Diffusion-weighted and Conventional MR Imaging in Neonatal Hypoxic Ischemia: Two-year Follow-up Study[1]

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Purpose: To establish the supplemental value of diffusion-weighted (DW) magnetic resonance (MR) imaging beyond conventional MR to predict clinical outcome after neonatal hypoxic ischemia (HI) at 2 years of age.

Materials and Methods: Forty-six infants with neonatal HI were enrolled in this prospective study, after approval by the local ethical committee and informed consent of the parents. Neonatal MR imaging ranged from 1 to 45 days after birth. Apparent diffusion coefficient (ADC) was measured in 14 brain regions. DW and conventional images were qualitatively scored for abnormalities, resulting in cumulative scores and patterns of damage. Surviving infants were scored for motor outcome at the age of 2 years, and outcome was classified as poor if the motor score was less than 70 or in case of death. Analyses were performed for the whole group, with additional analyses for the early (0–4 days after birth) and late (>4 days after birth) imaging groups.

Results: Twenty-five infants had a good outcome and 21 had a poor outcome. Only in the early imaging group, the infants with poor outcome had significantly lowered ADC values in several brain areas, with the posterior limb of the internal capsule being the most predictive (Wald score = 5.7; P = .017). Cumulative scores of DW imaging were the best predictor of poor motor outcome at the age of 2 years (Wald score = 7.2, $P < .01$). The basal ganglia and central cortex and the diffuse pattern of brain damage were highly associated with poor outcome (Fisher exact test = 29.8; $P < .001$).

Conclusion: In neonatal HI, DW imaging is a useful additional MR technique to predict the motor outcome at 2 years. Local ADC values had a limited value. Recognition of the patterns of brain damage with DW and conventional MR imaging can be used as a diagnostic tool in neonatal HI.

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Neonatal hypoxic ischemia (HI) is one of the main causes of severe cerebral palsy in term-born infants. Despite the developments in modern medicine, the frequency of neonatal HI is not further decreasing in developed countries (1). Clinical assessment of the severity of neonatal HI is most commonly performed by using the Sarnat score, which combines clinical condition and electroencephalographic recording and results in the following scores: Sarnat score I, mild neonatal encephalopathy; score II, moderate; or score III, severe (2).

Although brain ultrasonography is a standard diagnostic tool in neonates, it has limited value in neonatal HI (3,4). In contrast, conventional brain magnetic resonance (MR) imaging (T1 and T2 weighted) is very reliable in detection of brain damage after neonatal HI. On neonatal MR images, several patterns of cerebral damage after neonatal HI can be identified: *(a)* abnormalities in the basal nuclei and central cortex; *(b)* focal cortical abnormalities, including watershed areas; and *(c)* diffuse abnormalities (5–7).

Diffusion-weighted (DW) imaging is a sensitive MR technique for the detection of brain ischemia within the first 10 days after birth (8). Several groups have reported these patterns of brain damage with DW imaging (9–11). After neonatal HI, the severity of cerebral damage at conventional MR imaging relates to outcome at later age (5–7). Particularly, an abnormal signal intensity in the posterior limb of the internal capsule (PLIC) on a T1-weighted MR image is predictive of a poor outcome after neonatal HI (12). To date, the number of studies with regard to the predictive value of DW imaging on outcome of infants with neonatal HI are limited (13,14).

The purpose of our study was to establish the supplemental value of DW MR imaging beyond conventional MR to predict clinical outcome after neonatal HI at 2 years of age.

Advances in Knowledge

- Abnormalities on diffusion-weighted images are stronger predictors of motor outcome at 2 years than are conventional MR findings.
- Newborns with neonatal hypoxic ischemia but with normal conventional and diffusion-weighted MR images have a very high likelihood of a normal motor outcome at 2 years.
- Single apparent diffusion coefficient values in selected areas in infants with neonatal hypoxic ischemia are informative but cannot be used for prediction of outcome.

Materials and Methods

Patients

Between November 2000 and November 2002, 46 full-term (>37-week pregnancy; 27 male and 19 female) neonates with HI were enrolled in this prospective study (9) at our neonatal intensive care unit. The medical ethics committee of the hospital approved the research protocol, and parents gave informed consent. To include the range of mild to severe forms of neonatal HI, the infants fulfilled at least two of the following inclusion criteria: *(a)* signs of intrauterine asphyxia such as late decelerations or meconium-stained amniotic fluid; *(b)* umbilical cord artery pH lower than 7.10; *(c)* slow start of spontaneous breathing; *(d)* Apgar score (activity, pulse, grimace, appearance, and respiration) of less than 5 at 5 minutes; or *(e)* clinical status of hypoxic encephalopathy within 24 hours: lethargy, hypotonia, hyperreflexia, convulsions, segmental myoclonic seizures. Patients with dysmorphic syndromes, malformations, or evidence of intrauterine or perinatal infections and those who required surgical intervention during the neonatal period were excluded. In total, six neonates were excluded, four because of refusal of the parents to cooperate, one because of trisomy 21, and one because of congenital heart anomaly.

Implication for Patient Care

- Diffusion-weighted MR may be a valuable addition to a conventional MR.

