Additional Value of 3-Month Cranial Magnetic Resonance Imaging in Infants with Neonatal Encephalopathy following Perinatal Asphyxia

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Objective To assess the evolution of neonatal brain injury noted on magnetic resonance imaging (MRI), develop a score to assess brain injury on 3-month MRI, and determine the association of 3-month MRI with neurodevelopmental outcome in neonatal encephalopathy (NE) following perinatal asphyxia.

Methods This was a retrospective, single-center study including 63 infants with perinatal asphyxia and NE (n = 28 cooled) with cranial MRI <2 weeks and 2-4 months after birth. Both scans were assessed using biometrics, a validated injury score for neonatal MRI, and a new score for 3-month MRI, with a white matter (WM), deep gray matter (DGM), and cerebellum subscore. The evolution of brain lesions was assessed, and both scans were related to 18- to 24-month composite outcome. Adverse outcome included cerebral palsy, neurodevelopmental delay, hearing/visual impairment, and epilepsy.

Results Neonatal DGM injury generally evolved into DGM atrophy and focal signal abnormalities, and WM/watershed injury evolved into WM and/or cortical atrophy. Although the neonatal total and DGM scores were associated with composite adverse outcomes, the 3-month DGM score (OR 1.5, 95% CI 1.2-2.0) and WM score (OR 1.1, 95% CI 1.0-1.3) also were associated with composite adverse outcomes (occurring in n = 23). The 3-month multivariable model (including the DGM and WM subscores) had higher positive (0.88 vs 0.83) but lower negative predictive value (0.83 vs 0.84) than neonatal MRI. Inter-rater agreement for the total, WM, and DGM 3-month score was 0.93, 0.86, and 0.59.

Conclusions In particular, DGM abnormalities on 3-month MRI, preceded by DGM abnormalities on the neonatal MRI, were associated with 18- to 24-month outcome, indicating the utility of 3-month MRI for treatment evaluation in neuroprotective trials. However, the clinical usefulness of 3-month MRI seems limited compared with neonatal MRI. *(J Pediatr 2023;258:113402)*.

Neonatal encephalopathy (NE) due to perinatal asphyxia is often followed by neonatal death and impairments.[1,2] Early cranial magnetic resonance imaging (MRI), preferably <1 week after birth, has become the gold standard to assess brain injury and obtain prognostic information in infants with NE following perinatal asphyxia.[3] Neonatal MRI of the brain including diffusion-weighted imaging (DWI) has an excellent negative predictive value (NPV) for adverse neurodevelopmental outcome.[4] When abnormalities (eg, signal changes in the deep gray matter [DGM] or white matter and watershed [WM/WS]) are present, MRI can be repeated around 3 months of age to assess residual damage, which can include cysts, atrophy, or impaired myelination, among other findings.[5-7] Furthermore, a repeat MRI could help to assess the brain in an infant not progressing as expected or developing new symptoms.[8]

Bayley-III-NL	Dutch version of the Bayley Scales of Infant and Toddler Development, Third Edition	^{1}H-MRS	Proton magnetic resonance spectroscopy
		IHF	Interhemispheric fissure
		MRI	Magnetic resonance imaging
BGT	Basal ganglia and thalami	NE	Neonatal encephalopathy
DGM	Deep gray matter	NPV	Negative predictive value
DGMA	Deep gray matter surface area	PAIS	Perinatal arterial ischemic stroke
DWI	Diffusion-weighted imaging	PMA	Postmenstrual age
ECS	Extracerebral space	PPV	Positive predictive value
FHD	Frontal horn depth	SI	Signal intensity
FLAIR	Fluid-attenuated inversion recovery	WM	White matter
		WM/WS	White matter/watershed

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FG is an expert witness in legal cases of perinatal asphyxia and coinventor of 2-iminobiotin for neonatal neuroprotection. He has no financial activities related to the present manuscript to disclose. The authors have no conflicts of interest to disclose.

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Previous studies in infants with NE following perinatal asphyxia have reported that 3-month MRI findings relate to neurodevelopmental outcome.[9-13] However, the clinical utility of 3-month MRI is unknown, as research on its additional value compared with neonatal MRI alone is scarce and shows variable results.[8,10,12] Furthermore, these studies were performed before the implementation of therapeutic hypothermia and did not use DWI, which has improved the assessment of brain injury on neonatal MRI.[5] Considering the increasing amount of research on new neuroprotective treatments in addition to therapeutic hypothermia, a repeat MRI at 3 months also could be an important biomarker to assess treatment effects before long-term outcome data become available. Hence, a systematic score to quantify brain injury on MRI at this age is needed.

Therefore, the primary aims of this study were to describe the evolution of neonatal brain injury, develop a novel score to assess brain injury on 3-month MRI, and determine the additional value of 3-month MRI in relation to neurodevelopmental outcome at 18-24 months of age in infants with NE following perinatal asphyxia. In addition, we aimed to describe the association of 3-month MRI findings with neurodevelopmental outcome at 5.5 years of age and to describe the evolution of brain lesions on the 18- to 24-month MRI for infants in whom these data were available. We hypothesized that 3-month MRI findings would be associated with neurodevelopmental outcome, but that 3 months might be too early to show the sequelae of perinatal brain injury to its full extent.

Methods

Subjects and Ethics

A single-center, retrospective cohort study was performed on infants born at ≥36.0 weeks of gestation with NE following perinatal asphyxia admitted to the neonatal intensive care unit of our hospital between September 2003 and April 2020, with cranial MRI performed <2 weeks and repeated at 2-4 months after birth because of neonatal MRI abnormalities. The medical ethical review committee of our hospital approved this study using pseudonymized data. Written informed consent was obtained from parents of infants still in follow-up. Requirement for informed consent was waived for those discharged from follow-up. Inclusion criteria were (1) well-documented perinatal asphyxia (5-minute Apgar score ≤5, resuscitation, mechanical ventilation during ≥10 minutes' postpartum, pH <7.1, base excess <–16 mmol/L, or lactate >10.0 mmol/L in umbilical cord blood gas analysis or arterial, venous, or capillary blood gas analysis <1 hour after delivery) with NE (Thompson score ≥7, a discontinuous normal voltage or more suppressed background pattern on amplitude-integrated electroencephalography,[14] or [sub]clinical seizures), or (2) (sub)clinical seizures <48 hours after birth with neuroimaging findings highly suggestive of perinatal asphyxia and exclusion of another cause for the seizures. Infants with a gestational age at birth <36.0 weeks, central nervous system infections, congenital brain malformations, metabolic/genetic disorders, or no availability of neurodevelopmental outcome data were excluded. Finally, 63 infants were included (Figure 1). Data of some infants have been used previously.[4,11,15-23] Twenty-four infants from this study also were included in our previous publication on 3-month MRI biometrics.[11]

Neonatal MRI

Neonatal cranial MRI was performed <14 days after birth on a 1.5-T (n = 26) or 3.0-T (n = 37) system (Philips Medical Systems). Infants receiving mechanical ventilation were sedated using intravenous morphine (10 μg/kg). Before 2017, infants breathing spontaneously were sedated with chloral hydrate (50 mg/kg via a nasogastric tube) or an intramuscular injection of a combination of pethidine (2 mg/kg), chlorpromazine (0.5 mg/kg), and promethazine (0.5 mg/kg). Since 2017, only chloral hydrate has been used. The standard imaging protocol included T1- and T2-weighted imaging, DWI including apparent diffusion coefficient mapping, and proton magnetic resonance spectroscopy (^{1}H-MRS) of the basal ganglia/thalami (BGT) using an echo time of 144 or 288 milliseconds. Since 2013 susceptibility-weighted imaging also was performed. Neonatal MRIs were assessed by 3 investigators blinded to patient outcomes using the Weeke score.[4] Furthermore, injury was grouped according to the predominant pattern of injury: normal, mild WM/WS, moderate-severe WM/WS, mild DGM, moderate-severe DGM, near-total injury (moderate-severe injury in both DGM and WM/WS), and perinatal arterial ischemic stroke (PAIS).[24] Other lesions (eg, intraventricular hemorrhage) were categorized as miscellaneous.

