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CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

Early MRI in neonatal hypoxic-ischaemic encephalopathy treated with hypothermia: prognostic role at 2-year follow-up

Valérie Charon^{1,2}, Maïa Proisy¹, Gilles Bretaudeau³, Bertrand Bruneau¹, Patrick Pladys⁴, Alain Beuchée⁴, Gladys Burnouf-Rose⁵, Jean-Christophe Ferré⁶, Céline Rozel¹

Corresponding Author : Valérie Charon

va.charon@gmail.com; valerie.charon@chu-angers.fr

¹ CHU Rennes, Department of Paediatric Radiology, Hôpital Sud, 16 Boulevard de Bulgarie
35200 Rennes, France

² Permanent Adress : CHU Angers, Department of Paediatric Radiology, 4 rue Larrey,
49100 Angers, France

³ CHU Rennes, Paediatrics department, Centre d'Action Médico-Sociale Précoce, Hôpital
Pontchaillou, 2 rue Henri le Guilloux,
35000 Rennes, France

⁴ CHU Rennes, Paediatrics department, Neonatology and CIC 1414, Hôpital Sud, 16 Boulevard de
Bulgarie
35200 Rennes, France

⁵ CHU Rennes, Paediatrics department, Centre Hospitalier Public du Cotentin, 2 Rue Aristide Briand,
50130 Cherbourg-Octeville, France

⁶ CHU Rennes, Department of Neuroradiology, Hôpital Pontchaillou, 2 rue Henri le Guilloux,
35000 Rennes, France

Early MRI in neonatal hypoxic-ischaemic encephalopathy treated with hypothermia: prognostic role at 2-year follow-up

ABSTRACT

The prognostic role of early MRI (≤ 6 days of life) is still uncertain in hypoxic-ischaemic encephalopathy (HIE) treated with hypothermia.

Objective - To compare the prognostic value of early (≤ 6 days) and late MRIs (≥ 7 days) in predicting adverse outcome at 2 years old in asphyxiated term neonates treated with hypothermia.

Methods - This retrospective study included all asphyxiated neonates eligible for hypothermia treatment between November 2009 and July 2012. Two MRI scans were performed at a median age of day 4 (early MRI) and day 11 (late MRI). Two radiologists analysed independently each MRI. Imaging was classified as normal/subnormal or abnormal, using a visual analysis. Apparent diffusion coefficient (ADC) values were measured within predefined areas and posterior limb of internal capsule (PLIC) signal intensity was analysed. Neurodevelopmental outcome was assessed at 18-41 months (median age 24 months) as favourable or adverse.

Results - Of the 38 neonates followed up, 8 had an adverse outcome, all related to abnormal MRIs. Twenty-nine neonates had both MRIs sequentially. Both early and late MRIs yielded 100% sensitivity for adverse outcome by using the visual analysis. Early MRI had a higher specificity than late MRI (96.3% versus 89.3%). ADC measurements did not provide further information than visual analysis. PLIC signal abnormalities were a good predictor of adverse outcome on both MRIs.

Conclusion - Early MRI (≤ 6 days) was a good predictor of neurodevelopmental outcome at 2 years old. It could reliably guide intensive care decisions after the end of hypothermia treatment.

HIGHLIGHTS

1
2 Early (≤ 6 days) and later MRIs were both good adverse outcome predictors in HIE
3
4 Both MRIs had 100% sensitivity for adverse outcome
5
6 Early MRI had higher specificity and positive predictive value than late MRI
7
8 Early MRI could reliably help parents and neonatologists with intensive care decisions
9

KEYWORDS

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13 Neonates - Hypoxia-Ischaemia, Brain - Diffusion Magnetic Resonance Imaging -
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15 Hypothermia, Induced - Patient Outcome Assessment
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ABBREVIATIONS

21
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23 HIE Hypoxic-Ischaemic Encephalopathy
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25 MRI Magnetic Resonance Imaging
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27 ADC Apparent Diffusion Coefficient
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29 PLIC Posterior Limb of Internal Capsule
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31 RBL Revised Brunet-Lezine
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33 GMFCS Gross Motor Function Classification System
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35 DQ Developmental Quotient
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37 DWI Diffusion Weighted Imaging
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39 PPWMI Punctate Periventricular White Matter Injuries
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41 ROI Region Of Interest
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43 ROC Receiver Operating Characteristic
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45 AUC Area Under Curve
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47 OR Odds Ratio
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INTRODUCTION

Hypoxic-ischaemic encephalopathy (HIE) remains a major cause of term newborn death and neurological disability [1]. In neonates with moderate to severe HIE, whole-body hypothermia reduces mortality without increasing major neurodevelopmental disability in survivors at 18 months of age [2]. Clinical determination of prognosis was shown to be more difficult after hypothermia, particularly in the first four days of life [3]. Previous studies demonstrated that hypothermia treatment did not alter the good predictive value of magnetic resonance imaging (MRI) at 2 years of age, when performed in the first month of life [4–6].

Recent studies demonstrated that early MRI (performed in the first week of life) could reliably predict the extent and severity of brain injury observed on later MRI (performed after day 7, considering the first day of life as day 1) in asphyxiated neonates treated with hypothermia [7–11]. Nevertheless, to our knowledge, the prognostic value of early and late MRI had not been compared in these neonates. Early reliable imaging assessment of brain injury with a good prognostic value could help neonatologists and parents with intensive care decisions after the end of hypothermia treatment. We worked on the assumption that the prognostic value of early and late MRI would be similar.

The primary objective of this study was to compare the prognostic value of early and late MRI for adverse outcome at 2 years of age in neonates suffering from HIE treated with whole-body hypothermia. The secondary objectives were to assess the prognostic value of apparent diffusion coefficient (ADC) measurements within predefined brain areas and the prognostic value of posterior limb of internal capsule (PLIC) signal abnormalities.

MATERIALS AND METHODS

Patients

This retrospective study was approved by the local Ethics Committee. All parents signed a treatment authorization form and gave consent for imaging.

Consecutive neonates presenting with moderate or severe HIE in the neonatal intensive care unit of our university hospital between November 2009 and July 2012, and who were eligible for whole-body hypothermia based on the criteria of the French Society of Neonatology, were included (Table 1) [12]. The exclusion criteria were associated conditions that could influence outcome (major congenital abnormalities, genetic anomalies with neurodevelopmental retardation) and neonatal stroke.

Hypothermia was to be induced within the first 6 hours after birth and continued for 72 hours, with a target temperature between 33 and 34°C.

Neurodevelopmental outcome

All surviving neonates were evaluated by an experienced paediatric neurologist (X.X.) between 18 and 41 months and given a detailed neurodevelopmental examination. Neurodevelopmental outcome was assessed using the Revised Brunet-Lezine (RBL) scale whenever possible and the GMFCS (Gross Motor Function Classification System). The RBL scale is an early childhood psychomotor development scale covering four areas of neurodevelopment: movement and posture, coordination, language, and sociability. Four subscores can be calculated for each neurodevelopmental area and yield a global developmental quotient (DQ). This scale can be used for children aged from 2 to 30 months [14]. After 30 months, the RBL scale could not be used and the neurodevelopmental assessment was based on a detailed neurological assessment and GMFCS for motor outcome.

Favourable outcome was defined as either a normal neurological assessment (global DQ>85 when available, no cerebral palsy, no impact on day-to-day living) or mild to moderate neurological impairment (global DQ=70-85, and/or GMFCS level I to II, low impact on day-to-day living). Adverse outcome was defined as death or major disability (global DQ<70, and/or GMFCS level III to V, and/or significant impact on day-to-day living).

MRI acquisition

The MRI scans were performed as close as possible to day 4, on completion of hypothermia (early MRI), and day 11 (late MRI).

MR imaging was performed on a 1.5T whole-body system (Magnetom Symphony, Siemens Healthcare, Erlangen, Germany).

The imaging protocol included the following sequences: three-dimensional T1-weighted gradient echo (repetition time (TR)/echo time (TE)/inversion time (TI), 2040/3.9/1100 ms, slice thickness 1 mm) or T1-weighted spin echo in the axial, sagittal and coronal planes (TR/TE, 446-627/16-25 ms, slice thickness 4 mm), T2-weighted turbo spin-echo in the axial, sagittal and coronal planes (TR/TE, 4600-6490/90-103 ms, slice thickness 4 mm), and echo-planar-based diffusion-weighted imaging (DWI) (TR/TE, 2900-4000/81-99 ms, b values of 0 and 1000s/mm², slice thickness 5 mm) with automatically generated ADC maps.

Two different receive-only coils were used depending on neonate weight or whether the neonate was ventilated: knee or head coils. The knee coil did not enable three-dimensional imaging.

Image analysis

Two experienced paediatric radiologists (X.X. and X.X., 6 and 13 years' experience) independently assessed MR images using OsiriX® software (Pixmeo, Geneva, Switzerland). Early and late MRIs were assessed independently. The reviewers were blinded to the clinical details and outcome of the neonates but knew the age at the time of MRI. The differences were then resolved by consensus between the two reviewers.

