

Serial 1- and 2-Dimensional Cerebral MRI Measurements in Full-Term Infants after Perinatal Asphyxia

Laura G. Spring in 't Veld Linda S. de Vries Thomas Alderliesten
Manon J.N.L. Benders Floris Groenendaal

Department of Neonatology, Wilhelmina Children's Hospital/University Medical Center Utrecht, Utrecht, The Netherlands

Key Words

Perinatal asphyxia · Magnetic resonance imaging · Brain · Prediction · Neurodevelopment

Abstract

Objective: Cranial magnetic resonance imaging (MRI) is associated with neurodevelopmental outcome in full-term infants with neonatal encephalopathy (NE) following presumed perinatal asphyxia. The aim of this study is to relate 2-dimensional measurements of the basal ganglia and thalami (BGT) and cerebellum in the first week after birth and after 3 months with neurodevelopmental outcome at 18 months. **Methods:** Retrospectively, 29 full-term infants with NE following presumed perinatal asphyxia who had a cranial MRI in the first week after birth were studied serially. One- and 2-dimensional measurements were obtained and related to different patterns of brain injury, and neurodevelopmental outcome at 18 months. A Griffiths developmental quotient <85 or cerebral palsy was considered adverse. **Results:** On the first MRI, the adverse outcome group showed increased basal ganglia width (42.1 ± 0.1 vs. 40.3 ± 0.3 mm, $p < 0.001$), thalamic width (40.3 ± 0.1 vs. 39.3 ± 1.0 mm, $p <$

0.001), and basal ganglia surface ($1,230 \pm 21$ vs. $1,199 \pm 36$ mm², $p = 0.007$) compared to the favorable outcome group. In the BGT lesions group, basal ganglia width and thalamic width were increased compared to the watershed infarction group (42.1 ± 0.1 vs. 40.9 ± 0.8 mm, $p < 0.001$, and 40.3 ± 0.1 vs. 39.9 ± 0.5 mm, $p = 0.01$, respectively). On the second MRI, cerebellar width was larger in the favorable outcome group ($p = 0.025$). There was a greater increase in dimensions between both MRI time points for basal ganglia width ($p = 0.014$), basal ganglia surface ($p = 0.028$) and thalamic width ($p = 0.012$) in the favorable outcome group. **Conclusions:** One- and 2-dimensional measurements for basal ganglia surface, BGT width and cerebellar width are associated with neurodevelopmental outcome at 18 months.

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Introduction

Recent studies have shown that neonatal magnetic resonance imaging (MRI) plays an important role in the prediction of neurodevelopmental outcome, including cerebral palsy in full-term infants with neonatal enceph-

alopathy (NE) due to presumed hypoxia-ischemia [1–5]. Signal changes on MRI in several brain areas, but especially the basal ganglia and thalami (BGT), are significantly associated with an adverse neurodevelopmental outcome [5–7].

MRI at 3 months of age is sometimes used to assess the evolution of the lesions seen on the initial MRI. Cystic evolution may develop in the BGT and/or white matter, and these cysts are likely to develop in areas with very low apparent diffusion coefficient values on the neonatal MRI. More often there is no cystic evolution, but white matter atrophy with associated ventriculomegaly, and/or volume loss of the BGT on visual assessment, as has been described previously [8].

Cystic evolution in the BGT or the white matter is almost invariably associated with severe adverse neurological sequelae [9, 10]. In the absence of cystic evolution, but with visually apparent volume loss, outcome is more variable and more difficult to predict.

To the best of our knowledge, data on serial MRI in the first year after birth in surviving full-term infants with NE due to presumed hypoxic-ischemic encephalopathy are scarce [11]. One- and 2-dimensional (D) measurements on MRI have been reported in preterm infants at term equivalent age and compared with term controls, demonstrating a reduction in the bifrontal, biparietal, and transverse cerebellar diameters, and an increase in the left ventricular diameter [12].

The aim of this study was threefold: (1) to relate 1- and 2-D measurements of the BGT and cerebellum in the first week after birth with neurodevelopmental outcome at 18 months or more, (2) to relate changes in 1- and 2-D measurements of the BGT and cerebellum between birth and at 3 months of age with neurodevelopmental outcome at 18 months or more, and (3) to relate changes in 1- and 2-D measurements of the BGT and cerebellum in different patterns of injury: BGT lesions versus watershed (WS) infarction.