3-Month MRI

Repeat MRI was performed 2-4 months after birth on a 1.5-T (n = 27) or 3.0-T (n = 36) system, including T1- and T2-weighted imaging. Sedation was similar as described for neonatal MRI. A qualitative score was developed by 2 neonatologists with more than 30 years of experience in neonatal neuroimaging and an experienced pediatric neuroradiologist, based on existing neonatal MRI scores[4,25] and current literature on serial and late MRI of the brain.[7-10,12,17,26,27] Similar to the neonatal score, injury was separately scored for WM and cortex (WM subscore), DGM, and cerebellum (Table I).[4] The WM subscore consisted of the following items: enlargement of the extracerebral space (ECS) and interhemispheric fissure (IHF), WM volume loss, enlarged lateral ventricles, delayed myelination of the posterior limb of the internal capsule, anterior limb of the internal capsule or optic radiation, thinning of the corpus callosum, punctate WM lesions, hemorrhagic lesions, and abnormal WM signal intensity (SI) suggestive of gliosis, cysts, and cortical lesions (Figure 2).[4,7-10,12,25-27] The DGM subscore included enlargement of the third ventricle, abnormalities of the BGT (atrophy, cysts, abnormal SI), and mammillary body atrophy.[4,9,12,17,25,26] The cerebellum subscore included atrophy of the vermis or hemispheres, and hemorrhagic injury.[4,28] The total score was calculated by adding the subscores. Using this score, 3-month MRIs were assessed by

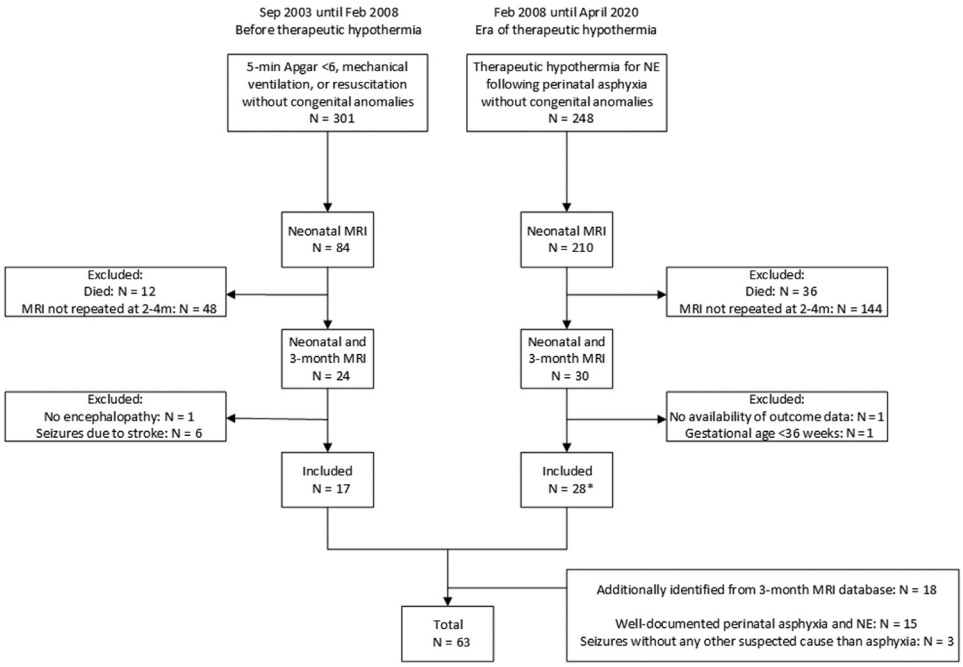


Figure 1. Flow diagram of the study sample. Infants were selected from a database of infants treated with therapeutic hypothermia and a database of infants born before the introduction of hypothermia with 5-minute Apgar score <6, resuscitation, or mechanical ventilation immediately after birth. An additional group of 18 noncooled infants (n = 15 not recognized within the therapeutic window or with seizures >6 hours after birth, n = 3 born before the era of therapeutic hypothermia) were identified from a database of infants admitted to our neonatal intensive care unit in whom cranial MRI was performed at 2-4 months of age. Finally, 63 infants were included: 59 had well-documented perinatal asphyxia with NE, and 4 had seizures without any diagnosis other than perinatal asphyxia. *One infant who received therapeutic hypothermia did not fulfill criteria for well-documented perinatal asphyxia but had seizures without any diagnosis other than perinatal asphyxia. *MRI*, magnetic resonance imaging; *NE*, neonatal encephalopathy (defined as Thompson score ≥7, a discontinuous normal voltage or worse background pattern on amplitude-integrated electroencephalography, or [sub]clinical seizures).

3 investigators blinded to patient outcomes but with knowledge of neonatal MRI findings to look for residual damage as in clinical practice. To determine inter-rater agreement, 14 scans were also scored by a pediatric neuroradiologist. In 12 infants, MRI also was repeated at 18-24 months using conventional imaging and a T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence to assess the subsequent evolution of the injury in infants with cerebral palsy (n = 4), suspected cerebral palsy (n = 3), or extensive neonatal MRI injury (n = 3), or because of abnormalities on neurological examination not explained by previous neuroimaging (n = 2).

Biometrics

MRI biometrics were assessed using the picture archiving and communication system. The scans were angulated along the course of the line through the nasion and below the vermis in midsagittal view, and between the hemispheres in coronal and axial view. An investigator blinded for patient outcomes manually measured the ECS (distance between cortex and edge of triangular sagittal sinus), IHF (shortest distance between the superior frontal gyri), lateral ventricles, third ventricle, DGM surface area (DGMA), cerebellar width, brain length, and brain width on neonatal and 3-month MRI. The DGMA was measured on a single axial section where maximally visible.[25] The ECS, IHF, brain length, and brain width were measured on the same axial section, as axial images showed the best quality. The lateral ventricles (frontal horn depth [FHD] and ventricular–hemispheric ratio, defined as midline–frontal horn distance divided by midline–cortical distance) and third ventricle were assessed in coronal view at the level of the foramen of Monro.[29] In case of asymmetry of the ventricles, ECS, or brain length, the mean of both sides was calculated. The cerebellar width was measured axially, looking for the largest diameter.[11] Where appropriate, measurements were corrected for postmenstrual age (PMA). To determine intraobserver variability, the same observer performed biometrics twice in 14 scans (neonatal n = 7, 3-month MRI n = 7) >2 weeks apart.