The mean gestational age was 40.2 weeks (range, 37.1–44.0 weeks). The median Apgar score was 2 at 1 minute (n = 44; range, 0–8) and 4 at 5 minutes (n = 43; range, 0–7). Thirty-three infants had neonatal convulsions. Sarnat scoring was performed by a neonatologist within 24 hours. The neonatologist was not aware of the results of the neonatal MR. A brain MR was performed in the neonatal period as soon as possible, on stabilization of the clinical situation of the child. Nevertheless, MR imaging ranged from 1 to 45 days after birth (grouped median, 5.5 days). The reasons for the late MR examination (after 14 days) were a failed MR examination due to movement artifacts in the first 2 weeks (n = 1), clinical instability (n = 1), and logistical reasons (referral to another hospital, n = 5).

Motor Development Assessment at the Age of 2 Years

The Bayley Scales of Infant Development (15) was used for the assessment of motor development at the age of 2 years. The test was performed by a trained pediatric physical therapist (P.E.M.v.S.), without knowledge of the neonatal morbidity and MR results. The test was performed in the department of physiotherapy. With

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Abbreviations:
ADC = apparent diffusion coefficient
DW = diffusion weighted
HI = hypoxic ischemia
PLIC = posterior limb of the internal capsule

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Guarantors of integrity of entire study, R.J.V., P.J.W.P.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, R.J.V., L.H., P.J.W.P.; clinical studies, R.J.V., P.E.M.v.S., L.H., F.B., P.J.W.P.; experimental studies, P.J.W.P.; statistical analysis, R.J.V., D.L.K., P.J.W.P.; and manuscript editing, all authors

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this test, motor performance is depicted as psychomotor developmental index, and we used normative data for the Dutch population in the analysis (16). Motor outcomes were defined as normal, when the psychomotor developmental index was at least 70, and poor, when the psychomotor developmental index was below 70 or when the infant died in the neonatal period. In one child, assessment was performed by means of telephone questioning, because the parents declined to visit the outpatient clinic. This child was assigned to the normal outcome group.

Neonatal MR Imaging

MR investigations were performed with a 1.5-T imager (Vision; Siemens AG, Erlangen, Germany). If necessary, oral chloral hydrate (50–100 mg/kg) was used for sedation of the infants. During the MR examination, pulse and saturation were measured continuously.

The imaging protocol included the following sequences: T1-weighted spin-echo (repetition time msec/echo time msec, 780/14), T2-weighted spin-echo (3000/22, 60, 120), and echo-planar–based DW (5100/137) sequence with *b* values of 50 and 1000 sec/mm^2 in three directions. From those images, apparent diffusion coefficient (ADC) maps were calculated. In some patients, the following sequences were also used: inversion recovery (repetition time msec/echo time msec/inversion time msec, 9000/60/350) and fluid-attenuated inversion recovery (9000/105/2200).

Qualitative Scoring of DW and Conventional MR Images

DW and conventional MR images were simultaneously reviewed for abnormalities by an experienced neuroradiologist (F.B., 16 years of experience), without knowledge of the clinical condition of the infants. The images were scored for abnormalities in the following 14 predefined brain areas: *(a)* Rolandic cortex, *(b)* parietal cortex, *(c)* frontal cortex, *(d)* occipital cortex, *(e)* centrum semiovale, *(f)* occipital white matter, *(g)* temporal white matter, *(h)* PLIC, *(i)* caudate nucleus, *(j)* putamen, *(k)* thalamus, *(l)* hippocampus, *(m)* brainstem, and *(n)* cerebellum.

A score of 0 indicated no abnormalities (normal), a score of 1 indicated possible abnormality, and a score of 2 indicated definite abnormality. Cumulative scores for DW and conventional MR images were constructed for each infant by summation of all scores for the 14 regions. A separate analysis was made for the appearance of the PLIC on T1-weighted images in relation to outcome.