Visual analysis of brain injury

Assessment of brain injury was based on a previously described simplified classification (Appendix) [11]. It distinguished normal/subnormal MR images including normal MRI, punctate periventricular white matter injuries (PPWMI) and watershed pattern with a Watershed (W) score ≤ 2 on the scoring system described by Barkovich et al. (single infarction or abnormal signal in anterior or posterior watershed white matter) [15], and abnormal MRI including watershed pattern with W score > 2 , central or diffuse patterns. Interobserver agreement is excellent (100%) according to this classification [11].

ADC measurements

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2 ADC measurements were performed bilaterally in 8 brain regions on ADC maps by a
3 paediatric radiologist (X.X.) using OsiriX® software (Pixmeo, Geneva, Switzerland) (Figure
4 1).
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9 Regions of interest (ROIs) were placed in the middle third of the PLIC, anterolateral
10 thalami, lentiform nuclei in the putamen, head of caudate nuclei, frontal and parietal-occipital
11 white matter at the level of the basal ganglia, semi-oval centres and cerebral peduncles in the
12 brain stem. These regions were chosen for their propensity to ischaemic damage with a
13 hypoxic injury [16,17]. The area of the regions of interest was 12-14mm² (circular ROIs),
14 except in the PLIC where it was 4-6mm² (square ROIs). The mean ADC values of the right
15 and left side were averaged for further analysis.
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Analysis of PLIC signal abnormalities

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23 We analysed changes in PLIC signal intensity as it is known to be a good predictor of
24 unfavourable outcome and brain injury on late imaging [18]. PLIC signal intensity was
25 considered as normal, equivocal or abnormal on the T1- and T2-weighted images and on
26 DWI, according to the same criteria as those described by Rutherford et al., with PLIC
27 hyperintensity on the DWI considered as an additional abnormal aspect.
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34 As normal signal intensity within the PLIC is related to its degree of myelination, we
35 focused on neonates with a corrected gestational age of over 40 weeks at the time of imaging
36 [18].
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Statistical analysis

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41 Data were analysed using MedCalc statistical software (version 12.5, Ostend, Belgium).
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43 Clinical and biological features were compared between groups by Fisher's exact test for
44 categorical data, and Mann-Whitney U test for continuous data.
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49 The relationship between the results of each MRI on visual analysis and neurological
50 outcome was assessed by Fisher's exact test. We calculated the predictive values for adverse
51 outcome at 2 years of age for each MRI among all the neonates with available follow-up data
52 and among neonates who had undergone both early and late MRIs sequentially. Predictive
53 values were provided with 95% CIs.
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58 The ability of ADC measurements on early MRI in predicting adverse outcome at 2
59 years of age was assessed using receiver operating characteristic (ROC) curves. The results
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2 were presented as areas under curves (AUCs) and odds ratios (ORs) with 95% confidence
3 intervals (CIs) using logistic regression.
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5 Finally, we calculated the predictive values for adverse outcome at 2 years of age for
6 PLIC signal abnormalities on both MRIs.
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8 We considered $p < 0.05$ as indicating a significant difference.
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10 11 12 13 **RESULTS**

14 Fifty neonates were treated with hypothermia for HIE between November 2009 and July 2012
15 (Figure 2).
16

17 Seven neonates were excluded. Five neonates were lost to follow-up before 18 months
18 of age (11.6%). Among these cases, one had abnormal early and late MRIs. The others had
19 normal readings or PPWMI on early and/or late MRIs.
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21 22 23 24 25 26 27 28 **Neonates' characteristics and outcome**

29 The mean gestational age of the 38 included neonates was 39 weeks and 4 days (range 36-
30 41+6). Thirty-two early MRIs were performed at a median age of day 4 (range 3-6), and 35
31 late MRIs at a median age of day 11 (range 7-21). Twenty-nine neonates underwent both
32 MRIs (76.3%).
33

34 Thirty neonates had a favourable outcome and 8 neonates had an adverse outcome (Figure 2).
35

36 Neonates with an adverse outcome had a significantly higher birth weight, but lower
37 cord pH level than those with a favourable outcome (Table 2). There was no difference in
38 other criteria of asphyxia between the two groups.
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40 Seven surviving neonates could not be assessed with the RBL scale; they were yet
41 evaluated by GMFCS. All of them had a favourable outcome.
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Prognostic value of early and late MRIs' visual analysis in predicting adverse outcome

Results of early and late MRI in each outcome group

The results of MRI, particularly the patterns of injury, were significantly different in the two outcome groups for both MRIs (Table 3).

In the adverse outcome group, all the neonates had abnormal MRIs with central or diffuse injuries on both early and late imaging.

In the favourable outcome group, only one neonate had an abnormal early MRI with diffuse injuries. His late MRI was also abnormal (Figure 3).

Late MRI was abnormal for two other neonates with a favourable outcome. They had moderate central injuries with mild signal abnormalities in the thalami and/or lentiform nuclei, which were not visible on early MRI performed at day 5. The neurological assessment was normal for one of these neonates at 23.3 months (DQ = 100). The second neonate had a normal motor development but a moderate language delay and some behavioral disorders with autism spectrum disorders, corresponding to a mild neurological impairment. He was assessed at 24,1 months, but as he did not cooperate for examination, we could not obtain a developmental quotient (Figure 4).

Four other neonates had mild to moderate neurological impairments, but their MRIs were normal/subnormal. The patterns of injury in neonates with mild to moderate neurological impairment were not significantly different from those with normal neurological assessment as determined by Fisher's exact test (not shown).

Prognostic value of abnormal early and late MRIs in predicting adverse outcome at 2 years of age

Early and late MRIs were both good predictors of outcome with 100% sensitivity and negative predictive value (Table 4).

Specificity and positive predictive value were lower than sensitivity and negative predictive value but remained good. Among all neonates with available follow-up data, they were slightly higher for early MRI (respectively 96.3% and 83.3%) than for late MRI (89.3% and 70%). Similarly, among the 29 neonates who had undergone both MRIs sequentially, the specificity and positive predictive value were slightly higher for early MRI (96% and 80%) than for late MRI (88% and 57.1%).

ADC measurements on early MRI

ADC measurements were good predictors of outcome on early MRI, according to the ROC analysis presented in Table 5. The best predictors of neurological outcome with the highest AUCs were ADC values within the posterior white matter, semi-oval centres and PLIC.

Both neonates who had normal early MRI and moderate central injuries on late MRI had ADC values above the cut-off value within the lentiform nuclei ($1.08 \times 10^{-9}/\text{mm}^2/\text{s}$ and $1.07 \times 10^{-9}/\text{mm}^2/\text{s}$), and likewise in the thalami ($1.18 \times 10^{-9}/\text{mm}^2/\text{s}$ and $1.16 \times 10^{-9}/\text{mm}^2/\text{s}$).

The neonate with diffuse injuries on both MRIs and a favourable outcome had ADC values below the cut-off value in all regions except the thalami ($0.92 \times 10^{-9}/\text{mm}^2/\text{s}$ within the thalami; $0.82 \times 10^{-9}/\text{mm}^2/\text{s}$ within the PLIC; $0.95 \times 10^{-9}/\text{mm}^2/\text{s}$ within the lentiform nuclei; $1.24 \times 10^{-9}/\text{mm}^2/\text{s}$ within frontal white matter; $1.03 \times 10^{-9}/\text{mm}^2/\text{s}$ within posterior white matter; $0.95 \times 10^{-9}/\text{mm}^2/\text{s}$ within the semi ovale center).

Abnormal signal intensity within the PLIC and outcome

Abnormal signal intensity within the PLIC was a good predictor of outcome for neonates with a corrected gestational age of over 40 weeks at the time of imaging.

PLIC signal abnormalities on late MRI predicted an adverse outcome with 100% sensitivity (95% CI [54-100]) and 100% specificity (95% CI [84.4-100]). For early MRI, sensitivity was also excellent (100% with 95% CI [47.9-100]), but specificity was lower (80% with 95% CI [51.9-95.4]). Three neonates in the favourable outcome group had an abnormal or equivocal PLIC appearance on early MRI on T1-weighted images. One of them showed also high intensity on DWI. However, ADC values within the PLIC were higher than $0.96 \times 10^{-9}/\text{mm}^2/\text{s}$ in the three cases. Late MRI with similar imaging parameters was performed for two of these neonates, in which PLIC signal intensity was normal.

PLIC signal intensity was normal on both MRIs for the neonates with abnormal early and/or late imaging and a favourable outcome.