Outcome

The primary outcome included neurodevelopmental outcome at 18-24 months, determined at 24 months with the Dutch version of the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III-NL), or 18-24 months using the Griffiths Mental Development Scales

Table I. 3-month MRI scoring form

Subscores		Sequence	0	1	2
White matter subscore					
1	Volume loss	T1/T2	No	Mild (widening of sulci)	Moderate-severe (sulci abutting the lateral ventricles)
	Specify location			Unilateral	Bilateral
2	Enlarged lateral ventricles	T1/T2	No	Mild	Moderate-severe
	Specify location			Unilateral	Bilateral
3	PLIC myelination*	T1	Normal	Equivocal/partially myelinated	Absent myelination
	Specify location			Unilateral	Bilateral
4	ALIC myelination*	T1	Normal	Unilateral delayed myelination	Bilateral delayed myelination
5	Optic radiation myelination*	T1	Normal	Unilateral delayed myelination	Bilateral delayed myelination
6	Corpus callosum	T1/T2	Normal	Focal thinning (<33%)	Generalized thinning (>33%)
7	Punctate white matter lesions	T1/T2	No	<6	≥6
8	Hemorrhagic lesions	T1/T2/SWI	No	Single lesion <1.5 cm	Single lesion ≥1.5 cm or multiple lesions
9	Cystic lesions	T1/T2	No	Unilateral	Bilateral
10	Gliosis white matter	T1/T2	No	Focal (1 lobe)	Extensive (>1 lobe)
	Specify location			Unilateral	Bilateral
11	Cortical injury	T1/T2	No	Focal (1 lobe)	Extensive (>1 lobe)
	Specify location			Unilateral	Bilateral
12	Enlarged subarachnoid space	T1/T2	No	Yes	
13	Enlarged interhemispheric fissure	T1/T2	No	Yes	
Deep gray matter subscore			0	1	2
1	Basal ganglia atrophy	T1/T2	No	Mild	Moderate-severe
	Specify location			Unilateral	Bilateral
2	Basal ganglia injury: cysts	T1/T2	No	Unilateral	Bilateral
3	Basal ganglia injury: gliosis	T1/T2	No	Unilateral	Bilateral
4	Thalamus atrophy	T1/T2	No	Mild	Moderate-severe
	Specify location			Unilateral	Bilateral
5	Thalamus injury: cysts	T1/T2	No	Unilateral	Bilateral
6	Thalamus injury: gliosis	T1/T2	No	Unilateral	Bilateral
7	Enlarged third ventricle	T1/T2	No	Yes	
8	Mammillary body atrophy†	T1/T2	No	Yes	
Cerebellum subscore			0	1	2
1	Hemispheric atrophy	T1/T2/DWI	No	Unilateral	Bilateral
2	Vermian atrophy	T1/T2	No	Mild	Moderate-severe
3	Hemorrhagic lesions	T1/T2/SWI	No	Single lesion <0.5 cm	≥0.5 cm or multiple lesions
Total score (white matter + deep gray matter + cerebellum)					

ALIC, anterior limb of the internal capsule; *DWI*, diffusion-weighted imaging; *MRI*, magnetic resonance imaging; *PLIC*, posterior limb of the internal capsule; *SWI*, susceptibility-weighted imaging.
*Information about the degree of expected myelination is available at https://www.mrineonatalbrain.com, Table 4.4.
†See also **Figure 1** by Annink KV, de Vries LS, Groenendaal F, Eijsermans R, Mocking M, van Schooneveld MMJ, et al. Mammillary body atrophy and other MRI correlates of school-age outcome following neonatal hypoxic–ischemic encephalopathy. Sci Rep 2021;11:5017.

when a Bayley-III-NL was not performed.[30,31] The composite adverse outcome included cerebral palsy, epilepsy, hearing or cerebral visual impairment (diagnosed by an ophthalmologist or otolaryngologist and need for a medical device and/or additional support), or neurodevelopmental delay (Griffiths Mental Development Scales developmental quotient <88, or Bayley-III-NL motor or cognitive composite score ≤85) which could be attributed to NE. The secondary outcome included neurodevelopmental outcome at 5.5 years, which was determined for a subset of children who had reached this age with the Dutch version of the Movement Assessment Battery for Children, Second Edition, and Wechsler Preschool and Primary Scale of Intelligence, Third edition. An adverse 5.5-year outcome included cerebral palsy, epilepsy, hearing or cerebral visual impairment, or neurodevelopmental delay (Dutch version of the Movement Assessment Battery for Children, Second Edition, ≤5th percentile and/or Wechsler Preschool and Primary Scale of Intelligence, Third edition, total IQ, verbal IQ, performance IQ, or processing speed ≤85).[32,33]

Statistical Analysis

Data were analyzed using SPSS 26.0 (IBM Corp). Baseline characteristics were compared between infants with and without adverse outcomes using the χ^2 and Mann–Whitney *U* tests. Continuous variables were reported as median with IQR, as most variables were not normally distributed. Linear regression analysis of infants with a normal 18- to 24-month outcome was performed to assess correlation of biometrics with PMA and determine the equation for correction. Biometrics correlating positively with PMA were corrected using the equation "corrected value = measured value – the slope × (PMA at repeat MRI—40)" for neonatal MRI, and "corrected value = measured value – the slope × (PMA at repeat MRI—52)" for 3-month MRI. The presence of multicollinearity between the variables concerning adverse outcome was explored. Intraobserver variability and interobserver agreement were determined using Cronbach alpha values. The association between outcome and biometrics or MRI scores was analyzed using Mann–-Whitney *U* tests in univariable analysis, and logistic regression for multivariable analysis. Receiver