Figure 1

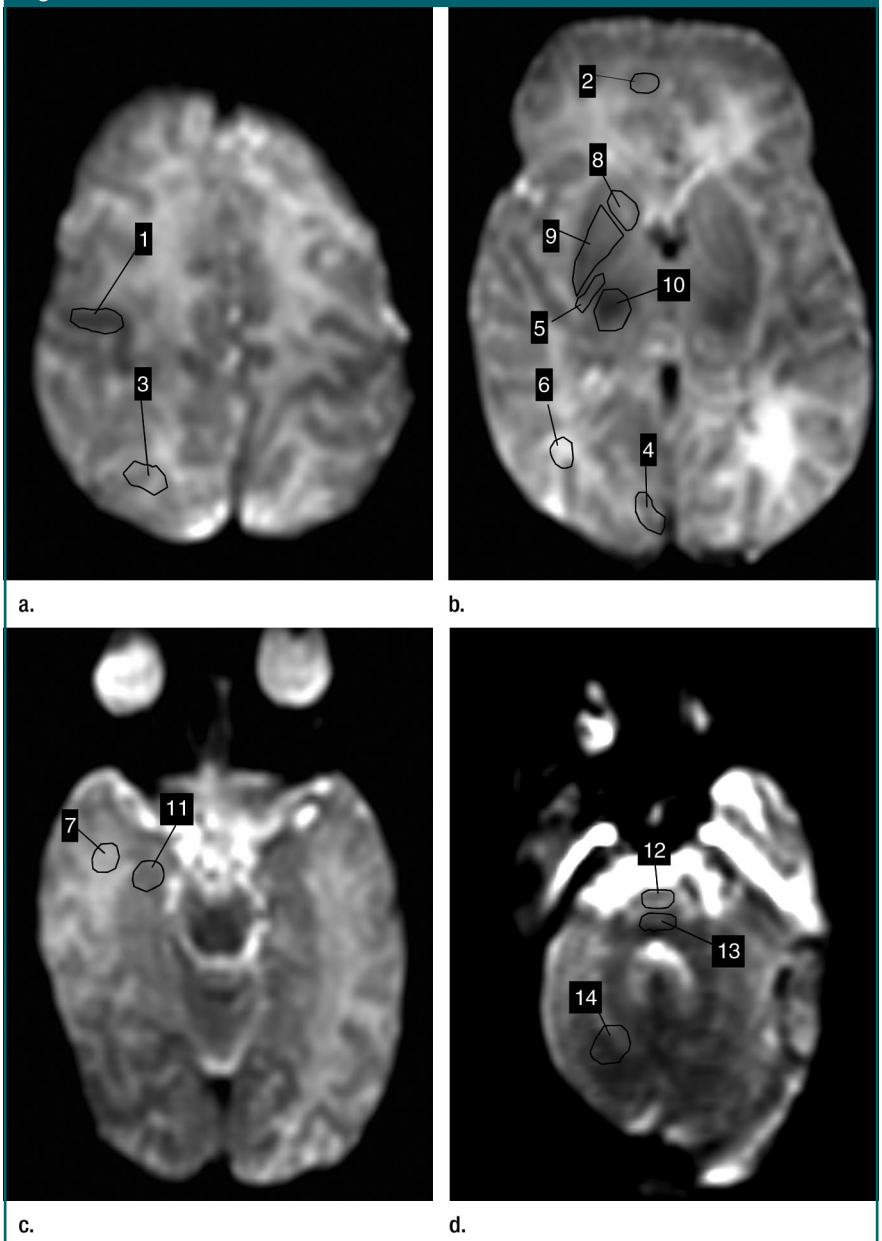

Figure 1: Placement of regions of interest on **(a–d)** MR images with low diffusion weighting (*b* = 50 sec/mm^2). **(a)** *1* = Rolandic cortex, *3* = parietal cortex. **(b)** *2* = frontal cortex, *4* = occipital cortex, *5* = PLIC, *6* = occipital white matter, *8* = caudate nucleus, *9* = putamen, *10* = thalamus. **(c)** *7* = temporal white matter, *11* = hippocampus. **(d)** *12* = brainstem, anterior part; *13* = brainstem, posterior part, *14* = cerebellum. Regions of interest were subsequently transferred to ADC maps.

Quantitative Regional ADC Measurements

The images of 44 patients were available for quantitative analysis of the ADC. For ADC measurements, the same regions were used as for the qualitative analysis, with the following exceptions: The ADC in the brainstem was measured in the anterior and posterior parts separately, since the visual analysis of ADC maps suggested two well-separated areas (Fig 1). In the centrum semiovale, no ADC was determined. The regions of interest were drawn on the images with low diffusion weighting (b = 50 sec/mm^2) and were then transferred to the corresponding ADC maps (Fig 1).

We used only ADC values of the right hemisphere. This was explicitly chosen to prevent the bias of measuring only obviously abnormal areas. In one infant, regions of interest for ADC measurement were placed in the left hemisphere due to massive hemorrhagic abnormalities in the right hemisphere. In one infant, ADC data of the occipital cortex were not available due to artifacts on the corresponding section. To include this infant in the logistic regression analysis, we selected the mean of all cortical and subcortical areas as replacement of the occipital ADC. One person (L.H.) without knowledge of the clinical outcome performed all measurements.

MR Patterns of Cerebral Damage

By using both DW and conventional MR images, each image was classified as normal or belonging to one of three patterns of cerebral damage in neonatal HI: *(a)* basal ganglia and central cortex; *(b)* focal abnormalities, including watershed infarctions; or *(c)* global damage. The classifier (R.J.V.) was not blinded to the clinical information of the infants.

Statistics

Differences in regional ADC values between infants with good and those with poor outcome were analyzed with an independent t test (equal variances not assumed), by using Bonferroni correc-