DISCUSSION

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3 The results from this study demonstrated that early and late MRI were both good predictors of
4 death or major disability at 2 years of age, with 100% sensitivity. Early MRI offered better
5 specificity than late MRI. ADC measurements and an abnormal PLIC appearance were also
6 good predictors of adverse outcome on early MRI. These results are relevant because the
7 availability of early reliable prognostic information is important to help neonatologists and
8 parents with intensive care decisions after the end of hypothermia treatment.
9

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11 We reported excellent 100% sensitivity and negative predictive values, and good
12 specificity and positive predictive values (96.3% and 83.3% for early MRI; 89.3% and 70%
13 for late MRI) for both MRIs using the simplified classification. Previous studies reported
14 results similar to ours in neonates treated with hypothermia, but with more variation in MRI
15 timing (MRI performed in the first month of life) [4,6]. They also found excellent sensitivity
16 (88-90%) and negative predictive value (91%), as well as lower specificity (65-82%) and
17 positive predictive value (62-76%).
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19
20 In our study, the lower specificity of MRI was due to one case of diffuse brain injury
21 visible on both MRIs and two cases of moderate central injuries visible on late MRI only,
22 with an unexpected favourable outcome. Central injuries and more extensive or diffuse
23 injuries are known to be associated with a poor prognosis with or without hypothermia
24 treatment; but some moderate central injuries and, more rarely, diffuse injuries have been
25 observed in neonates with a normal neurodevelopmental outcome [4–6,19–25].
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28 Some studies suggested that early MRI, and particularly DWI, could underestimate
29 brain lesions [26–29]. We actually observed two cases with normal early MRI, but central
30 injuries on late MRI, yet associated with a good prognosis. One of these neonates had yet a
31 moderate language delay and some behavioural disorders, and need a close follow-up by
32 paediatric neurologist. It could be of great importance to detect this kind of subtle brain
33 injuries on a late MRI systematically performed when early MRI is normal, in order to adapt
34 the neurodevelopmental follow up during the first years of life.
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37 Surprisingly, we observed two other cases with similar moderate central injuries visible on
38 late imaging, with an adverse outcome. However, they both had abnormal early MRIs with
39 the injuries visible to the same or a greater extent on DWI. These observations support the
40 idea that early MRI is a good predictor of outcome, and in these cases was a better predictor
41 than late MRI.
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2 The strength of our study lies in the sequential performance of early and late MRI for
3 a large number of the neonates included (76.3%). Among the 29 neonates who had both MRIs
4 and among all the neonates followed up (38 neonates), we reported similar good predictive
5 values for both MRIs. It was interesting to focus on neonates who had undergone sequential
6 early and late MRIs. Indeed, the predictive values of each MRI were more comparable as they
7 involved the same population.
8

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10 To our knowledge, no previous article has compared the predictive values of early and late
11 MRIs for death or severe neurological impairment at 2 years of age including so many
12 patients treated with hypothermia. In this study, we confirmed that early MRI had a predictive
13 value at least as good as late MRI, as was expected given the excellent agreement between
14 early and late MRIs [8–11]. Our results were inconsistent with the results of a meta-analysis
15 which suggested that the discriminatory power of late MRI (days 8–30) was higher than that
16 of early MRI (days 1–7), with late MRI showing higher sensitivity (99%) than early MRI
17 (85%) [30]. However, early MRI assessment was based on studies relating to non-cooled
18 neonates who underwent only one MRI, with a small number of patients (≤ 26 neonates) and
19 a generally shorter follow-up interval (12 months).
20

21
22 Focusing on the selected area, the ADC values of early MRI were consistent with the
23 outcome. The highest AUCs were obtained for ADC values within the posterior white matter,
24 semi-oval centres and PLIC, with excellent sensitivity but lower specificity for most of the
25 areas. Previous studies, which mainly focused on non-cooled neonates, demonstrated higher
26 specificity of ADC measurements, particularly in the basal ganglia and PLIC [17,21,23,31–
27 34].
28

29
30 In our study, the ADC measurements added little to the visual analysis as a prognostic tool.
31 The only case with abnormal early MRI and a favourable outcome had a lowered ADC in all
32 areas except for the thalami, which confirmed the visual impression of reduced diffusivity.
33 ADC was not reduced in the thalami because ADC measurements concerned the anterolateral
34 thalami, whereas the posterior part of the thalami was affected on DWI.
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36
37 Several cut-off values of ADC with 100% positive predictive value of poor outcome have
38 been suggested in the literature mainly in the lentiform nuclei and PLIC [17,33–35]. With all
39 these cut-off values, the positive predictive value of ADC remained low in our study. This
40 highlights the poor inter-scanner ADC quantification reproducibility.
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43 However, these studies mostly concerned non-cooled neonates. One limitation to the
44 interpretation of our results regarding the prognostic value of ADC measurements was the
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1 performance of early MRI during hypothermia for 4 neonates. ADC values depend on
2 temperature (2.4% per 1°C change), thus they would be expected to be slightly lower in
3 neonates during hypothermia (around 8.4% additional decrease if whole-body temperature is
4 maintained at 33.5°C) [36]. This would slightly change our results but would not change the
5 conclusions to any great extent.
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8 We did not assess interobserver reproducibility for ADC measurements in this study, but a
9 previous study reported excellent interobserver agreement of 0.9 [26].
10

11
12 Finally, we showed that PLIC signal abnormalities were a good predictor of adverse
13 outcome on both MRIs in neonates with a corrected gestational age of over 40 weeks. On late
14 MRI, we found 100% specificity, which was consistent with the Rutherford et al. results [18].
15 On early MRI, PLIC signal abnormalities were slightly less efficient in predicting outcome,
16 with lower specificity, since 3 neonates had an isolated equivocal or abnormal PLIC aspect on
17 early imaging and a favourable outcome. We assume that this was due to PLIC isolated
18 myelination delay, since ADC was not reduced and in two cases the PLIC signal intensity
19 normalized on late MRI. The high intensity within the PLIC on early DWI in one neonate
20 might be due to an anisotropy artefact, as the ADC was not lowered.
21

22 It was previously suggested that PLIC signal abnormalities on T1-weighted images might
23 take up to 4 days to appear [18,19,23]. In our study, there was no false negative of this sign on
24 both MRIs. However, all the neonates with an adverse outcome had their early MRI at day 4
25 or 5.
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28 There are limitations to our study. Early MRI could not be performed at the same time
29 for all neonates, due either to a worrying condition or organisational issues. However, early
30 MRIs were all performed between days 3 and 6, and it has been described that greatest
31 reduction in diffusivity was observed between days 2 and 6 in cooled neonates [36].
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34 The number of patients included was small. We therefore had to separate the neonates
35 into two outcome groups (favourable or adverse) for the results about the prognostic value of
36 MRI to be significant and reliable.
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39 In addition, there was a small number of neonates with an adverse outcome.
40 Surprisingly, we observed a lower rate of neonates with an adverse outcome (21%) than in
41 previous studies including a greater number of patients (30-46%) [4-6]. In our study, there
42 were yet more neonates with severe encephalopathy than in two out of three of these studies
43 (46% versus 21-25%) [5,6]. Moreover, only two neonates in the adverse outcome group
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1 survived. This low rate of surviving neonates could be related to certain decisions to forgo
2 life-sustaining treatment, based on a number of arguments about poor prognosis and probably
3 including imaging.
4

5 The retrospective design of our study induced certain limitations, as the wide follow-
6 up range (18-41 months). Yet, the median time to follow-up remained within our limit of two
7 years of age. There were also some technical limitations previously identified, particularly as
8 we used two different coils with different parameters for T1-weighted imaging[11].
9 Moreover, advanced MRI techniques such as spectroscopy and diffusion tensor imaging were
10 not available in our center during the study period. In combination with conventional imaging
11 and DWI, they would likely be even more valuable in predicting outcome.
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21 CONCLUSION

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24 Early MRI including diffusion-weighted imaging is a good predictor of adverse outcome in
25 HIE treated with hypothermia, yielding a sensitivity of 100% based on a simple visual
26 analysis. It tended to be a better predictor of outcome than late MRI. ADC measurements
27 might help to confirm reduced diffusivity but did not provide any valuable additional
28 information than simple visual analysis in predicting neurological outcome, whereas the
29 analysis of PLIC appearance was seen to help in predicting neurological outcome on both
30 MRIs.
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37 Early MRI could be a reliable aid for managing intensive care treatment and parent
38 counselling since a normal/subnormal MRI would offer a reassuring prognosis. However, late
39 MRI should still be systematically performed when early MRI is normal, in order to detect
40 more subtle injuries that might induced mild to moderate neurological impairments needing a
41 closer follow-up. When early MRI is abnormal, this study has shown that prognostication
42 should be made with cautious (as favourable outcome is still possible), but that repeating a
43 later MRI added little, if any, further information.
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50 Further studies with a larger number of neonates and longer follow-up are needed, particularly
51 involving the addition of clinico-biological, electrophysiological intensive care data, and
52 advanced MRI techniques.
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FIGURES LEGENDS