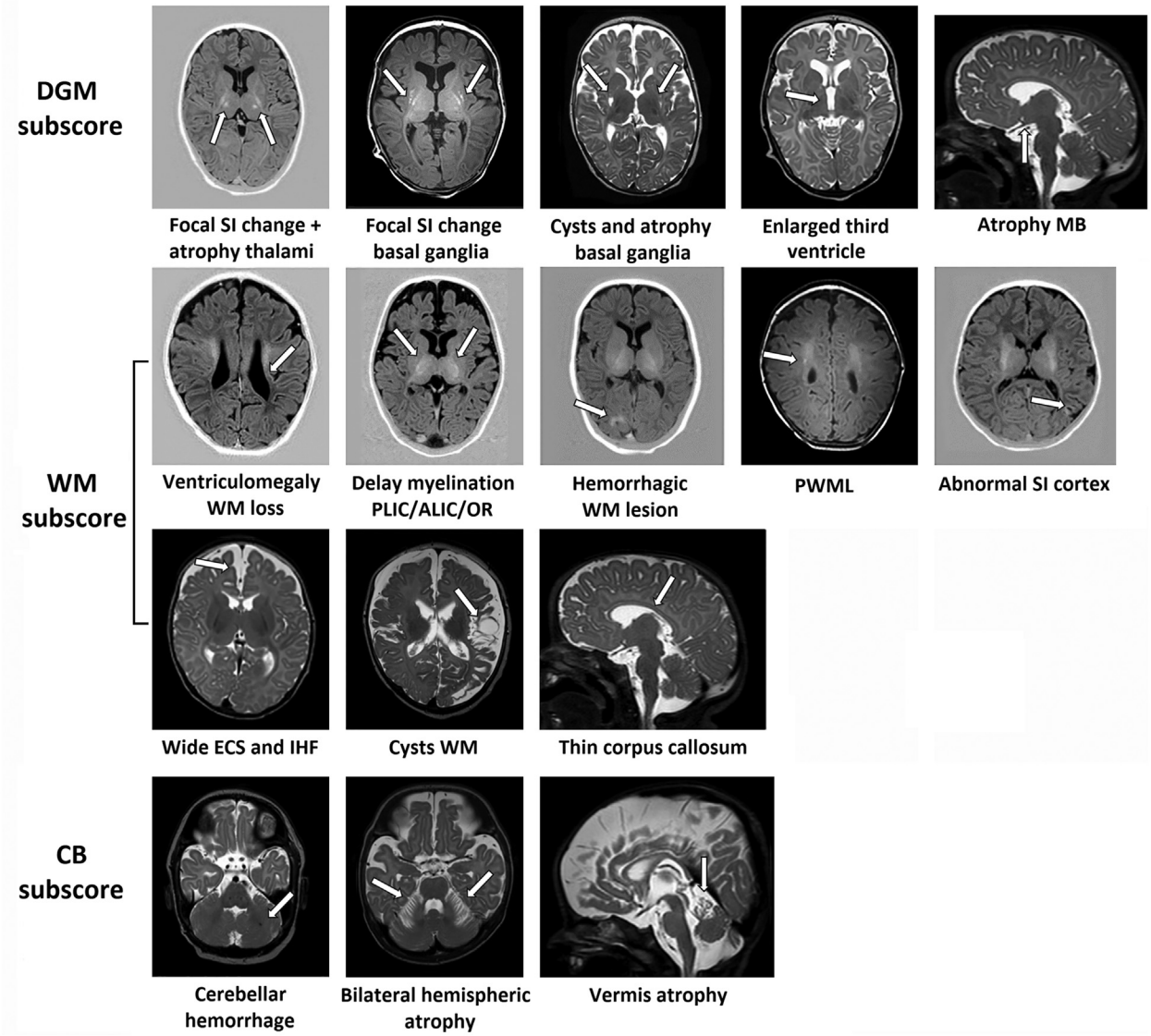


Figure 2. Examples of the items to be scored with the 3-month MRI score. *White arrows* mark the abnormalities of interest. *ALIC*, anterior limb of the internal capsule; *CB*, cerebellum; *MB*, mammillary body; *PLIC*, posterior limb of the internal capsule; *OR*, optic radiation.

operating characteristic curves were generated using GraphPad Prism 9.3.0 for biometrics and MRI scores. Predictive values were calculated per optimal cut-off value for the neonatal MRI score, and per a cut-off value of 0.50 for the multivariable 3-month model for an adverse 18- to 24-month outcome.

Results

Subjects

Of the 63 included infants, 23 (37%) had an adverse 18- to 24-month outcome. Except for outcome variables, baseline characteristics were comparable between infants with and without the composite adverse outcome at 18-24 months of age (**Table II**).

Evolution of Lesions

On neonatal MRI, 36 infants showed predominantly WM/WS injury. Of the 12 infants with mild WM/WS injury on neonatal MRI, 9 showed WM volume loss, 5 showed abnormal SI of the WM and/or cortex, and 2 showed WM cysts at 3 months. Among those with moderate-to-severe WM/WS injury (n = 20), 16 showed WM volume loss, 11 showed abnormal SI of the WM and/or cortex, and 4 showed WM cysts. Of the 20 infants with punctate WM lesions, these were still visible on 3-month MRI in 6. Of the 4 infants with PAIS, all showed focal abnormal SI of the WM and/or cortex. Three of them showed cavitation with (n = 2) and without (n = 1) WM volume loss and 1 showed WM volume loss without cavitation. Thirty-four of the 36 infants with predominantly WM/WS injury also demonstrated

Table II. Baseline characteristics of the infants with and without the composite adverse outcome at 18-24 months of age

Characteristics	Normal outcome, n = 40 Median (IQR) or No. (%)	Adverse outcome, n = 23 Median (IQR) or No. (%)	*P* value
Mode of delivery			.124
Vaginal	13 (33)	12 (52)	
Cesarean delivery	27 (68)	11 (48)	
Perinatal sentinel event	20 (50)	9 (39)	.405
Male sex	24 (60)	16 (70)	.448
Gestational age, wk	40.0 (3.2)	40.3 (2.4)	.079
Birth weight, g	3380 (815)	3420 (460)	.558
Apgar 1 min	2 (3)	2 (3)	.668
Apgar 5 min	5 (3)	5 (4)	.914
pH umbilical artery	6.98 (0.28)*	6.98 (0.26)†	.884
Base excess umbilical artery, mmol/L	−16 (11)‡	−18 (12)†	.946
Hypothermia treatment	21 (53)	7 (30)	.090
Included in pharmacologic trial§	5 (13)	1 (4)	.289
Sarnat stage			.908
Mild	2 (5)	1 (4)	
Moderate	38 (95)	22 (96)	
Severe	0 (0)	0 (0)	
Last determined Thompson score	7 (5)¶	5 (13)**	.953
Worst aEEG background pattern during admission			.256
CNV	3 (8)	4 (17)	
DNV	14 (35)	1 (4)	
BS	12 (30)	9 (39)	
CLV	0 (0)	0 (0)	
FT	2 (5)	3 (13)	
Not available	9 (23)	6 (26)	
Seizure activity on aEEG			.547
No seizures	6 (15)	6 (26)	
Suspected seizures	4 (10)	0 (0)	
Single seizure	2 (5)	0 (0)	
Repetitive seizures	17 (43)	10 (44)	
Status epilepticus	1 (3)	3 (13)	
Not available	10 (25)	4 (17)	
Field strength, neonatal MRI			**.028**
1.5 Tesla	13 (33)	14 (61)	
3.0 Tesla	27 (68)	9 (39)	
Field strength, 3-mo MRI			.097
1.5 Tesla	14 (35)	13 (57)	
3.0 Tesla	26 (65)	10 (44)	
Bayley-III-NL motor composite score††	110 (15)‡‡	88 (30)§§	.108
Bayley-III-NL cognitive composite score	105 (19)‡‡	87 (22)¶¶	**.011**
Griffiths developmental quotient††	102 (13)***	86 (13)†††	**.002**
Cerebral palsy	NA	14 (61)	
Epilepsy‡‡‡	NA	5 (22)	
Cerebral visual impairment	NA	2 (9)	
Hearing impairment associated with NE	NA	4 (17)	

aEEG, amplitude-integrated electroencephalography; *BS*, burst-suppression; *CLV*, continuous low voltage; *CNV*, continuous normal voltage; *DNV*, discontinuous normal voltage; *FT*, flat-trace; *NA*, not applicable.

Significant *P* values are set in bold.

*Data available for 33 infants.

†Data available for 13 infants.

‡Data available for 29 infants.

§Three infants were included in a trial on 2-Iminobiotin (trial registration NCT01626924 on https://trialsearch.who.int/) and 3 in a trial on neonatal allopurinol (trial registration NCT03162653).

¶Data available for 25 infants.

**Data available for 9 infants.

††Only analyzed for infants without cerebral palsy.

‡‡Data available for 22 infants.

§§Data available for 4 infants.

¶¶Data available for 5 infants.

***Data available for 17 infants.

†††Data available for 6 infants.

‡‡‡Epilepsy diagnosed with an electroencephalogram or use of maintenance antiepileptic drugs.

predominantly mild DGM abnormalities on neonatal MRI. Fourteen showed abnormal SI in the thalami (n = 13 mild, n = 1 moderate-severe), 1 had mild abnormalities in both the thalami and basal ganglia, and 1 showed mild SI abnormalities in the basal ganglia without abnormalities of the thalami. Four infants had decreased NAA and/or increased lactate on ^{1}H-MRS in the DGM without structural DGM abnormalities. The remaining infants had abnormal SI in the PLIC (n = 3), the mammillary bodies (n = 2), or a combination of abnormalities in the PLIC, mamillary bodies, brain

stem, and/or hippocampus with or without ^{1}H-MRS abnormalities (n = 9). At 3 months, 2 infants showed mild atrophy of the thalami, 1 demonstrated mild atrophy of both the basal ganglia and thalami, 22 had mammillary body atrophy, and 12 showed enlargement of the third ventricle.