Subjects

This retrospective study is based on data derived from our NE database consisting of 158 infants with a cranial MRI during the first week after birth who were admitted to the level 3 neonatal intensive care unit of the Wilhelmina Children's Hospital/University Medical Center in Utrecht between July 2002 and July 2009 following perinatal asphyxia. Some of these infants have been described previously [5].

Perinatal asphyxia was defined as having at least 3 of the following criteria: fetal heart rate abnormalities, meconium-stained

amniotic fluid, delayed onset of respiration, arterial cord or early postnatal blood pH <7.1, 5-min Apgar score <7, or multiorgan failure, with subsequent development of NE during the first days after birth [1]. Following discharge from the neonatal intensive care unit, infants were seen in the follow-up clinic at 3, 9, and 18 months of age.

Fifty-eight infants were excluded because of various reasons: death (n = 24), loss to follow-up (n = 12), first MRI performed after the first week (n = 12), chromosomal abnormalities (n = 2), gestational age <36 weeks (n = 2), postmortem MRI only (n = 1), coronal angulation of MRI (n = 1), or no MRI available for review (n = 4).

Twenty-nine of the 100 survivors had a second MRI at 3 months of age and were eligible for the present study. The second MRI was performed to assess the evolution of the lesions seen on the first MRI. Out of these 29 infants, a subgroup of 19 infants with BGT lesions (n = 6) or WS (n = 13) diagnosed on the first MRI, was created for analyzing differences in several parameters between these two patterns of brain injury [11]. The other 10 infants were diagnosed as having perinatal arterial ischemic stroke without involvement of BGT (n = 6), white matter injury (n = 2), cerebral venous sinus thrombosis (n = 1), or no parenchymal lesions (n = 1). The MRI of this infant was repeated on parental request.

The ethics committee of the University Medical Center Utrecht, Utrecht, The Netherlands, stated that based on Dutch legislation the need for informed consent was waived for this study.

Methods

Without knowledge of their outcome, 2-D measurements were placed (L.G.S.i.V.) on T1- or T2-weighted MRI, located on the slice just above the superior colliculus (fig. 1).

This slice was chosen because the superior colliculus is easily recognizable and reproducible measurements can be performed. Measurements of maximum total brain length and maximum total brain width were obtained. Basal ganglia width was measured as grey matter width from left to right at the level of the transition from the anterior to posterior limb of internal capsule, and basal ganglia length was measured from the anterior to posterior transition of white to grey matter.

Thalamic width was measured from left to right, with the most lateral margin of the posterior limb of internal capsule functioning as a limit. One infant with asymmetry of the basal ganglia was not included in the study. Thereafter, the surface area of the brain at this slice and the surface of the BGT were calculated using the ellipse formula since both the brain and the basal ganglia showed an ellipsoid shape (fig. 1). The cerebellar width was also measured using T1- or T2-weighted images, looking for the largest cerebellar width. Measurements were reviewed by M.J.N.L.B., F.G. and L.S.d.V., neonatologists with more than 10 years of experience in MRI assessment.

All 29 infants were divided into 2 outcome groups by L.G.S.i.V. (reviewed by L.S.d.V.), based on outcome data of the Griffiths Mental Development Scales (GMDS) [12] at 18 months or more. At the time of the measurements, L.G.S.i.V. was unaware of the outcome data.

A favorable outcome was defined as not having any evidence of development of cerebral palsy and a developmental quotient on