Figure 2

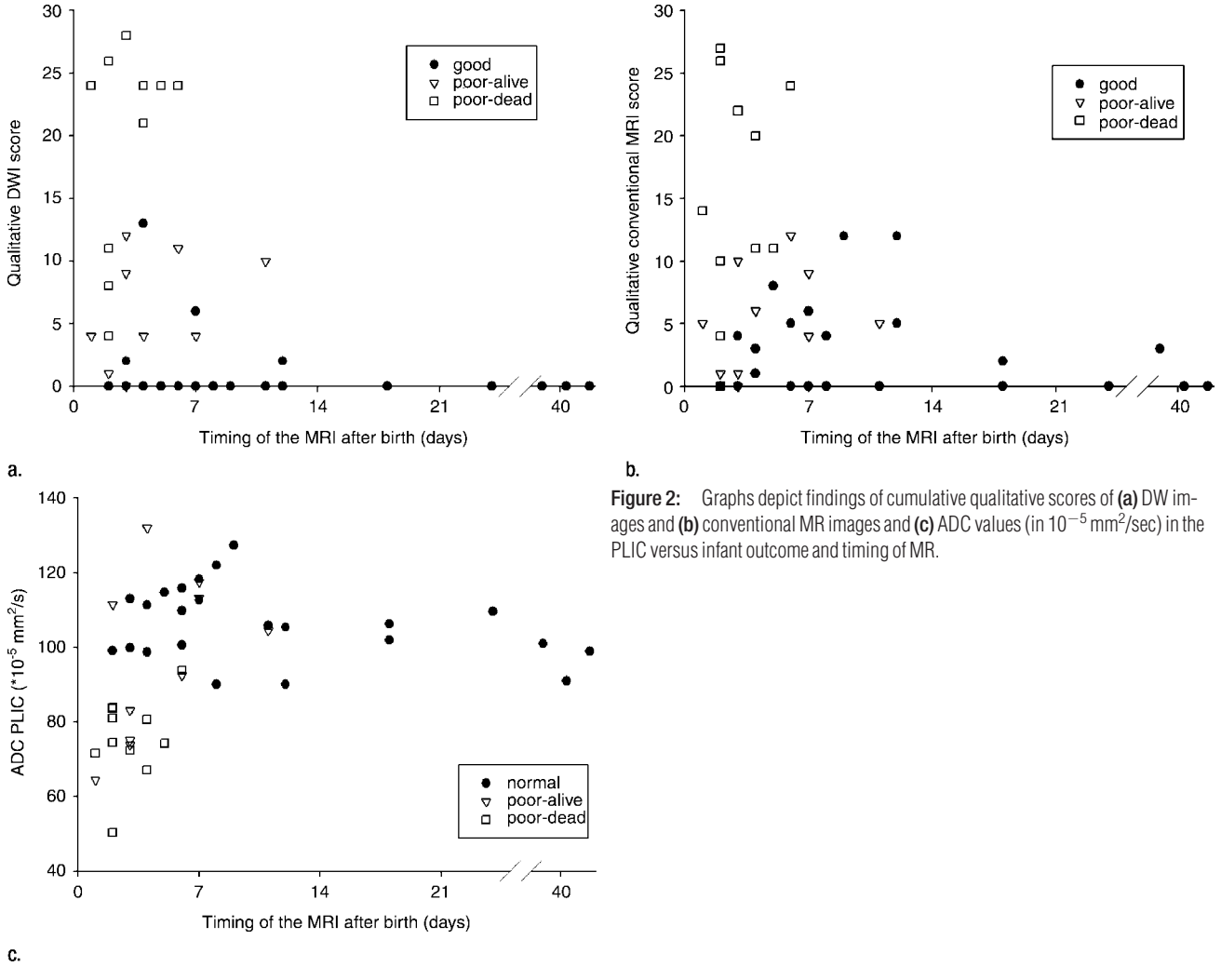

Figure 2: Graphs depict findings of cumulative qualitative scores of **(a)** DW images and **(b)** conventional MR images and **(c)** ADC values (in 10^{-5} mm^2/sec) in the PLIC versus infant outcome and timing of MR.

tion for multiple comparisons. Since ADC values are presumably dependent on the timing after a hypoxic event, for this analysis, data were divided into an early imaging group (0–4 days after birth) and a late imaging group (>4 days).

Prediction of outcome was assessed with forward selection logistic regression analysis. We assessed the predictive value of the following MR characteristics: cumulative scores of DW images, cumulative scores of conventional MR images, combined cumulative scores of DW and conventional MR images, score of the PLIC, and regional ADC values. Timing of the MR examination (days after childbirth) was included in all logistic regression analyses.

For the early and late imaging groups, receiver operating characteristic curves were constructed for the qualitative score of conventional MR and DW images and for the most predictive ADC. Regional ADC values were tested for correlation with Pearson correlation test. A Fisher exact test was used to establish a possible relation between pattern of brain damage, clinical characteristics, and outcome after neonatal HI. We considered $P < .05$ as indicating a significant difference. All statistical tests were performed with SPSS (version 12.0.1; SPSS, Chicago, Ill).

Table 1

ADC Values for Infants with Good and Poor Outcome

	Early Imaging Group (0–4 d after birth)		Late Imaging Group (> 4 d after birth)	
Brain Area	Good Outcome ($n = 6$)	Poor Outcome ($n = 16$)	Good Outcome ($n = 17$)	Poor Outcome ($n = 5$)
Rolandic cortex	126.4 ± 18.5	84.3 ± 25.9*	123.5 ± 14.5	125.3 ± 12.6
Parietal cortex	169.4 ± 13.5	143.5 ± 36.9	155.6 ± 26.2	144.4 ± 43.1
Occipital cortex	133.1 ± 23.4	108.8 ± 30.1	123.1 ± 17.0	137.9 ± 31.3
Frontal cortex	139.2 ± 17.5	105.7 ± 29.5	130.2 ± 13.5	138.2 ± 28.6
Occipital white matter	122.8 ± 27.9	105.0 ± 25.8	122.6 ± 13.7	137.5 ± 15.8
PLIC	106.1 ± 7.6	80.0 ± 18.8*	106.3 ± 10.9	104.4 ± 11.2
Temporal white matter	156.4 ± 14.7	133.0 ± 25.7	144.5 ± 20.6	147.9 ± 33.9
Caudate nucleus	128.6 ± 5.9	105.4 ± 28.2	122.7 ± 14.2	132.8 ± 31.3
Putamen	113.8 ± 5.1	90.9 ± 23.4*	111.5 ± 13.1	113.3 ± 11.6
Thalamus	105.9 ± 4.9	78.8 ± 22.3*	107.2 ± 12.1	109.5 ± 25.3
Hippocampus	142.5 ± 9.4	117.1 ± 26.6*	132.5 ± 20.8	149.4 ± 19.2
Brainstem (dorsal)	104.1 ± 14.9	102.7 ± 32.5	100.3 ± 8.8	103.5 ± 8.3
Brainstem (ventral)	121.5 ± 13.1	111.5 ± 14.4	112.3 ± 16.6	121.8 ± 28.3
Cerebellum	132.2 ± 11.4	126.1 ± 11.9	121.4 ± 11.7	133.3 ± 4.7

Note.—Data are mean ADC values ($\times 10^{-5}$ mm^2/sec) ± standard deviation.