Nineteen infants demonstrated abnormalities mainly involving the DGM on neonatal MRI, including the thalami in n = 13 and the basal ganglia in n = 12. Of the 8 infants with mild DGM predominant injury pattern on neonatal MRI, 2 showed abnormal SI and atrophy of the DGM on their 3-month MRI. Of those with moderate-to-severe DGM injury (n = 8), all showed abnormal DGM SI, 6 showed DGM atrophy, and 2 showed cysts in this region (Figure 3). Among the 3 infants with PAIS in the DGM, 1 showed abnormal DGM SI at 3 months, and none showed cavitation or atrophy of the DGM.

The 3 infants with near-total injury all showed WM volume loss and abnormal SI of the WM and cortex at 3 months. One had bilateral WM cysts, 1 had bilateral cysts in the basal ganglia, 2 showed DGM atrophy, and 1 showed focal abnormal SI in the thalamus.

All 12 infants in whom MRI also was performed at 18-24 months showed more extensive abnormal SI in the WM suggestive of gliosis, independent of the neonatal predominant pattern of injury (Figure 3). In 6 infants, neonatal MRI was performed beyond the first week. For 5 of these 6 infants, 3-month MRI demonstrated injury in locations that did not seem affected on neonatal MRI (thin corpus callosum n = 4, mamillary body atrophy n = 1, atrophy of the cerebellar vermis n = 1, WM volume loss and WM cyst n = 1, enlargement of the IHF and ECS n = 1).

Biometrics and Primary Outcome

The adverse outcome group had a smaller DGMA, and larger FHD on 3-month MRI (Table III). The FHD and DGMA were negatively associated (P = .002). The increase in brain width and DGMA between neonatal and 3-month MRI was smaller, and the increase of the FHD was larger in the adverse outcome group. The increase in brain width and DGMA between neonatal and 3-month MRI were positively associated (P < .001), and the difference in FHD and DGMA were negatively associated (P = .001). Cronbach alpha values for intraobserver variability for repeated FHD, DGMA, and brain width measurements were all >0.98.

MRI Scores and the Primary Outcome

Cronbach alpha for the interobserver agreement was 0.93 for the total 3-month MRI score, 0.86 for the WM subscore, and 0.59 for the DGM subscore. Linear regression showed no mutual association between the 3-month subscores. The total, WM, and DGM scores for 3-month MRI were associated with the composite adverse outcome at 18-24 months in univariable analysis (Table III). Multivariable logistic regression analysis including the 3-month DGM and WM subscores showed that both subscores were associated with the composite adverse outcome (WM subscore OR 1.1, 95% CI 1.0-1.3, DGM subscore OR 1.5, 95% CI 1.2-2.0). The neonatal MRI score was also significantly associated with the composite adverse outcome. Of the neonatal subscores, only the DGM score was associated with an adverse outcome (OR 1.4, 95% CI 1.2-1.6 without ^{1}H-MRS and 1.3, 95% CI 1.1-1.6 including ^{1}H-MRS). Receiver operating characteristic curves of the neonatal DGM subscore, DGMA measurements, and 3-month model including the WM and DGM score are presented in Figure 4. Sensitivity, specificity, positive predictive value (PPV), and NPV were 0.67, 0.93, 0.83, and 0.84 for the neonatal DGM subscore with ^{1}H-MRS, and 0.65, 0.95, 0.88, and 0.83 for the 3-month model. Among the 36 infants with neonatal WM/WS predominant pattern of injury, of whom 34 also had DGM injury, only the neonatal DGM score (P = .027) and 3-month DGM score (P = .035) were associated with adverse 18- to 24-month outcome, whereas the WM scores were not.

Therapeutic Hypothermia

Subgroup analysis of the cooled infants showed no difference in birth characteristics and the degree of encephalopathy between those with (n = 7) and those without (n = 21) the composite adverse outcome at 18-24 months. Cooled infants with an adverse outcome had a larger FHD (P = .015) and smaller DGMA (P = .005) on 3-month MRI and showed a smaller increase in DGMA between the scans (P = .010). Other biometrics were comparable.

Of the neonatal MRI scores, the total score with (P = .038) and without ^{1}H-MRS (P = .031) and the DGM subscore with (P = .009) and without ^{1}H-MRS (P = .007) were associated with the composite adverse outcome. Of the 3-month MRI score, greater total scores (P = .003) and DGM subscores (P = .001) were associated with the composite adverse outcome at 18-24 months.

Outcome at 5.5 Years of Age

Forty-four children had reached the age of 5.5 years: 11 had a normal outcome, 31 had an adverse outcome (Table IV). For 2 children, outcome was unavailable because of discharge from follow-up. Fourteen children with an adverse outcome at 5.5 years were considered normal at 18-24 months: most had neonatal WM/WS injury (n = 8). Six of these 8 infants showed mammillary body atrophy on the 3-month MRI. The others had PAIS (middle cerebral artery n = 1, DGM n = 2), mild DGM injury (n = 1), abnormal mammillary bodies (n = 1), and a sinovenous thrombosis (n = 1) on neonatal MRI. Infants with adverse 5.5-year outcomes had higher total and DGM subscores (P = .045 and P = .002, respectively), and lower cerebellum injury scores (P = .003) for neonatal MRI, and higher 3-month DGM subscores (P = .042). The WM subscores were not associated with 5.5-year outcomes. Brain width on 3-month MRI was smaller in the adverse outcome group (median 94.5 [IQR 7.3] vs 101.0 mm [IQR 6.3], P = .027). Other biometrics were comparable. Among the 26 infants with WM/WS predominant pattern of injury who had reached 5.5 years of age, the neonatal WM (P = .047) and DGM subscores (P = .003) were associated with adverse outcome. The 3-