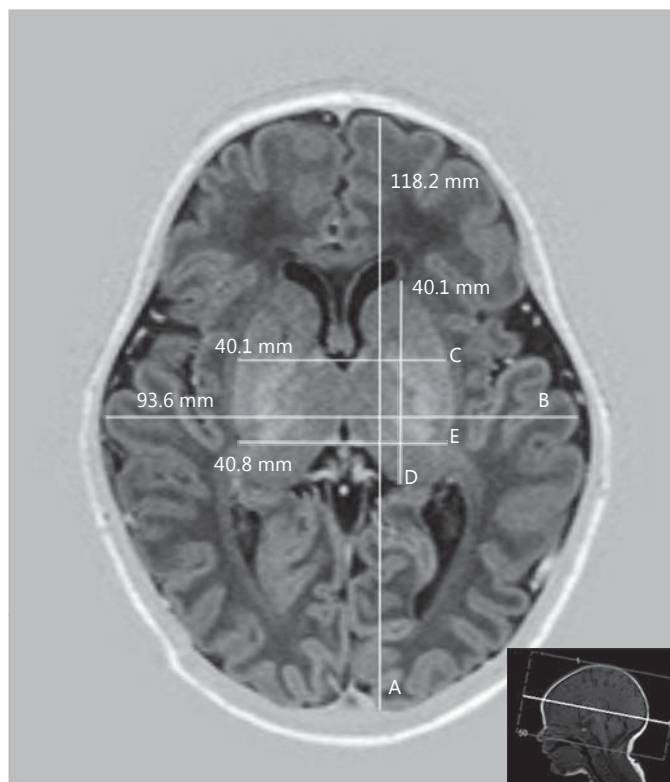


Fig. 1. 1- and 2-D measurements: total brain length (A); total brain width (B); basal ganglia width (C); basal ganglia length (D); thalamic width (E). 2-D surface area whole brain = $\pi \cdot \frac{1}{2}A \cdot \frac{1}{2}B$. Basal ganglia surface = $2 (\pi \cdot \frac{1}{4} C \cdot \frac{1}{2} D)$.

the GMDS of at least 85. Children in the adverse outcome group developed cerebral palsy and/or had a developmental quotient <85.

Statistics

Analyses were performed for the first and second MRI in 29 infants. Absolute differences were calculated between the parameters on the first and second MRI. Measurements in infants with favorable and adverse outcomes were corrected for postmenstrual age at the first MRI, using calculated growth of both outcome groups separately. No correction was used for the surface area of the brain at the slice of measurement, as infants were scanned at both time points within a narrow postmenstrual age range, and the surface area did not increase significantly within this narrow age range.

Independent sample Student *t* tests were used to compare measurements of infants with a favorable or adverse outcome, and to compare findings in the infants with BGT or WS patterns of injury. A *p* value of 0.05 was considered significant.

With a sample size of 29 infants (12 adverse outcomes, 17 favorable outcomes) a difference of 1.33 SD in basal ganglia or thalamic diameter could be demonstrated with an alpha of 0.05 and a power of 0.90.

Table 1. Baseline clinical characteristics

	Serially scanned infants		<i>p</i>
	Favorable outcome (n = 17)	Adverse outcome (n = 12)	
Gender, M/F	8/9	7/5	0.566
Gestational age, weeks	40 ¹ / ₇ ± 1 ⁴ / ₇	39 ⁵ / ₇ ± 1 ² / ₇	0.472
Birth weight, g	3,366 ± 536	3,211 ± 516	0.445
5-min Apgar score	6.9 ± 2.3	5.2 ± 3.0	0.080
Lactate ^a	12.1 ± 7.6	13.6 ± 7.0	0.650
Umbilical cord pH ^b	6.99 ± 0.20	6.99 ± 0.17	0.950
Hypothermia, n (%)	3 (21)	0	0.083
PMA 1st MRI, weeks	40 ⁶ / ₇ ± 1 ⁴ / ₇	40 ³ / ₇ ± 1 ² / ₇	0.395
PMA 2nd MRI, weeks	54 ⁰ / ₇ ± 2 ⁰ / ₇	53 ⁵ / ₇ ± 1 ⁶ / ₇	0.685

Values are expressed as mean ± SD, unless otherwise stated. PMA = Postmenstrual age. ^a Lactate is known in 86%. ^b Umbilical cord pH is known in 76%.

Results

Baseline clinical characteristics were compared between infants with favorable and adverse outcomes. There were no significant differences in gender, gestational age, birth weight, Apgar score, lactate, umbilical cord pH, and age at MRI time points. Only 3 infants in the present study had received hypothermia (table 1).

Parameters versus Outcome – First MRI

The mean basal ganglia width in the adverse outcome group was 42.1 ± 0.1 mm compared to 40.3 ± 0.3 mm in the favorable outcome group (*p* < 0.001, table 2). Basal ganglia surface area was also bigger in the adverse outcome group (*p* = 0.007, table 2). The mean thalamic width was larger in the adverse outcome group compared to the favorable outcome group (*p* < 0.001, table 2). Cerebellar width was larger in the favorable outcome group (*p* = 0.028, table 2). There were no significant differences between the favorable and adverse outcome groups for the 2-D brain surface area on one slice.

Parameters versus Outcome – Second MRI

At the second time point, a significant difference was found between the mean cerebellar width in the favorable outcome group versus the adverse outcome group (*p* = 0.025, table 2). No significant differences were noted for the 2-D brain surface area on one slice, basal ganglia surface, basal ganglia width, and thalamic width between the favorable and adverse outcome groups.