* Significant difference ($P < .05$) between good and poor outcome group (independent t test, using Bonferroni correction factor for multiple comparisons).

Results

Clinical Outcome

Twenty-five infants had a good outcome and 21 had a poor outcome, 11 of whom died in the neonatal period. One infant died of lung problems and 10 died of general effects of severe HI. Ten infants had Sarnat score I, 26 had Sarnat score II, and 10 had Sarnat score III. All infants with Sarnat score I had a good motor outcome. Eleven infants with Sarnat score II had a poor motor outcome (10 survived, one died). All infants with a Sarnat score III died in the neonatal period (Fisher exact test = 22.5, $P < .01$). Thirty-three infants had neonatal seizures, 21 of whom had a poor outcome and 12 of whom had a good outcome (Fisher exact test = 20.1, $P < .01$).

Qualitative Scoring of DW and Conventional MR Images

Infants with poor outcome ($n = 21$) had higher cumulative scores for DW images (mean ± standard deviation, 13.2 ± 9.7) than for conventional MR images (10.2 ± 8.7, $t = -2.1$, $P < .05$). Infants with a good outcome had low scores for cumulative DW images (0.9 ± 2.8) and higher scores for conventional images (2.9 ± 3.7), though not significantly ($t = 1.9$, $P = .06$). Figure 2a and 2b shows the distribution of qualitative scores in relation to the timing of MR imaging.

The cumulative score for DW images was the best predictor of a poor motor outcome (Wald score = 7.2, $df = 1$, $P < .01$). This result was not changed after exclusion of the deceased infants (Wald score = 6.1, $df = 1$, $P = .01$). The addition of the conventional MR images score to the DW images score did not improve the predictive value of the DW images score alone.

In a separate analysis, an abnormal signal intensity of the PLIC on T1-weighted images significantly predicted poor outcome (Wald score = 5.2, $df = 1$, $P = .022$). However, after exclusion of the deceased infants, the abnormal PLIC no longer predicted a significant outcome.

Quantitative Regional ADC Measurements

In the early imaging group (0–4 days), infants with a poor outcome ($n = 16$) had lower mean ADC values in all 14 areas; the values were significant in the Rolandic cortex, PLIC, putamen, thalamus, and hippocampus, in comparison to infants with a good outcome ($n = 6$; Table 1). In the late imaging group (>4 days), infants with poor outcome ($n = 5$) had similar or even higher ADC values in comparison to the infants with a good outcome ($n = 17$), although the differences were not significant. In the early imaging group, correlations between ADC values in the Rolandic cortex, PLIC, putamen, thalamus, and hippocampus were high (Pearson correlation test, $\rho = .68–.84$; all $P < .001$).

The ADC of the internal capsule was the strongest independent predictor of a poor motor outcome (Wald score = 5.7; $df = 1$; $P = .017$). However, after exclusion of the deceased infants, the ADC of the internal capsule was no

longer significantly predictive of a poor outcome. Figure 2c shows the distribution of the ADC values in the internal capsule in relation to the outcome and timing of the MR imaging. From this figure it is clear that all infants with an ADC value in the PLIC lower than 85 × 10^{-5} mm^2/sec had a poor outcome (ie, poor motor outcome or death).

Combined Analysis of Clinical Characteristics, Visual MR Scores, and ADC Measurements

Analysis with inclusion of clinical characteristics (Apgar score, Sarnat score, and seizures), ADC values, cumulative score of DW images, and cumulative score of conventional MR images showed that the score of DW images was the best predictor of a poor outcome.

Receiver operating characteristic curves were constructed that showed that the area under the curve for qualitative scores of DW images was 0.87 for early imaging group and 0.98 for late imaging group, that for qualitative scores of conventional MR images was 0.79 for early imaging group and 0.87 for late imaging group, and that for ADC of the PLIC was 0.90 for early imaging group and 0.53 for late imaging group (Fig 3).

MR Patterns of Cerebral Damage

The clinical outcome in relation to MR patterns is shown in Table 2. Findings of neonatal MR in 13 patients were classified as normal. Another 13 patients had the pattern of basal ganglia lesions and central cortex damage. Children with abnormalities in basal ganglia and central cortex predominantly on DW images have a higher likelihood of a poor motor outcome (Fig 4) than do children with abnormalities in this area restricted to conventional MR images (Fig 5).

Twelve infants had focal lesions (medial cerebral artery territory, $n = 3$; posterior cerebral artery territory, $n = 2$; multifocal infarctions and/or watershed, $n = 7$). Figure 6 shows an example of focal cerebral damage in relation to a good outcome. Eight infants had a pattern of diffuse cerebral damage, and all died in the neonatal period. Typical for this pattern is the high signal intensity on DW images in the cortex and low signal intensity in the cerebellum (Fig 7).

