excellent agreement) (Table 4). There was no important difference in performance between the group imaged earlier and the group imaged later. T2-weighted imaging demonstrated good performance, with excellent agreement for the detection of infarction in the group imaged later (Table 4).

For punctate white matter lesions, T1-weighted imaging scored best in the whole group and in the group of infants imaged earlier (excellent agreement) (Table 4). However, in the group of patients imaged later, FLAIR scored better than T1-weighted imaging (with moderate agreement, vs poor agreement for T1-weighted imaging) (Table 4).
For nonpunctate white matter lesions, T2-weighted imaging scored best (moderate agreement; however, there was poor correlation for the group of infants imaged later), while the other techniques all had bad performance (poor agreement) in the depiction of these lesions (Table 4).

Combined pulse sequences

Diffusion-weighted imaging and T1-weighted imaging were chosen as the first step because of their best performance in individual injury patterns and because there was generally good interobserver agreement (moderate to excellent agreement) for these pulse sequences (Table 4). For all individual assessments, after the first step, k values increased when T2-weighted imaging was added. When FLAIR and contrast-enhanced imaging were added, k values did not increase (Table 5). Thus, in our study group, FLAIR and contrast-enhanced imaging did not contribute to the detection of hypoxic-ischemic brain injury. In all infants, global cerebral maturation was compatible to the postconceptional age of the infant (39).

Table 5 K values for performance of combined pulse sequences.

	All Infants			**Infants Imaged ≤ 4 Days after Birth**				**Infants Imaged > 4 Days after Birth**	
Pulse Sequence Combination	**Agreement between Rater 1 and Reference Standard**	**Agreement between Rater 2 and Reference Standard**	**Inter-observer Agreement**	**Agreement between Rater 1 and Reference Standard**	**Agreement between Rater 2 and Reference Standard**	**Inter-observer Agreement**	**Agreement between Rater 1 and Reference Standard**	**Agreement between Rater 2 and Reference Standard**	**Inter-observer Agreement**
DWI, T1	0.30	0.22	0.61	0.88	0.82	0.30	0.47	0.36	0.83
DWI, T1, T2	0.48	0.66	0.36	0.94	1	1	0.65	0.65	0.45
DWI, T1, T2, FLAIR	0.48	0.66	0.36	0.94	1	1	0.65	0.65	0.45
DWI, T1, T2, FLAIR, contrast enhanced	0.48	0.66	0.36	0.94	1	1	0.65	0.65	0.45

DWI = diffusion-weighted imaging

Discussion

To our knowledge, ours is the first study to systematically assess the contribution of different MR imaging pulse sequences in the demonstration of hypoxic-ischemic brain injury in term-born neonates. Our results show that the combination of T1- and T2-weighted imaging and diffusion-weighted imaging is best in these patients.

ICCs calculated for the purpose of evaluating the performance of the separate pulse sequences in depicting hypoxic-ischemic brain injury were moderate to excellent, except for contrast-enhanced imaging. When we assessed performance for specific injury patterns, we also obtained moderate to excellent ICC. However, the overall k values, which relate the performance of separately assessed pulse sequences to the reference standard, seem low. The reason probably is that two experienced investigators independently scored 11 brain injury entities with five different, randomly mixed pulse sequences. In our opinion, this could have contributed to the low k values. By randomly mixing all sequences in all patients, blindness of the investigators was better guaranteed because recollection of patients by recognizing their MR images would be almost impossible. Also, the possible influence on the assessment of one pulse sequence of the findings with another pulse sequence in the same patient was excluded. During the consensus reading, images obtained with all pulse sequences were viewed together, enabling detection of not only obvious lesions but also more subtle lesions. The more subtle lesions were probably missed with the individual pulse sequences. When we evaluated larger groups, as we did in evaluating the performance of the separate pulse sequences in depicting one of the four most prevalent injury patterns, ICCs increased.

The combination of T1- and T2-weighted imaging and diffusion-weighted imaging was best for depicting hypoxic-ischemic brain lesions in the early neonatal period in our study group. From the clinical perspective, it is well known that the type of hypoxic-ischemic brain injury influences the performance of the different pulse sequences. For lesions in the basal ganglia, thalamus, and posterior limb of the internal capsule and for punctate white matter lesions, T1-weighted imaging scored best. For infarction, diffusion-weighted imaging scored best in the group imaged later, and T2-weighted imaging scored second best. Nonpunctate white matter lesions were only reliably detected with T2-weighted imaging.