Table 2. Results: parameters versus outcome

	Favorable outcome (n = 17)	Adverse outcome (n = 12)	p
1st MRI			
BG width, mm	40.3±0.3	42.1±0.1	<0.001
Th width, mm	39.3±1.0	40.3±0.1	<0.001
CB width, mm	54.0±3.0	52.4±0.1	0.028
BG surface, mm ²	1,199±36	1,230±21	0.007
2-D surface area whole brain, mm ²	7,160±395	7,087±273	0.588
2nd MRI			
BG width, mm	46.1±3.0	44.7±3.5	0.268
Th width, mm	44.2±2.8	42.3±2.7	0.085
CB width, mm	71.0±3.4	68.0±2.9	0.025
BG surface, mm ²	1,485±112	1,370±138	0.070
2-D surface area whole brain, mm ²	9,256±922	8,791±643	0.144
Difference between 1st MRI and 2nd MRI			
BG width, mm	5.8±3.0	2.6±3.5	0.014
Th width, mm	4.9±2.9	2.0±2.7	0.012
CB width, mm	16.9±4.0	15.5±2.9	0.322
BG surface, mm ²	286±125	167±150	0.028
2-D surface area whole brain, mm ²	2,097±964	1,704±784	0.255
BG = Basal ganglia; CB = cerebellar; Th = thalamic.			

Parameters versus Outcome – Difference between First and Second MRI

The mean increase in basal ganglia width for the favorable outcome group was larger compared to the adverse outcome group ($p = 0.014$, table 2). The mean increase in basal ganglia surface was $286 \pm 125 \text{ mm}^2$ for the favorable outcome group versus $167 \pm 150 \text{ mm}^2$ for the adverse outcome group ($p = 0.028$, table 2). The increase in thalamic width was larger in the favorable outcome group than in the adverse outcome group ($p = 0.012$, table 2). Absolute differences between first and second MRI in both outcome groups were not significantly different for the 2-D brain surface area on one slice and cerebellar width.

Parameters versus Pattern of Injury on the First MRI

There were significant differences in basal ganglia width and basal ganglia surface area between the BGT group and the WS group. Basal ganglia width was larger in infants with the BGT pattern of injury than in infants with the WS pattern of injury ($p < 0.001$, table 3). Thalamic width was also larger in the BGT group compared

Table 3. Results: parameters versus pattern of injury

	BG lesion (n = 6)	WS infarction (n = 13)	p
1st MRI			
BG width, mm	42.1±0.1	40.9±0.8	<0.001
Th width, mm	40.3±0.1	39.9±0.5	0.010
CB width, mm	52.4±0.2	54.2±1.5	0.001
BG surface, mm ²	1,227±22	1,222±21	0.649
2-D surface area whole brain, mm ²	7,049±298	7,294±210	0.053
2nd MRI			
BG width, mm	43.8±4.3	46.1±3.6	0.240
Th width, mm	42.0±3.6	43.6±2.9	0.300
CB width, mm	67.7±2.4	70.2±4.2	0.190
BG surface, mm ²	1,386±150	1,434±125	0.473
2-D surface area whole brain, mm ²	9,124±628	8,805±881	0.438
Difference between 1st MRI and 2nd MRI			
BG width, mm	1.6±4.3	5.1±3.6	0.080
Th width, mm	1.7±3.6	3.8±3.0	0.211
CB width, mm	15.4±2.5	16.0±4.3	0.728
BG surface, mm ²	159±160	212±129	0.452
2-D surface area whole brain, mm ²	2,076±690	1,511±851	0.175
BG = Basal ganglia; CB = cerebellar; Th = thalamic.			

to the WS group ($p = 0.01$, table 3). Cerebellar width was bigger in the group with the WS pattern of injury ($p = 0.001$, table 3). Cerebellar changes could not be identified on any of the images. There were no significant differences for the 2-D brain surface area on one slice and basal ganglia surface between both patterns of injury at first MRI.

Parameters versus Pattern of Injury on the Second MRI

There were no significant differences in parameters between the BGT group and the WS group on the second MRI.

Parameters versus Pattern of Injury: Difference between First and Second MRI

Infants with a BGT pattern of injury had a smaller increase between both MRIs compared to infants with a WS pattern of injury, although this did not reach significance ($p = 0.08$). Other differences in parameters of both MRIs were not significantly different between both patterns of injury.