When associating the different types of injury with outcome at 2 years of age (Fisher exact test = 29.8; $P <$

Figure 3

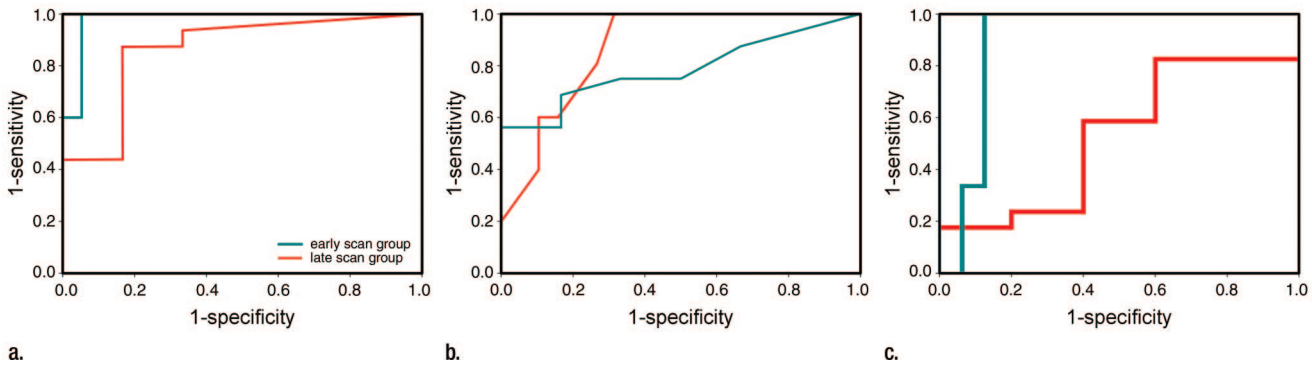

Figure 3: Receiver operating characteristic curves for prediction of a poor outcome at 2 years. The area under the curve for **(a)** qualitative scoring of DW images was 0.87 for early imaging group and 0.98 for late imaging group, that for **(b)** qualitative scoring of conventional MR images was 0.79 for early imaging group and 0.87 for late imaging group, and that for **(c)** ADC of the PLIC was 0.90 for early imaging group and 0.53 for late imaging group.

Table 2

Patterns of Brain Damage in Relation to Motor Outcome at 2 Years

	Early Imaging Group (0-4 d after birth)			Late Imaging Group (>4 d after birth)			
Pattern	No. of Infants	DW Images Score*	Conventional MR Images Score*	No. of Infants	DW Images Score*	Conventional MR Images Score*	Total No. of Infants
Normal	2/0	0/NA	0/NA	11/0	0/NA	0/NA	13
Multifocal	3/1	5/0	3/10	6/2	13/5	8/8	12
Basal ganglia	1/8	0/11	8/7	2/2	0/7	9/7	13
Global	0/7	NA/19	NA/15	0/1	NA/24	NA/24	8

Note.—Data are for good outcome/poor outcome. The different types of injury were significantly associated with outcome at 2 years of age in both early (Fisher exact test = 11.5; $P = .003$) and late (Fisher exact test = 10.0; $P = .012$) imaging groups.

* Values are mean visual scores. NA = not applicable.

.001), the basal ganglia and central cortex and diffuse type of damage have the poorest prognosis. This result remained similar when the tests were performed for the early imaging group (Fisher exact test = 11.5; $P = .003$) and the late imaging group (Fisher exact test = 10.0; $P = .012$).

Discussion

In this prospective study of infants with neonatal HI, we found that presence of convulsions and higher Sarnat scores (scores II and III) were associated with poor outcome. However, 36% of the infants with seizures and 42% of the infants with Sarnat score II had a good motor outcome at the age of 2 years. These results merit research toward further development of diagnostics, and we demonstrated the value of both qualitative and quantitative DW imaging in neonatal HI and showed the value of the MR technique for predicting outcome in a clinical representative cohort.

In infants with a poor outcome, lowered ADC values were found in the basal nuclei (thalamus and putamen), the PLIC, the Rolandic cortex, and the hippocampus in the early imaging group, these findings are in line with those of other studies (8,13). Remarkably, this reduction was only observed in the early imaging group. The ADC of the PLIC has the highest predictive value in our population. A possible explanation for this finding is that the patient cohort contained a large number of very severely injured infants who eventually died. For clinical practice, it is important to acknowledge that all infants with an ADC value in the PLIC lower than 85×10^{-5} mm^2/sec had a poor outcome (ie, poor motor outcome or death). Hunt and co-workers (13) also included deceased infants in their poor outcome group and stated that that was a possible confounder in their study. Indeed, exclusion of the deceased infants altered our results with respect to prediction of motor outcome at 2 years of age. On the basis of our study results and those of Hunt et al, we assume that the infants with the lowest ADC values in the PLIC have the most severe brain damage. This assumption is supported by findings of a small combined neuropathologic and imaging study (17) that showed a clear relation between in vivo ADC changes in the PLIC and postmortem cytotoxic edema in the cortex, hippocampus, and putamen.