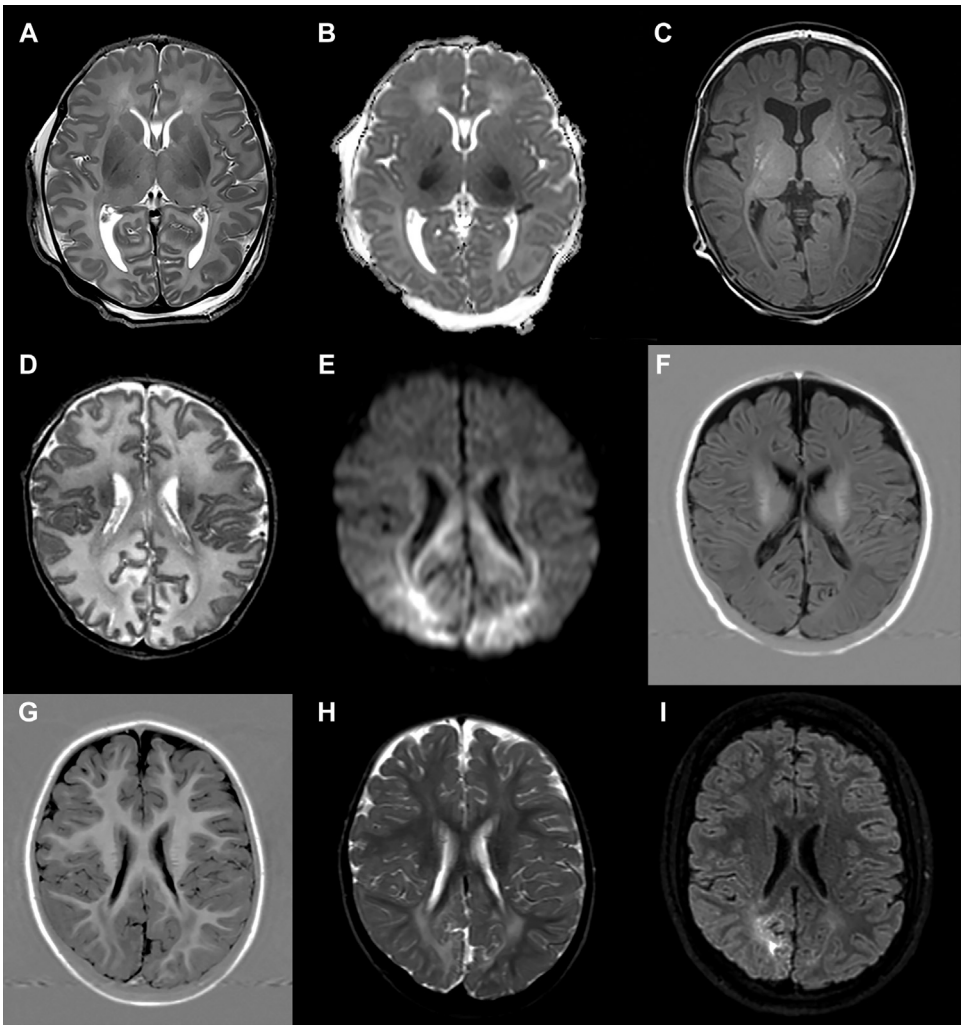


Figure 3. Example of the evolution of injury in an infant with DGM injury (*upper row*) and an infant with WM/WS injury (*middle* and *lower rows*). The infant with DGM injury showed abnormal signal intensity predominantly in the thalami and in the basal ganglia and left optic radiation on **A,** T2-weighted imaging and **B,** apparent diffusion coefficient mapping in the neonatal period (MRI day 3). At 3 months, abnormal high signal intensity and atrophy of the basal ganglia and delayed myelination of the anterior and posterior limb of the internal capsule were visible on T1-weighted imaging on **C**, whereas the thalami seemed relatively spared. As described previously, this difference could be due to spread of injury further to the basal ganglia, which was not yet visible at neonatal MRI at day 3.[22] This infant developed severe bilateral spastic cerebral palsy (GMFCS IV). The infant with WM/WS injury showed abnormal signal intensity in the occipital lobes on **D,** T2-weighted imaging and **E,** DWI on MRI performed on day 10. **F,** At 3 months, T1-weighted imaging showed widening of the IHF and ECS, as well as WM volume loss and reduced occipital cortical infolding. MRI was also performed at **G** and **H,** 16 months and **I,** at 10 years of age, which showed extensive injury involving the visual cortex on a **G,** T1-weighted; **H,** T2-weighted; **I,** and FLAIR sequence. The infant developed cerebral visual impairment and epilepsy and had an abnormal motor and PIQ score at 5.5 years of age (M-ABC <5th percentile, PIQ 68). The VIQ was normal (98). *DGM*, deep gray matter; *DWI*, diffusion-weighted imaging; *ECS*, extracerebral space; *FLAIR*, fluid-attenuated inversion recovery; *GMFCS*, Gross Motor Function Classification System; *IHF*, interhemispheric fissure; *M-ABC*, Dutch version of the Movement Assessment Battery for Children, Second Edition; *PIQ*, performance intelligence quotient; *VIQ*, verbal intelligence quotient; *WM/WS*, white matter/watershed.

month MRI subscores were not associated with adverse outcome in these infants.

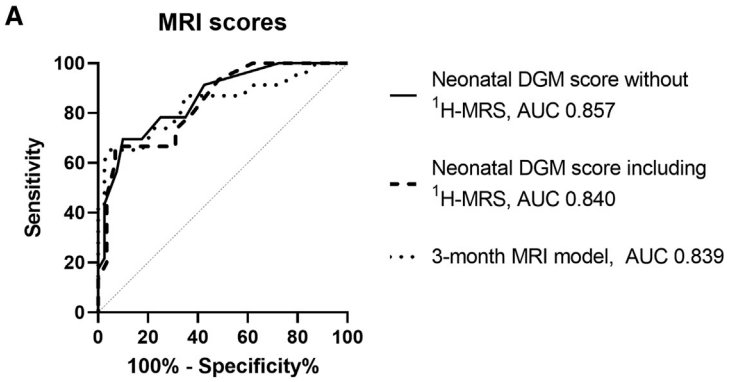
Discussion

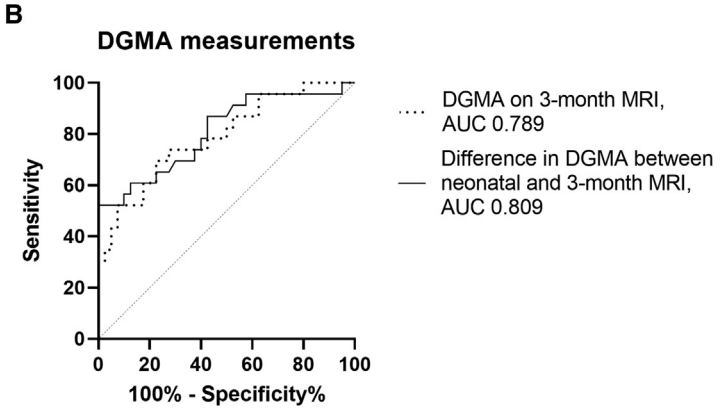
Unlike previous works, our study evaluated 3-month cranial MRI in cooled and noncooled infants with NE following perinatal asphyxia by relating qualitative findings and biometrics with neurodevelopmental outcome. We have developed a comprehensive scoring system to quantify brain injury systematically on 3-month MRI, and we have provided data on a group of infants that could serve as a reference sample to assess the effect of new neuroprotective therapies at an early stage. Our study showed that mainly DGM abnormalities on

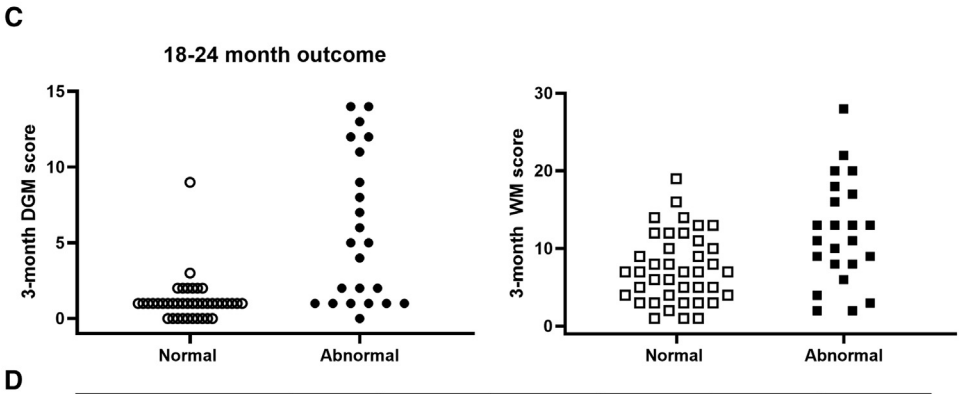
Table III. MRI biometrics and MRI scores for infants with a normal outcome vs infants with an adverse outcome at 18-24 months