All 6 infants with injury of the BGT, and 6 of the 21 infants with white matter involvement or stroke ($n = 9$) or WS lesions ($n = 13$) had an adverse neurodevelopmental outcome. The 2 infants with cerebral venous sinus thrombosis or no visible lesions had a normal outcome.

Discussion

2-D MRI measurements were performed in a group of infants with NE due to presumed hypoxic-ischemic encephalopathy during the first week after birth, and at 3 months.

On the first MRI, the mean thalamic width, the mean basal ganglia width, and surface area were significantly larger in the adverse outcome group compared with the favorable outcome group. Mean BGT width was also larger in the BGT pattern of injury group compared to the WS pattern of injury group, most likely due to edema.

The significant differences between both MRIs can be explained by the increase in basal ganglia growth in the favorable outcome group and the initial decrease in basal ganglia width due to resolution of edema, followed by restricted growth in the adverse outcome group.

Injury to the BGT is considered to be due to acute asphyxia, often following an acute sentinel event, while WS injury is considered to be due to prolonged partial asphyxia [1, 7, 13]. Swelling of the basal ganglia can be seen on visual assessment, but has to the best of our knowledge not been assessed with 1- or 2-D measurements. The increased BGT measures were indeed related to an adverse outcome. All infants with changes of the BGT on diffusion-weighted MRI had an adverse outcome. The absolute difference in growth between both scans was also significant, suggesting that the absolute difference of basal ganglia surface between the first and second MRI is useful for the prediction of outcome. The same holds true for thalamic width and basal ganglia width. Significant differences in growth can occur between the first and second MRI, suggesting sustained effects of perinatal asphyxia.

The total number of infants receiving hypothermia in the present study was low since hypothermia was introduced in 2008 at the end of the inclusion period of the present study [14]. It is possible that those receiving hypothermia had reduced swelling of the deep grey nuclei. Since the MRI in these 3 infants with therapeutic hypothermia was performed after rewarming, we do not think that the findings have a major impact on our results.

The last parameter which was assessed was the cerebellar width. There was a positive association between mea-

surements performed on the first and second MRI and subsequent outcome, suggesting better growth in the favorable outcome group. Involvement of the cerebellum after perinatal asphyxia has been described previously with involvement of Purkinje cells and neurons of the granule cell layer, and volume loss later in life [11]. At present it is unknown whether cerebellar growth disturbance is the result of primary lesions in the cerebellum or whether it represents secondary atrophy or degeneration related to supratentorial brain damage [15, 16].

The present study focused on surviving infants after severe perinatal asphyxia. In these infants, prediction of neuromotor development may be difficult, and simple tools are urgently needed. The strength of this study is that sequential MRIs are not often performed and that the effect of brain injury on early growth has not been assessed so far. The use of 1- or 2-D measurements is easy to perform without the need for special software [12]. Measurements can be performed during or soon after completion of the examination and information is readily available.

The present study has some limitations which need to be addressed. The study population is not totally representative for all infants with perinatal asphyxia because some infants with perinatal asphyxia and an adverse outcome did not have an early MRI as they were too unstable to be transported to the scanner during the first week after birth. Previous studies in our institute have shown that all infants who died had abnormalities in the BGT on both cranial ultrasound scans as well as on postmortem examinations [16]. Inclusion of the infants who died who represent the infants with the most severe forms of perinatal asphyxia would probably not have changed the outcome of the present study. In addition, the difference in the BGT width and surface was relatively small between the infants with a favorable and adverse outcome. Again, the most severely affected infants did not survive to be included in the group who had a second MRI. Future studies in a larger group of infants who were treated with therapeutic hypothermia are needed to validate our findings.

Another limitation is that we were unable to compare infants with injury with healthy infants because at present we are not allowed to perform MRI on healthy infants. However, we were able to analyze and compare infants with normal MRI or with different patterns of injury on their first MRI, such as WS pattern of injury, BGT pattern of injury, and perinatal arterial ischemic stroke without involvement of the BGT [10].

The number of infants with longitudinal measurements was limited since a decision to perform a second MRI was based on the presence of abnormalities seen on

the first MRI. Nevertheless, significant differences between good and poor outcome groups could be demonstrated even in this relatively small group.

In conclusion, performing 1- and 2-D measurements of basal ganglia width, basal ganglia surface, thalamic width, and cerebellar width in the first week after perinatal asphyxia at term age and preferably in combination with measurements at 3 months might aid in the prognosis of early neurodevelopmental outcome.

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Disclosure Statement

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