The predictive value of the visibility

Figure 4

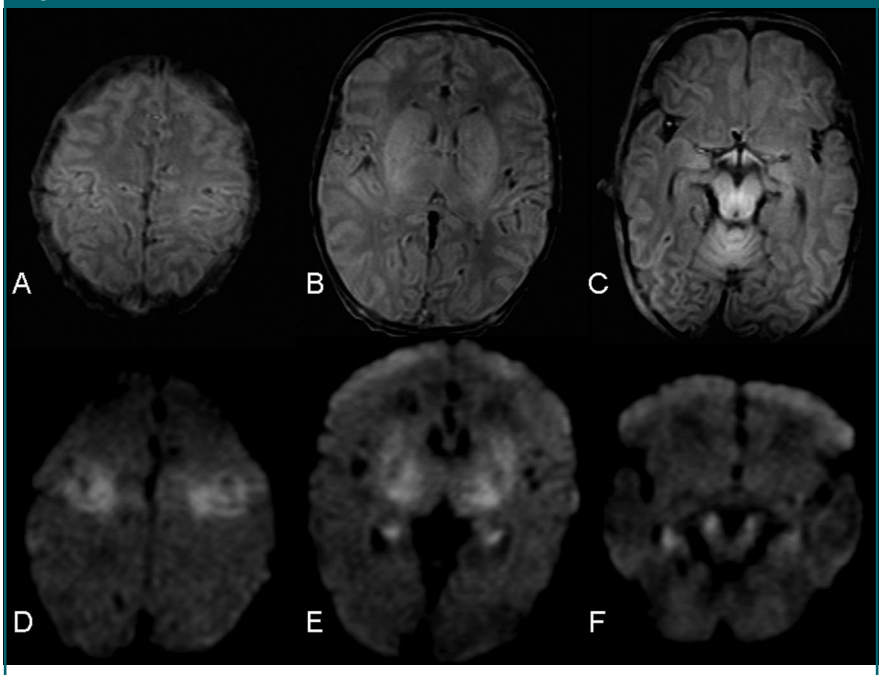

Figure 4: MR images at day 3 in an infant with basal ganglia and central cortex pattern of cerebral damage and a poor motor outcome. *A–C,* T1-weighted MR images with absence of normal high signal intensity in the internal capsule. *D–F,* DW images ($b = 1000$ sec/mm^2) show hyperintense signal in the Rolandic cortex, basal ganglia, hippocampus, and cerebral peduncle.

Figure 5

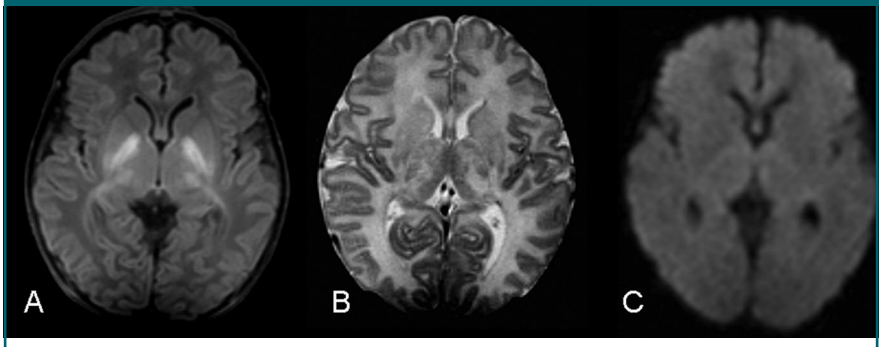

Figure 5: MR images at day 9 in an infant with basal ganglia and central cortex pattern of cerebral damage and a good motor outcome at the age of 2 years. *A,* T1-weighted image with an abnormal high signal intensity in the globus pallidus and, to a lesser extent, in the thalamus. *B,* T2-weighted image with an irregular, abnormal high signal intensity in the thalamus and, to a lesser extent, in the globus pallidus. *C,* DW image ($b = 1000$ sec/mm^2) without abnormalities.

of the PLIC on T1-weighted images (12) could be confirmed in this study, but the predictive value for a poor motor outcome was lower than that of the other MR characteristics. This might be explained by the fact that shortly after birth, the PLIC can appear normal on T1-weighted images, despite clear abnormalities at DW imaging and abnormal spectroscopy findings showing lactate (19).

Figure 6

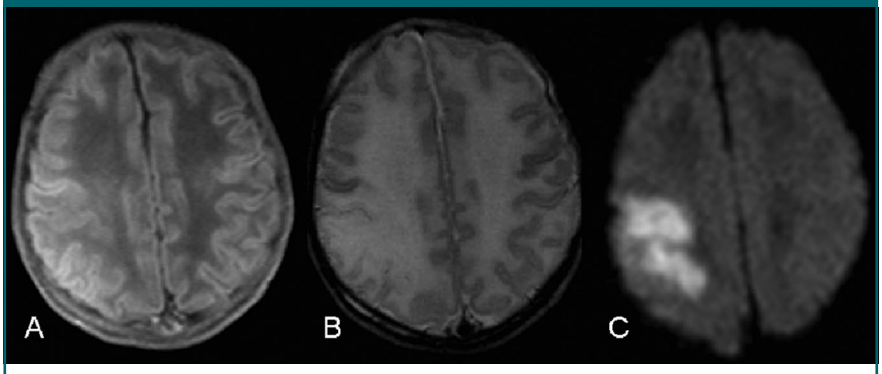

Figure 6: MR images at day 3 in an infant with a good motor outcome at the age of 2 years and an infarct in the right parietal region. *A,* High signal intensity on T1-weighted MR image. *B,* An abnormal cortical ribbon on T2- weighted MR image. *C,* High signal intensity on DW image ($b = 1000$ sec/mm^2).