Biometrics and scores	Normal outcome (n = 40) Median (IQR)	Adverse outcome (n = 23) Median (IQR)	*P* value
Biometrics on neonatal MRI			
PMA at neonatal MRI, wk	40.4 (3.2)	41.2 (2.3)	.085
Extracerebral space, mm	2.1 (1.3)	2.5 (1.0)	.407
Interhemispheric fissure, mm	1.7 (1.0)	1.8 (1.1)	.170
Ventricular-hemispheric ratio	0.3 (0.0)*	0.3 (0.0)†	.275
Frontal horn depth, mm	4.4 (1.5)‡	5.0 (2.0)†	.081
Third ventricle width, mm	3.5 (1.5)	3.7 (0.5)	.092
DGMA, mm^2§	1205 (114)	1278 (134)	.104
Brain width, mm§	86.6 (5.2)	87.7 (5.4)	.138
Brain length, mm§	106.6 (6.1)	108.0 (5.1)	.416
Cerebellar width, mm§	52.9 (3.6)	52.6 (3.6)	.674
Biometrics on 3-mo MRI			
PMA at 3-mo MRI, wk	53.2 (1.7)	54.1 (2.1)	**.016**
Extracerebral space, mm	4.1 (2.6)*	4.8 (2.7)†	.235
Interhemispheric fissure, mm	3.5 (1.9)	4.8 (3.2)†	.124
Ventricular-hemispheric ratio	0.3 (0.0)	0.3 (0.0)†	.272
Frontal horn depth, mm	6.0 (1.5)	7.6 (2.8)†	**<.001**
Third ventricle width, mm	4.9 (1.2)	4.9 (1.7)	.196
DGMA, mm^2§	1472 (105)	1340 (212)	**<.001**
Brain width, mm§	98.1 (8.9)	95.1 (8.4)	.077
Brain length, mm§	121.5 (9.0)	121.9 (10.6)	.864
Cerebellar width, mm§	69.6 (4.4)	68.0 (3.5)	.116
Difference between early and 3-mo MRI			
Weeks	12.9 (2.2)	13.3 (2.0)	.365
Extracerebral space, mm	2.4 (2.5)*	2.6 (2.8)†	.321
Interhemispheric fissure, mm	1.8 (2.1)	3.0 (3.3)†	.276
Ventricular-hemispheric ratio	0.0 (0.0)*	0.0 (0.0)†	.699
Frontal horn depth, mm	1.5 (1.5)‡	2.9 (2.0)†	**.005**
Third ventricle width, mm	1.3 (1.6)	1.2 (1.3)	.898
DGMA, mm^2	270 (142)	67 (279)	**<.001**
Brain width, mm	11.9 (8.3)	9.0 (6.8)	**.008**
Brain length, mm	16.4 (7.4)	14.4 (7.9)	.346
Cerebellar width, mm	16.5 (4.3)	15.9 (3.7)	.110
Predominant pattern of injury neonatal MRI			.088¶
Miscellaneous	4 (10)	1 (4)	
WM/WS injury			
Stroke mainly in WM/WS	3 (8)	1 (4)	
Mild WM/WS	9 (23)	3 (13)	
Moderate-to-severe WM/WS	14 (35)	6 (26)	
DGM injury			
Stroke mainly in DGM	3 (8)	0 (0)	
Mild DGM	6 (15)	2 (9)	
Moderate-severe DGM	1 (3)	7 (30)	
Near-total injury	0 (0)	3 (13)	
Neonatal MRI injury score			
Total score not including ^{1}H-MRS	11 (10)	21 (10)	**<.001**
Total score including ^{1}H-MRS	11 (12)**	19 (10)††	**.008**
WM score	7 (9)	10 (8)	.061
DGM score not including ^{1}H-MRS	2 (6)	10 (7)	**<.001**
DGM score including ^{1}H-MRS	3 (7)**	11 (9)††	**<.001**
Cerebellum score	0 (0)	0 (0)	.437
Additional injury score	0 (1)	0 (1)	.736
3-mo MRI injury score			
Total score	8 (8)	18 (10)	**<.001**
WM score	7 (7)	11 (9)	**.006**
DGM score	1 (1)	5 (10)	**<.001**
Cerebellum score	0 (0)	0 (0)	.423

Significant *P* values are set in bold.
*Data available for 39 infants.
†Data available for 22 infants.
‡Data available for 38 infants.
§Corrected for PMA.
¶Analyzed as miscellaneous vs WM/WS injury vs BGT injury.
**Data available for 29 infants.
††Data available for 15 infants.







D

	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
DGM score neonatal MRI	≥8	0.70	0.90	0.80	0.84	0.83
DGM score neonatal MRI including ¹H-MRS	≥10	0.67	0.93	0.83	0.84	0.84
3-month MRI model	>0.5	0.65	0.95	0.88	0.83	0.84
Corrected DGMA on 3-month MRI ($mm^{2)}$	<1402	0.70	0.78	0.64	0.82	0.75
Difference in DGMA between neonatal and 3-month MRI (mm^2)	<70	0.52	1.00	1.00	0.78	0.83

Figure 4. **A,** Receiver operating characteristic curves of the neonatal DGM subscore and 3-month model for the composite adverse outcome at 18-24 months; **B,** receiver operating characteristic curves of the DGMA measurements; and **C,** individual scores on the 3-month DGM subscore (*left*) and WM subscore (*right*) for infants with a normal outcome and infants with an adverse outcome at 18-24 months. **D,** Cross-tabulation analysis demonstrated that the 3-month MRI model had higher PPV but lower NPV compared with the neonatal DGM subscore.

Table IV. Outcomes and MRI scores for infants with a normal outcome at 5.5 years of age vs those with an abnormal outcome

	Normal outcome (n = 11)		Adverse outcome (n = 31)		*P* value
Outcomes and score	Available for n (%)	Median (IQR) or n (%)	Available for n (%)	Median (IQR) or n (%)	
M-ABC-2-NL total score percentile*	9 (82)	60 (63)	18 (58)	11 (32)	**.015**
WPPSI-III-NL					
Total IQ	7 (64)	105 (18)	15 (48)	94 (15)	**.016**
Verbal IQ	7 (64)	106 (24)	23 (74)	93 (27)	**.026**
Performal IQ	6 (55)	110 (11)	21 (68)	89 (30)	**.020**
Processing speed	6 (55)	103 (11)	18 (58)	76 (31)	**.003**
Adverse outcome	NA	NA			
Cerebral palsy			31 (100)	11 (35)	
M-ABC-2-NL ≤5th percentile			18 (58)	8 (26)	
Abnormal cognitive score					
Abnormal performal IQ			21 (68)	3 (10)	
Abnormal verbal IQ			23 (74)	2 (6)	
Abnormal processing speed			18 (58)	3 (10)	
Multiple domains			23 (74)	9 (29)	
Epilepsy*			30 (97)†	3 (10)	
Cerebral visual impairment			31 (100)	2 (6)	
Hearing impairment associated with NE			31 (100)	2 (6)	
Neonatal MRI injury score					
Total score not including ^{1}H-MRS	11 (100)	12 (9)	31 (100)	19 (9)	**.045**
Total score including ^{1}H-MRS	7 (64)	11 (13)	19 (61)	19 (6)	.164
White matter score	11 (100)	9 (8)	31 (100)	11 (9)	.380
DGM score not including ^{1}H-MRS	11 (100)	0 (2)	31 (100)	7 (9)	**.002**
DGM score including ^{1}H-MRS	7 (64)	1 (9)	19 (61)	8 (9)	**.032**
Cerebellum score	11 (100)	0 (4)	31 (100)	0 (0)	**.003**
Additional injury score	11 (100)	0 (1)	31 (100)	0 (1)	.493
3-mo MRI injury score					
Total score	11 (100)	10 (7)	31 (100)	14 (14)	.160
White matter score	11 (100)	8 (7)	31 (100)	11 (12)	.366
Deep gray matter score	11 (100)	1 (1)	31 (100)	2 (4)	**.042**
Cerebellum score	11 (100)	0 (0)	31 (100)	0 (0)	.460