We could not find data about the diagnostic value of T1- and T2-weighted pulse sequences in imaging hypoxic-ischemic abnormalities. This is probably because these pulse sequences were used routinely from the moment MR imaging was introduced in neonates and because many investigations deal with the overall sensitivity of MR imaging for depicting hypoxic-ischemic abnormalities and not with separate pulse sequences (1-16).

Although most authors do not advocate FLAIR imaging for visualizing hypoxic-ischemic lesions, a few do value FLAIR imaging (19,41,42). Iwata et al. (42) stated that periventricular areas of low intensity on FLAIR images were a good predictor of chronic white matter damage in preterm and term infants; however, they did not study the diagnostic value of FLAIR. Sie et al. (41) found that, for depicting cystic lesions in preterm and term infants with hypoxic-ischemic brain damage,

the FLAIR technique was more sensitive than inversion- recovery imaging and T1- and T2 - weighted imaging. However, FLAIR could not replace T1- and T2-weighted imaging because of its failure in depicting myelination well. In addition, imaging was performed with a mean postnatal age of 16 days ± 11 and a range of 3-40 days, so the infants Sie et al. studied were generally older than our patients. Our findings support the opinion that FLAIR images do not contribute substantially to the detection of hypoxic-ischemic lesions in neonates.

Regarding the use of contrast-enhanced imaging in perinatal asphyxia, Westmark et al. (21) found that the presence of contrast enhancement might indicate more severe brain damage. However, they did not assess the diagnostic value of contrast enhancement. In our study, contrast enhancement did not contribute to the detection of hypoxic-ischemic brain abnormalities. In our hospital, until recently, we routinely used contrast -enhanced imaging in neonates who underwent MR imaging because of perinatal asphyxia. However, on the basis of the results of our study, we believe that contrast-enhanced imaging is not warranted in these sick patients, and we do not use contrast-enhanced imaging in these patients anymore.

T1-weighted images, not diffusion-weighted images, were best for depicting lesions in the basal ganglia and thalamus. This is compatible with the findings of Forbes et al.(28), who found that abnormalities in the deep white or gray matter were not as well depicted by diffusion-weighted imaging as cortical damage in term infants with hypoxic-ischemic damage.

In our patient group, diffusion-weighted imaging scored best for the depiction of infarctions in all groups. This is compatible with results in the literature (23,30,32-34). There was no important difference between the group imaged earlier and the group imaged later in our study. We were surprised by this observation, because we expected early pseudonormalization, with findings at diffusion-weighted imaging becoming normal within 1 week after the insult (29,36).

MR spectroscopy was left out of our analysis because we aimed to assess the pulse sequences used most often in daily practice. In addition, in our hospital, MR spectroscopy is not routinely used in neonates. ADC values were also left out of the analysis. ADC measurements are useful, especially for revealing abnormalities when conventional imaging or diffusion-weighted imaging do not show abnormalities-for example, in diffuse brain damage (43). However, it is known that normal ADC values during the first week after an insult do not necessarily indicate normal tissue (31). Because we wanted to select the best *imaging* technique for categories of hypoxic-ischemic brain injury and because we wanted to test only MR imaging techniques and pulse sequences that are frequently used in daily practice, we do not report ADC measurements as part of our study results (32).

Our study was limited in that our reference standard (the consensus interpretation) was an internal one. Although our primary aim was to elucidate the optimal techniques and pulse sequences for visualizing hypoxic-ischemic brain damage in the early neonatal period, long-term follow-up MR imaging to confirm the neonatal findings would strengthen our results. However, we did not perform follow-up imaging because this is an extra burden on these children and does not have implications in terms of the management of their conditions. Long-term clinical

follow-up is needed to assess whether the optimal combination of MR imaging techniques and pulse sequences enables reliable prediction of neurological outcome in neonates with hypoxic-ischemic brain damage and thus the *clinical* importance of our results.

In conclusion, we found that the combination of T1- and T2-weighted MR imaging and diffusion-weighted imaging is best for the detection of hypoxic-ischemic brain injury in the early neonatal period in term-born infants. FLAIR and contrast-enhanced imaging do not contribute to this. Contrast-enhanced imaging does not seem to be warranted in term-born infants suspected of having or known to have hypoxic-ischemic brain damage.

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