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3 **Fig. 1 a-c** Placement of the regions of interest for measurement of apparent diffusion coefficient
4 values in the semi-oval centres (a), frontal white matter, head of caudate nuclei, lentiform nuclei,
5 posterior limb of internal capsule, anterolateral thalami, parietal-occipital white matter (b) and cerebral
6 peduncles (c)
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13 **Fig. 2** Flow chart of patients
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18 **Fig. 3 a-f** Male neonate of 41 + 6 weeks' gestation with diffuse injuries on early MRI at day 4 (**a-c**)
19 and late MRI at day 9 (**d-f**) and a favourable outcome (normal neurological assessment at 23 months
20 with a global developmental quotient of 97). **a-b** Early diffusion-weighted imaging (DWI) and
21 corresponding apparent diffusion coefficient maps with hyperintensity in the hippocampi (bottom
22 arrows), the thalami (top arrows) (a), and the perirolandic, frontal and parietal white matter (arrows)
23 (b). **c** Axial T1-weighted imaging with hyperintensity in the bilateral insular cortex (arrows). **d** Axial
24 T2-weighted images on late MRI with mild hyperintensity in the thalami (arrows). **e-f** Axial T1-
25 weighted images on late MRI with normal hyperintensity within the PLIC (arrows), mild
26 intraventricular haemorrhage in the left occipital ventricular horn (*) (e) and hyperintensity within the
27 insular cortex (arrows) (f)
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36 **Fig. 4 a-d** Female neonate of 39 weeks' gestation with normal early MRI, abnormal late MRI
37 (moderate central lesions) and a favourable outcome. **a-b** Normal early imaging (day 5) at the level of
38 the basal ganglia with axial diffusion-weighted imaging (a), and axial T2-weighted imaging (b); PLIC
39 signal intensity was normal (arrows). **c-d** Late imaging (day 12) at the same level with mild
40 hyperintensity on axial T1-weighted images within the thalami (bottom arrows) and normal
41 hyperintensity within the PLIC (top arrows) (c) and axial T2-weighted images with hyperintensity
42 within the thalami (bottom arrows) and the posterior part of the lentiform nuclei (top arrows) (d)
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2 **TABLES LEGENDS**
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7 **Table 1.** Eligibility criteria for whole body hypothermia (French Society of Neonatology)
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10 **Table 2** Neonates' characteristics for the two outcome groups
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13 **Table 3** Results of early and late MRIs in favourable and adverse outcome groups
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17 **Table 4** Prognostic capability of abnormal MRI in predicting adverse outcome at 2 years of
18 age according to the simplified classification for all neonates followed up in the study and for
19 neonates who had both MRIs sequentially
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24 **Table 5** Receiver operating characteristic analysis using ADC values on early MRI as a
25 predictor of adverse outcome at 2 years of age (32 neonates assessed)
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Gestational age \geq 36 weeks

Birth weight \geq 1800g

Signs of perinatal asphyxia

- Acute perinatal event (severe foetal heart rate abnormalities, cord prolapse, placental abruption, etc.)
- And at least one of the following criteria:
 - Apgar score \leq 5 at 10 minutes
 - Mechanical ventilation or intubation at 10 minutes of life
 - Metabolic acidosis (within 60 minutes of birth)
 - cord, arterial, venous or capillary blood pH $<$ 7
 - or base deficit \geq 16mmol/L
 - or lactate level \geq 11mmol/L

Moderate or severe encephalopathy (in terms of clinical staging as described by Sarnat and Sarnat [13] and electrical features if available)

	Number of patients	Favourable outcome [†]	Number of patients	Adverse outcome [†]	p value
Gestational age (w+d)	30	39+5 (38+2-40+6)	8	40+2 (39+4-41)	0.267
Birth weight (g)	30	3170 (2775-3460)	8	3600 (3070-3872,5)	0.049
Male sex	30	17 (57)	8	3 (37)	0.438
Mode of delivery	30		8		
Spontaneous birth		16 (53)		3 (37)	
Caesarean		14 (47)		5 (63)	0.693
Severity of encephalopathy before hypothermia	23		8		
Moderate		15 (65)		2 (25)	
Severe		8 (35)		6 (75)	0.097
Meconium-stained amniotic fluid	29	21 (72)	7	2 (29)	0.073
Anticonvulsants in intensive care unit	29	19 (66)	8	8 (100)	0.078
Cord pH level	21	7 (6.93-7.18)	4	6.80 (6.8-6.89)	0.041
pH level 1h	24	7.26 (7.08-7.33)	8	7.25 (7.12-7.30)	0.811
Lactate level 1h (mmol/L)	23	8.7 (4.78-13.53)	8	13.10 (7.9-15.2)	0.191
Base deficit, (mmol/L)	17	9 (4.75-13.5)	7	12 (5.25-16)	0.546
5-minute Apgar score	29	4 (3-5)	8	3.5 (1.5-4.5)	0.400
10-minute Apgar score	26	5.5 (4-7)	8	5 (4-6.5)	0.582
Time of first MRI (d)	27	4 (4-5)	5	4 (4-4)	0.270
Time of second MRI (d)	28	12 (10.5-14)	7	9 (9-11)	0.014
Age at follow-up (m)	30	24 (23.5-26.8)	2	23.6 (22.9-24.3)	0.392
Death	30	0 (0)	8	6 (75)	-
Global DQ - med (range)	23	97 (78.5-109)	2	57 (52-62)	-
Posture DQ		98 (55-118)		52.5 (36-69)	-
Coordination DQ		99 (83-117)		49 (35-63)	-
Language DQ		89 (71-115)		61 (49-73)	-
Sociability DQ		100 (70-111)		68 (67-69)	-

[†]Continuous and ordinal data are expressed as median (interquartile range), categorical data are expressed as number of patients (%), except when specified

DQ = developmental quotient

		Early MRI (N=32)			Late MRI (N=35)		
	Pattern of injury	Favourable outcome [†] (N=27)	Adverse outcome [†] (N=5)	p value	Favourable outcome [†] (N=28)	Adverse outcome [†] (N=7)	p value
Normal/ subnormal MRI	Normal	15	0		14	0	
	PPWMI	9	0		10	0	
	Watershed (W score ≤2)	2	0		1	0	
Abnormal MRI	Watershed (W score >2)	0	0	<0.001	0	0	<0.001
	Central	0	2		2	4	
	Diffuse	1	3		1	3	

[†] Data are numbers of patients

N = number of neonates, PPWMI = punctate periventricular white matter injuries

Numbers in bold are false positives of MRI abnormalities in predicting adverse outcome

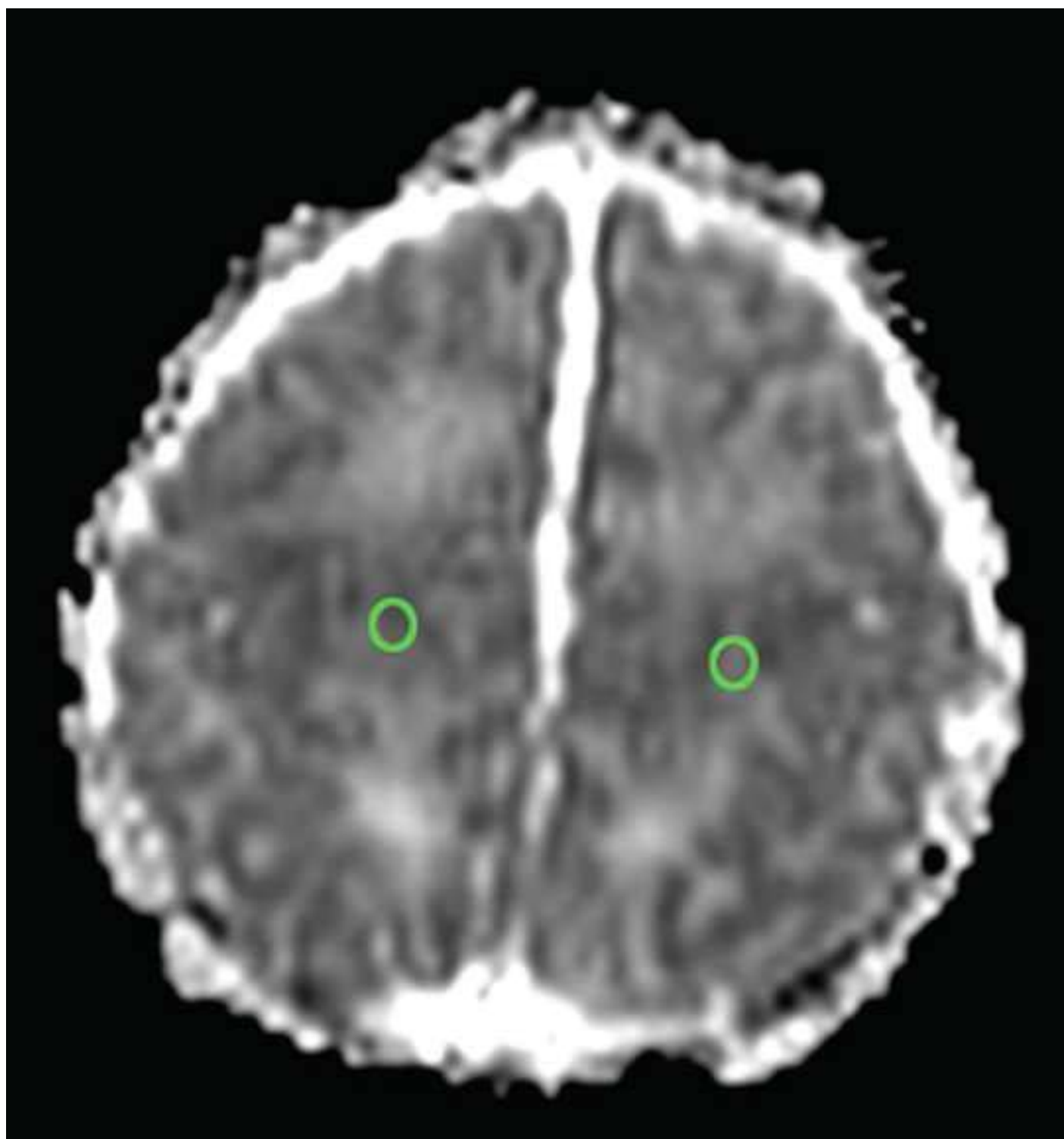
	All neonates with available follow-up data		Neonates who had both MRIs sequentially	
	Early MRI	Late MRI	Early MRI	Late MRI
	N = 32	N = 35	N = 29	N = 29
Se	100 (47.8-100)	100 (59-100)	100 (39.8-100)	100 (39.8-100)
Sp	96.3 (81-99.9)	89.3 (71.8-97.7)	96 (79.6-99.9)	88 (68.8-97.5)
PPV	83.3 (35.9-99.6)	70 (34.8-93.3)	80 (28.4-99.5)	57.1 (18.4-90.1)
NPV	100 (86.8-100)	100 (86.3-100)	100 (85.2-100)	100 (84.6-100)