^{1}H-MRS, proton magnetic resonance spectroscopy; *M-ABC-2-NL*, Dutch version of the Movement Assessment Battery for Children, Second Edition; *MRI*, magnetic resonance imaging; *NA*, not applicable; *WPPSI-III-NL*, Wechsler Preschool and Primary Scale of Intelligence, Third edition.
Significant *P* values are set in bold.
*Diagnosed with an electroencephalogram or use of maintenance antiepileptic drugs.
†For 1 infant with cerebral palsy and epilepsy at 2 years of age, it was not documented whether the infant still had seizures or used antiepileptic drugs at preschool age.

3-month MRI were associated with 18- to 24-month outcome. Comparing neonatal and 3-month MRI scores, the neonatal DGM score had higher sensitivity and NPV, whereas the 3-month model had higher specificity and PPV.

The association of 3-month MRI findings with neurodevelopmental outcome following NE has been demonstrated in several studies, which mainly included noncooled infants.[8-13] Only a few studies also compared MRI at 2-4 months with neonatal MRI.[8,10,12] A study from 1991 describing early (≤4 days), intermediate (2-4 weeks), and late (>1 month) MRI in 30 infants with perinatal asphyxia concluded that severe brain injury could already be recognized within the first week, but the authors did not elaborate on the additional value of late MRI.[12] In agreement with our findings, Belet et al reported that 4-month and 4-year MRI had the highest PPV for abnormal outcome, whereas neonatal MRI had the highest NPV in a study on 24 non-cooled infants with NE.[10] Another study from 1990 relating neonatal, 4-month, and 8-month MRI with neurodevelopmental outcome in 15 infants with NE due to perinatal asphyxia suggested that NE sequelae were not fully apparent before 8 months.[8] In line with these findings, our results suggest that the presence and severity of WM injury may not yet be fully visible at 3 months. Our study group has previously demonstrated that measurements of the DGMA and cerebellum were associated with 18-month outcome of infants with NE following perinatal asphyxia, of whom 3 of 29 received hypothermia.[11] In the current study mainly DGMA measurements were related to 18- to 24-month outcome, also in the subset of cooled infants.

Based on our results, the clinical utility of repeating MRI at 3 months seems limited for infants who show lesions on the neonatal MRI. The sensitivity and inter-rater agreement of the 3-month model were not as good as the neonatal DGM score,[4] which could be explained by the use of DWI for neonatal MRI, allowing easier identification of abnormalities by revealing acute ischemia.[5] The sensitivity of the neonatal score may be lower when neonatal MRI is performed beyond 10 days after birth, when pseudo-normalization of DWI abnormalities occurs.[5] Subjective judgment on the presence of BGT atrophy most likely resulted in worse agreement for the 3-month DGM score. Measurement of the DGMA on 3-month MRI allows a more objective analysis and had higher sensitivity for the composite adverse outcome but is more time-consuming and requires correction for PMA. All infants with an MRI at 18-24 months showed abnormal

SI of the WM more clearly than on 3-month MRI, especially on the FLAIR sequence. The FLAIR sequence is not yet helpful in the first months after birth, as high signal from injury cannot be distinguished from the hyperintense unmyelinated WM.[34] Our findings suggest that 3 months is too early to obtain information on myelination and gliosis. If additional information is considered valuable, it should be considered to repeat MRI in the second year, when the deep WM completes its myelination and high signal on T2 or FLAIR sequence indicates WM injury.[34]

The neonatal and 3-month DGM scores were associated with adverse 5.5-year outcomes, whereas DGMA biometrics were not. Beyond BGT abnormalities, mainly associated with adverse motor outcomes,[5] the qualitative DGM scores also contain items related to long-term cognitive outcomes (eg, mammillary body injury).[17] They may therefore be better associated with outcome at 5.5 years. The neonatal cerebellum injury score was lower in the adverse outcome group, possibly because of the small number of infants with cerebellar injury. Interestingly, one-third of the children with an adverse outcome at 5.5 years were considered normal at 18-24 months, with the majority having neonatal WM/WS injury. This supports previous data that long-term follow-up of infants who were born with perinatal asphyxia and showed neonatal MRI abnormalities is important, especially for those with WM/WS injury in whom deficits may appear at a later age.[35] Our 3-month MRI score should be validated in larger cohorts to investigate its association with long-term outcome.

Strengths of this study include the development of a comprehensive score for 3-month MRI in addition to use of biometrics to objectively measure various brain structures without special software. Neonatal MRI and outcomes were assessed using validated instruments, although different examinations to assess neurodevelopmental outcome were used. Our study is limited by the lack of a control group, as 3-month MRI is not routinely performed in infants born with perinatal asphyxia without neonatal MRI abnormalities. We, however, previously demonstrated that early neonatal MRI, performed before pseudonormalization of DWI abnormalities occurs, has good NPV, ie, almost all infants without MRI abnormalities had good 5-year outcomes.[4] Nevertheless, cognitive impairments can become apparent beyond this age.[17] Our study sample mostly consisted of infants with moderate NE, as most of those with severe NE died and therefore had no 3-month MRI. This, however, represents clinical practice, with a repeat MRI in these infants being exceptional. Our 3-month score could not be validated in another cohort, as most centers do not perform 3-month MRI, and some findings on biometrics may have become significant due to multiple comparisons. However, this is less likely as the significantly different biometrics between the normal and abnormal outcome groups were mutually associated.

Currently, there are many experimental neuroprotective treatments under development to improve the outcome of infants with perinatal asphyxia who suffer from brain injury despite cooling.[36,37] Although the clinical utility of 3-month MRI, in the presence of a neonatal MRI, seems limited, the 3-month MRI may have potential to serve as an early biomarker to assess the effect of neuroprotective strategies before neurodevelopmental outcome can be assessed. This study provides a systematic score to assess brain injury at 3 months, and data on a group of infants with brain injury despite cooling that could serve as a reference population. The value of 3-month MRI may be further improved by advanced imaging techniques, eg, diffusion tensor imaging, and 3D volumetry.[38,39]

In conclusion, quantitative and qualitative findings on 3-month MRI are associated with 18- to 24-month outcome among infants with NE following perinatal asphyxia and neonatal MRI abnormalities. Three-month MRI allows early evaluation of new neuroprotective strategies and prognostication for infants without neonatal MRI. However, its clinical utility in addition to a neonatal MRI performed within the applicable time frame of DWI is limited. Future studies should explore the association of 3-month MRI with long-term outcome and the utility of advanced imaging techniques and volumetric measurements, which may improve its value. ■

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