Figure 7

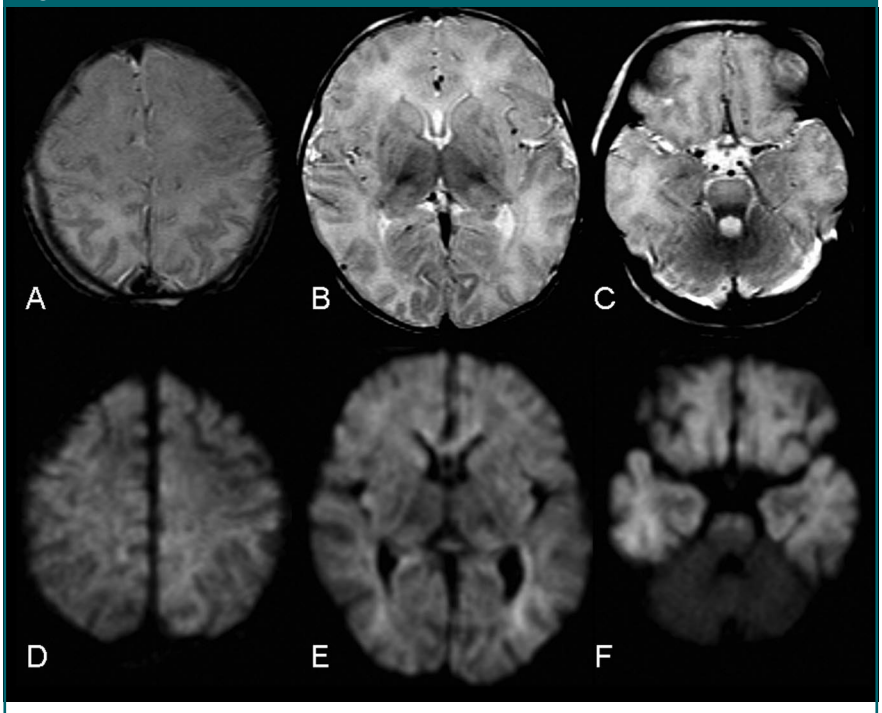

Figure 7: MR images at day 6 in an infant with a diffuse pattern of cerebral damage, who died in the neonatal period. *A–C,* T2-weighted images with abnormal cortical rim throughout the entire cortex, an abnormal high signal intensity in the basal ganglia, and high signal intensity in the frontal periventricular areas. *D–F,* DW images ($b = 1000$ sec/mm^2) show a global high signal intensity in the cortex and basal ganglia. The cerebellum has a normal low signal intensity (also described as the white cerebrum [9]) and the cerebral peduncles have a high signal intensity.

The focus of this article is on the discrimination between poor and good outcome. The poor outcome group included both infants with a poor developmental outcome and infants who died in the neonatal period. While realizing that this is a rather crude method, we think that prediction of a poor outcome can be an important factor in further medical decisions in a very sick neonate.

An important finding in this study was that all infants with normal neonatal MR findings had a good motor outcome at the age of 2 years. Although this was a relatively long follow-up period compared with that in previous studies, the cognitive development still has to evolve in these infants, and further follow-up is needed to confirm these results.

Findings of this study have further shown that different patterns of brain damage clearly relate to the motor outcome. Patterns of basal ganglia and central cortex and diffuse damage were most predictive of an adverse outcome, which is in agreement with findings by Miller and co-workers (18). For clinical purposes, this is very important since pattern recognition is the mainstay of clinical imaging.

A possible confounder in the interpretation of ADC values is the timing of the neonatal MR imaging. In some of the affected brain areas (such as cortex and basal ganglia), the ADC value may show a typical temporal evolution with an initial decrease, a pseudonormalization, followed by an increase taking place within 2 weeks (19). This is supported by our observation that in the early imaging group (0–4 days after birth), lowered ADC values were significantly associated with a poor outcome, whereas in the late imaging group (>4 days) there was no significant difference. Some authors reported that a reduced ADC value in the PLIC does not show this biphasic behavior, possibly because the damage in white matter is due to Wallerian degeneration (13,20). Be-

cause an identical and early timing of the MR investigation in all patients with neonatal HI is not feasible due to a variable clinical situation of the infant and for logistic reasons, possible changes of ADC over time should be taken into account. Therefore, the predictive ADC value of a single area seems limited and should only be used to confirm the abnormality of a DW image.

This study had several limitations, starting with a limited number of included infants. Considering other follow-up studies (18,21) of asphyxiated and preterm infants, it is likely that from our group of infant with a normal outcome at 2 years, an additional number of children will develop learning and behavioral problems at school age. A possible bias is the inclusion of deceased infants, since decision of treatment withdrawal might partially be based on the results of the neonatal MR imaging. However, by excluding these cases, the infants with more severe brain damage would have been missed, a problem also reported by others (15). Therefore, we performed analyses both for the whole group and for the surviving infants. A major confounder in this study was the timing of the MR, which has a rather large range. Therefore, logistic regression analysis was performed, with the timing of the MR as a factor. A practical limitation was that visual scoring of the MR images was performed by only one rater. However, this experienced neuroradiologist was blinded to the clinical data, as was the physiotherapist. In addition, the combination of blinded visual MR scoring and blinded clinical scoring will, in our opinion, limit the potential biases in this study. Further, we used only ADC values of the right hemisphere, but this was explicitly chosen, in line with another study (15), to prevent the bias of measuring only obviously abnormal areas (13). Spectroscopy was not part of our imaging protocol, although several groups have indicated that elevated lactate can predict poor outcome (14,20,22), but the predicting value also depends on the timing of the MR imaging (14,20).

DW MR imaging provides additional information about brain damage in neonatal HI, compared with conventional MR imaging, and improves the diagnostic value of MR imaging. Therefore, we suggest that DW imaging should be part of the standard imaging protocol in neonatal HI, which should also include conventional MR, because none of the MR techniques is solely suitable for prediction of outcome in neonatal HI. Although the predictive value of ADC is limited due to changes over time, a low ADC has a relatively high predictive value. For instance, an ADC value of the internal capsule lower than 85×10^{-5} mm^2/sec is highly prognostic for a poor outcome. Further, we advise to classify the pattern of brain damage as seen on MR images, since this can be done in a clinical imaging setting.

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