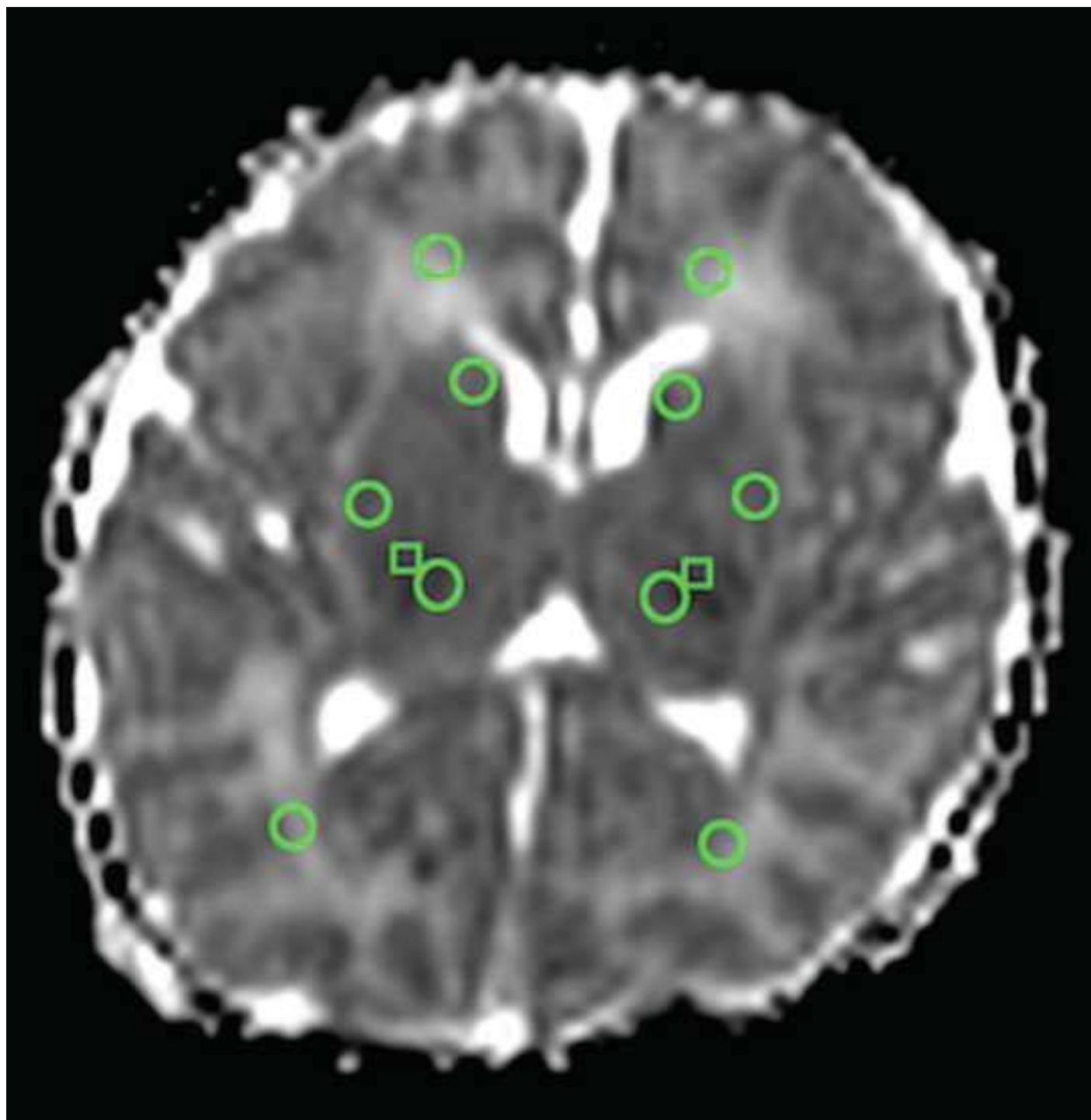
Data are percentages (95% confidence interval)

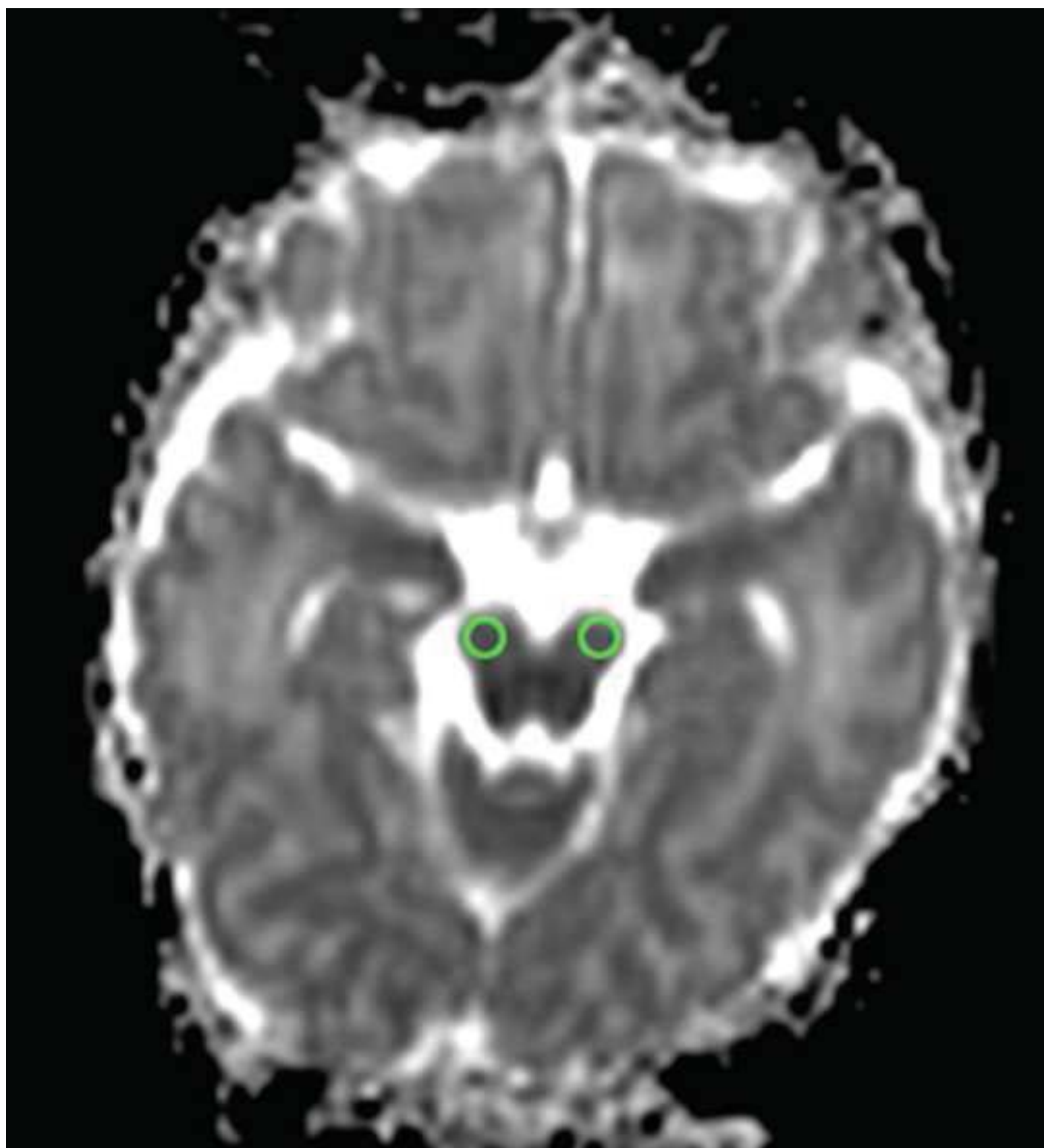
N = number of neonates, Se = sensitivity, Sp = specificity, PPV = positive predictive value, NPV = negative predictive value

Region	AUC (95% CI)	OR (95% CI)	Cut-off ($10^{-9}/\text{mm}^2/\text{s}$)	Se (%)	Sp (%)	PPV (%)	NPV (%)
PWM	0.92 (0.77-0.99)	0 (0-0.29)	≤ 1.35	100	74.1	41.7	100
SC	0.87 (0.71-0.96)	0 (0-0.38)	≤ 1.13	80	88.9	57.1	96
PLIC	0.84 (0.66-0.94)	0 (0-0.54)	≤ 0.96	100	66.7	35.7	100
CN	0.82 (0.65-0.93)	0 (0-0.22)	≤ 1.21	100	55.6	29.4	100
CP	0.80 (0.63-0.92)	0 (0-1.66)	≤ 1.05	100	55.6	29.4	100
LN	0.79 (0.61-0.91)	0 (0-0.58)	≤ 1.01	80	74.1	36.4	95.2
FWM	0.77 (0.58-0.9)	0 (0-0.75)	≤ 1.53	80	66.7	30.8	94.7
Thalami	0.69 (0.5-0.84)	0 (0-0.42)	≤ 0.82	60	96.3	75	92.9

ADC = apparent diffusion coefficient, AUC = area under curve, CI = confidence interval, OR = odds ratio, PWM = posterior white matter, SC = semi-oval centres, PLIC = posterior limb of internal capsule, CN = head of caudate nuclei, CP = cerebral peduncles, LN = lentiform nuclei, FWM = frontal white matter, Se = sensitivity, Sp = specificity, PPV = positive predictive value, NPV = negative predictive value







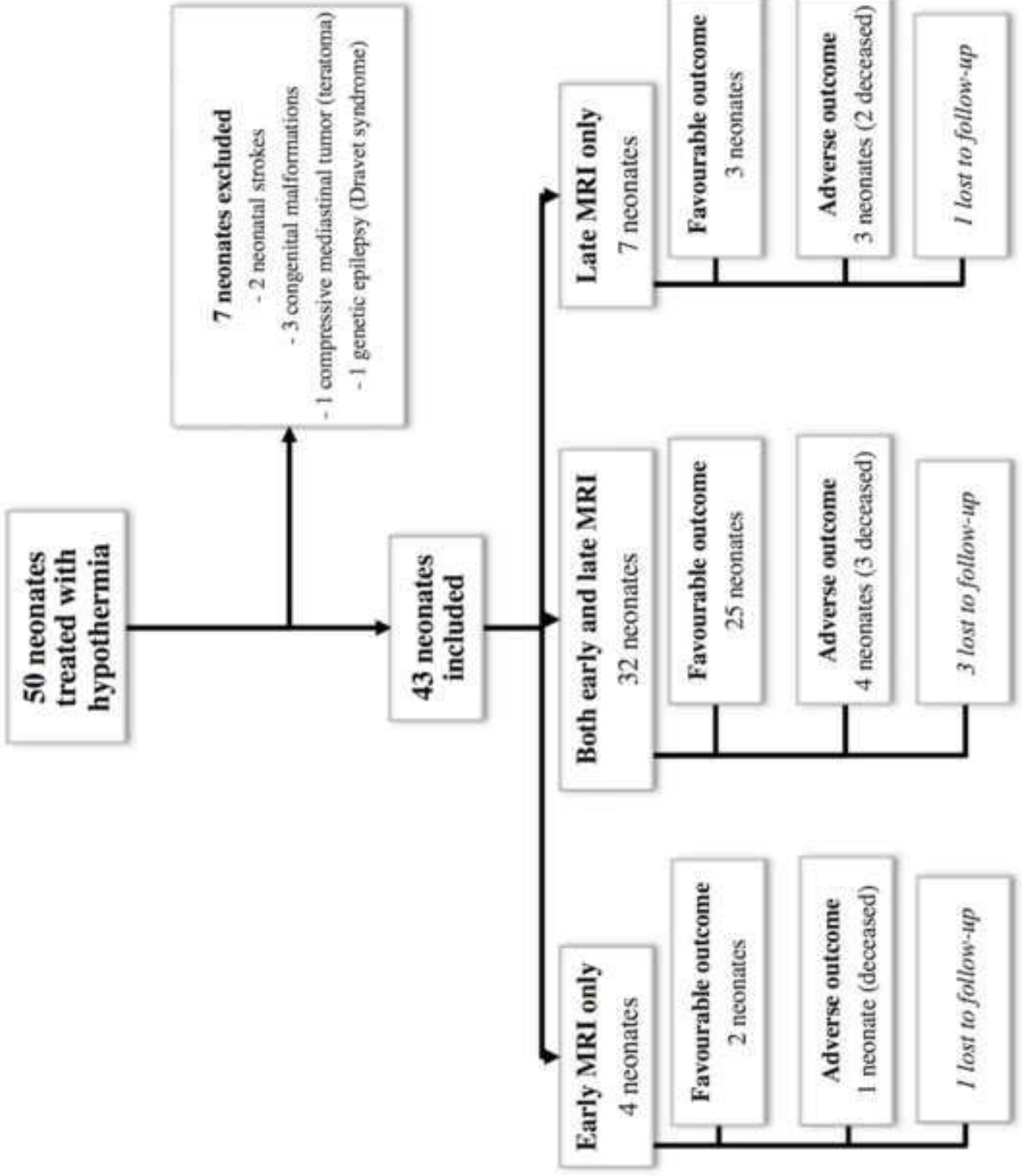
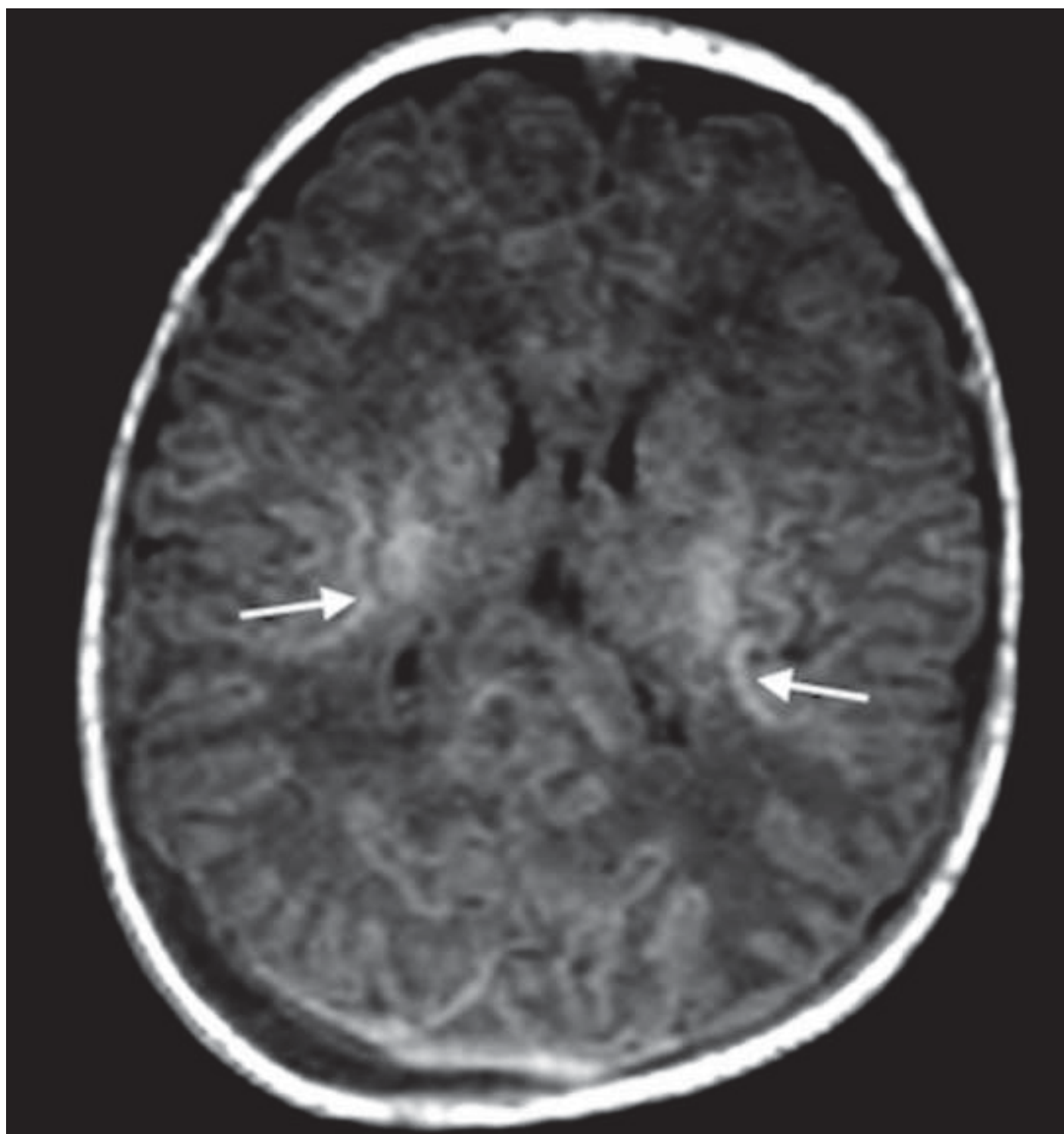
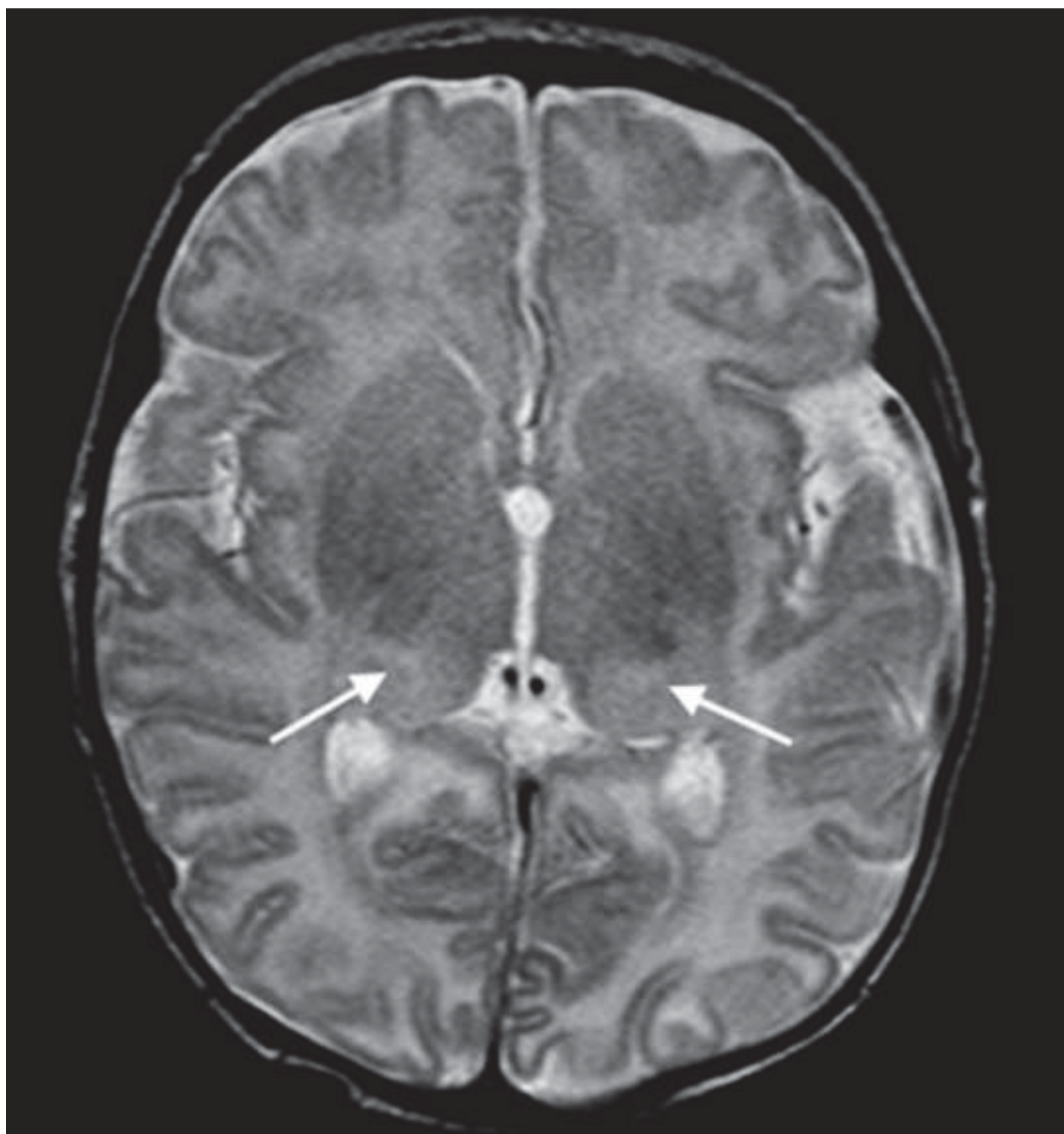
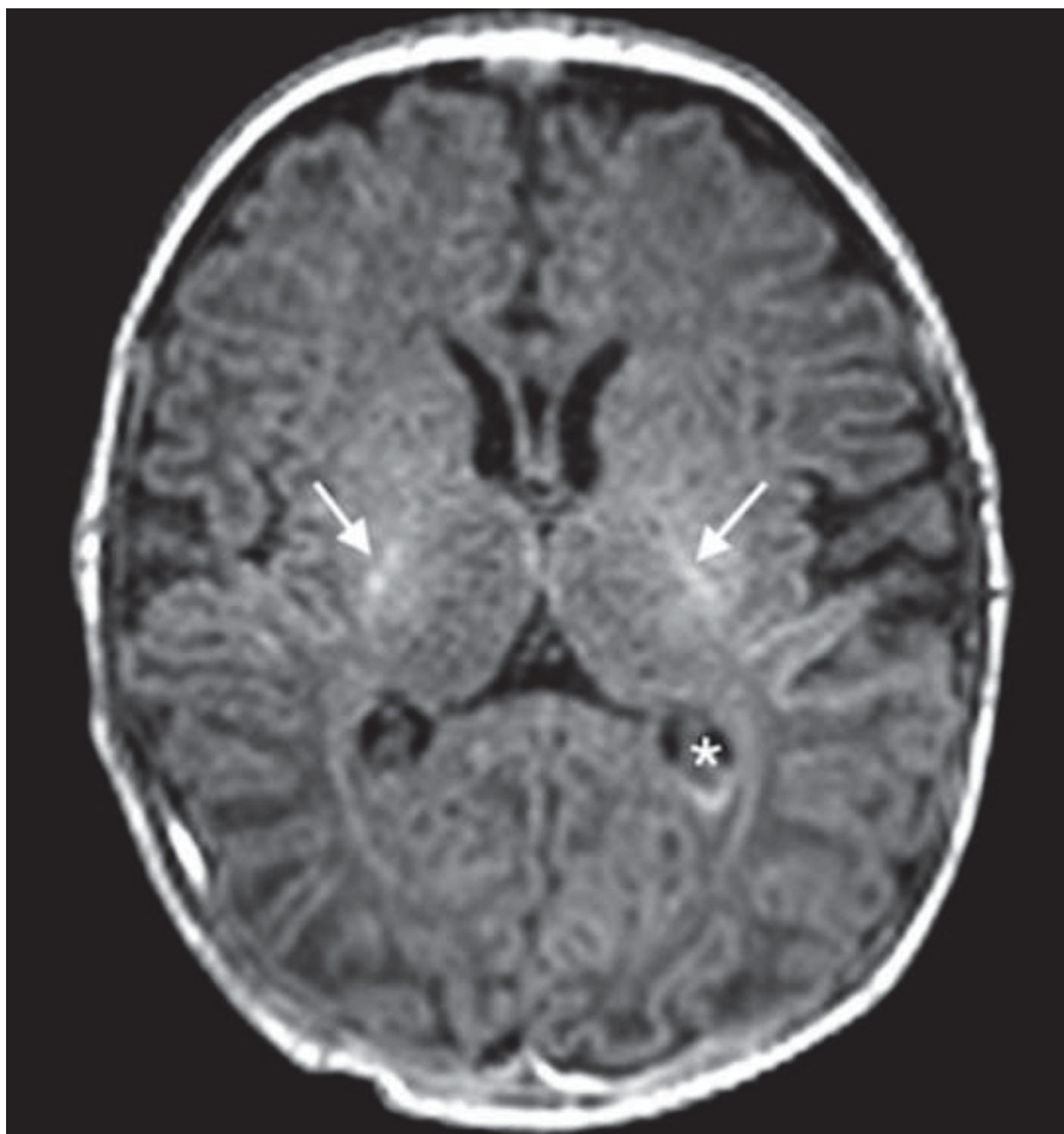
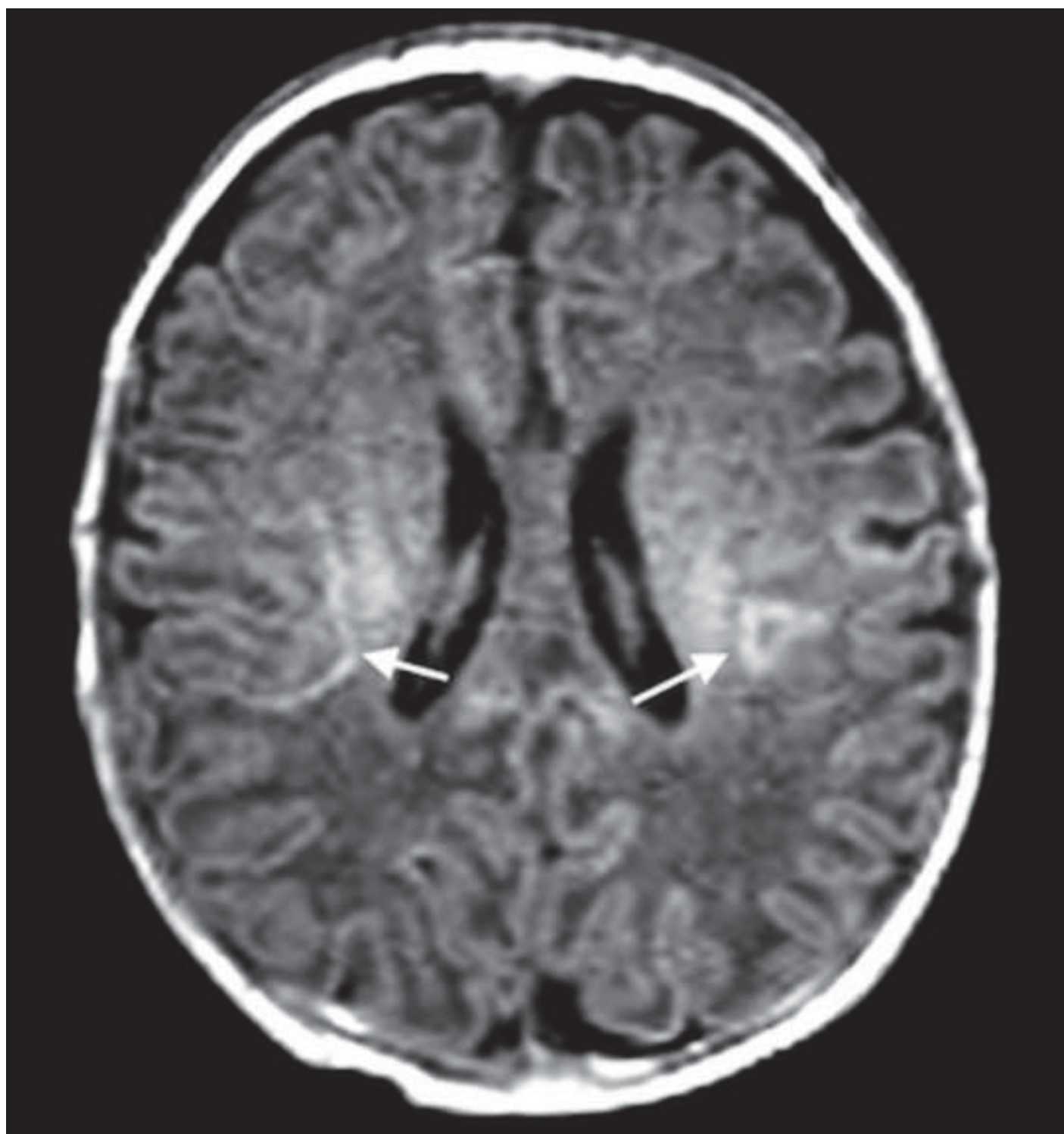


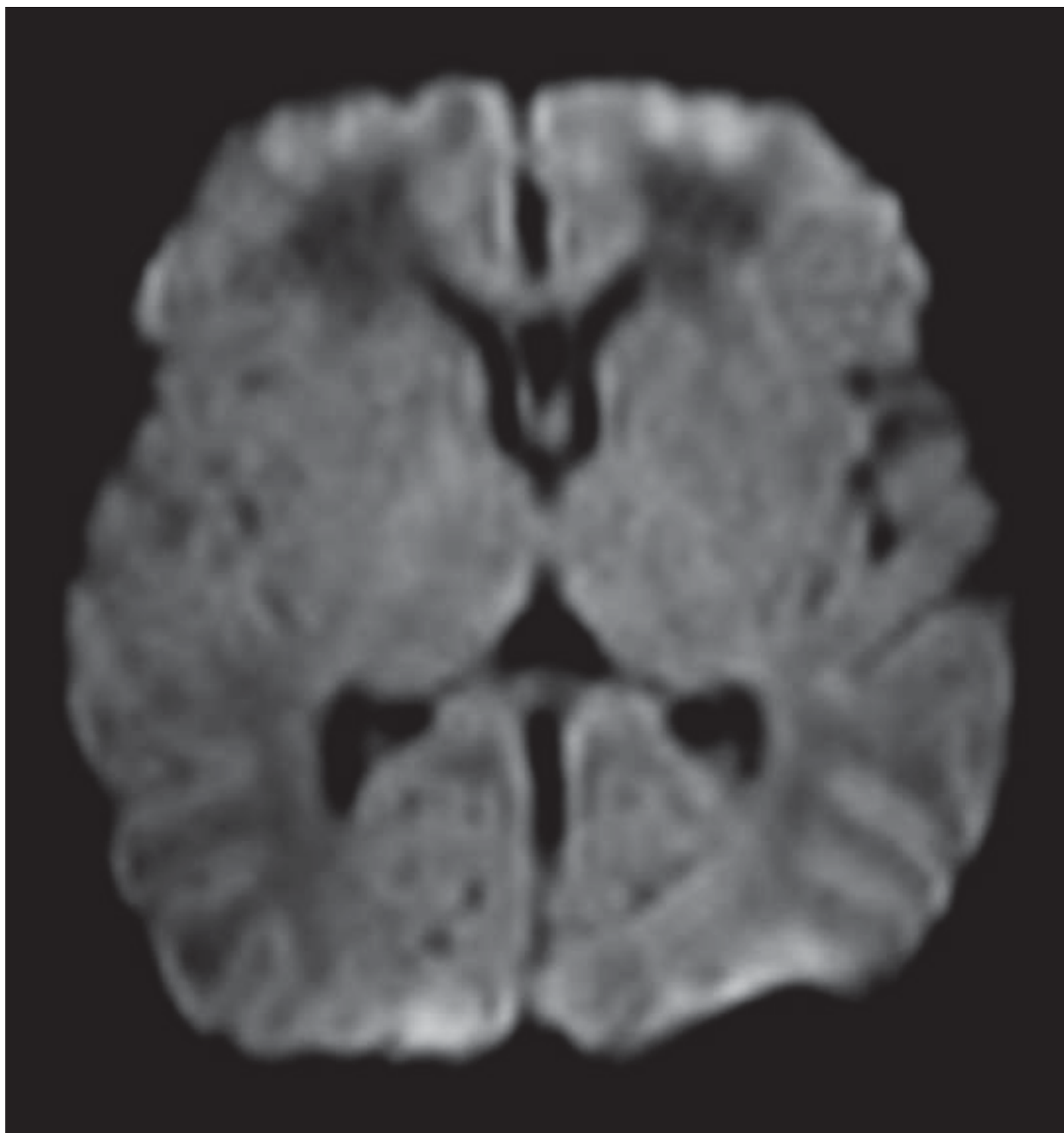
Figure 2

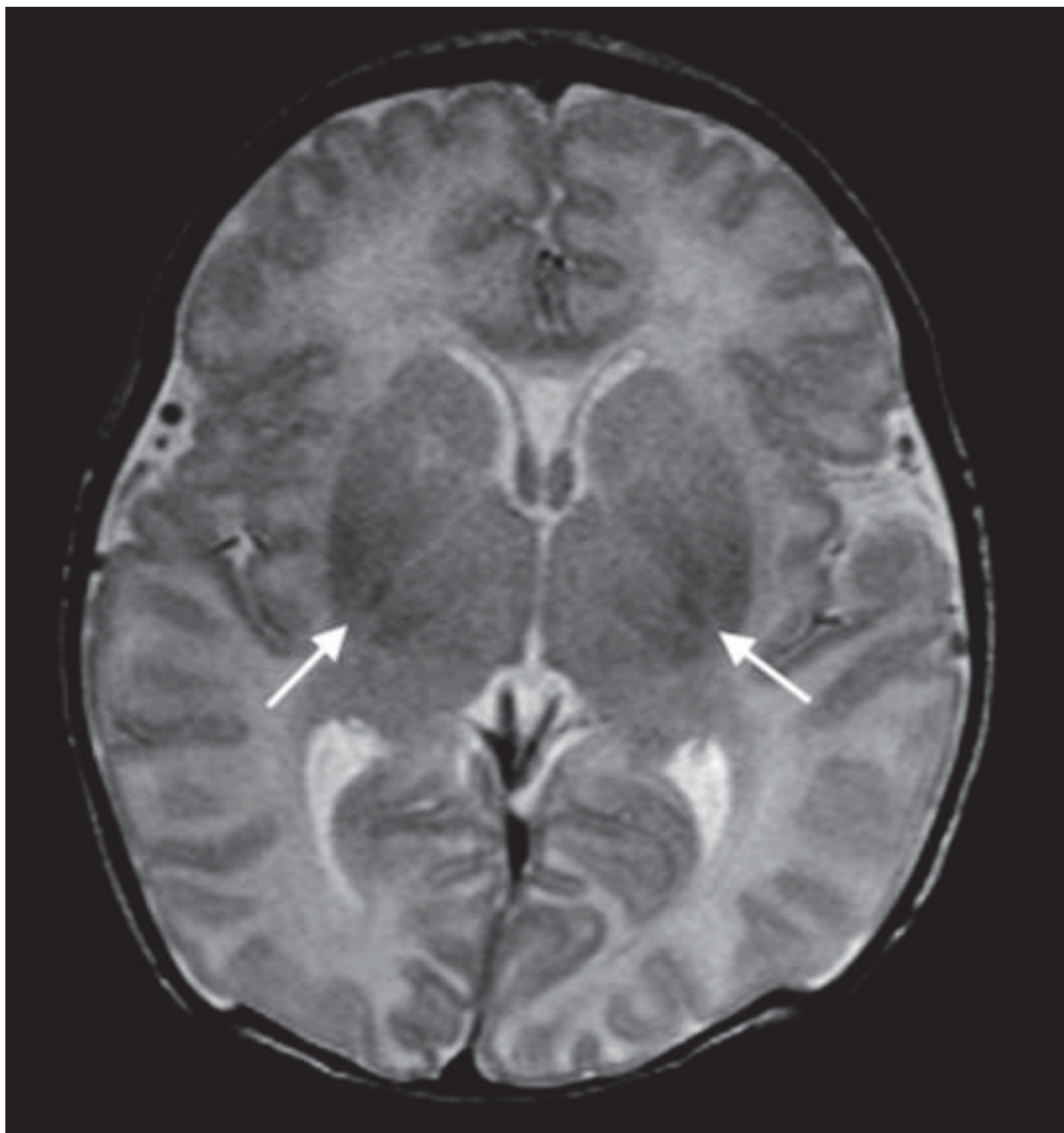


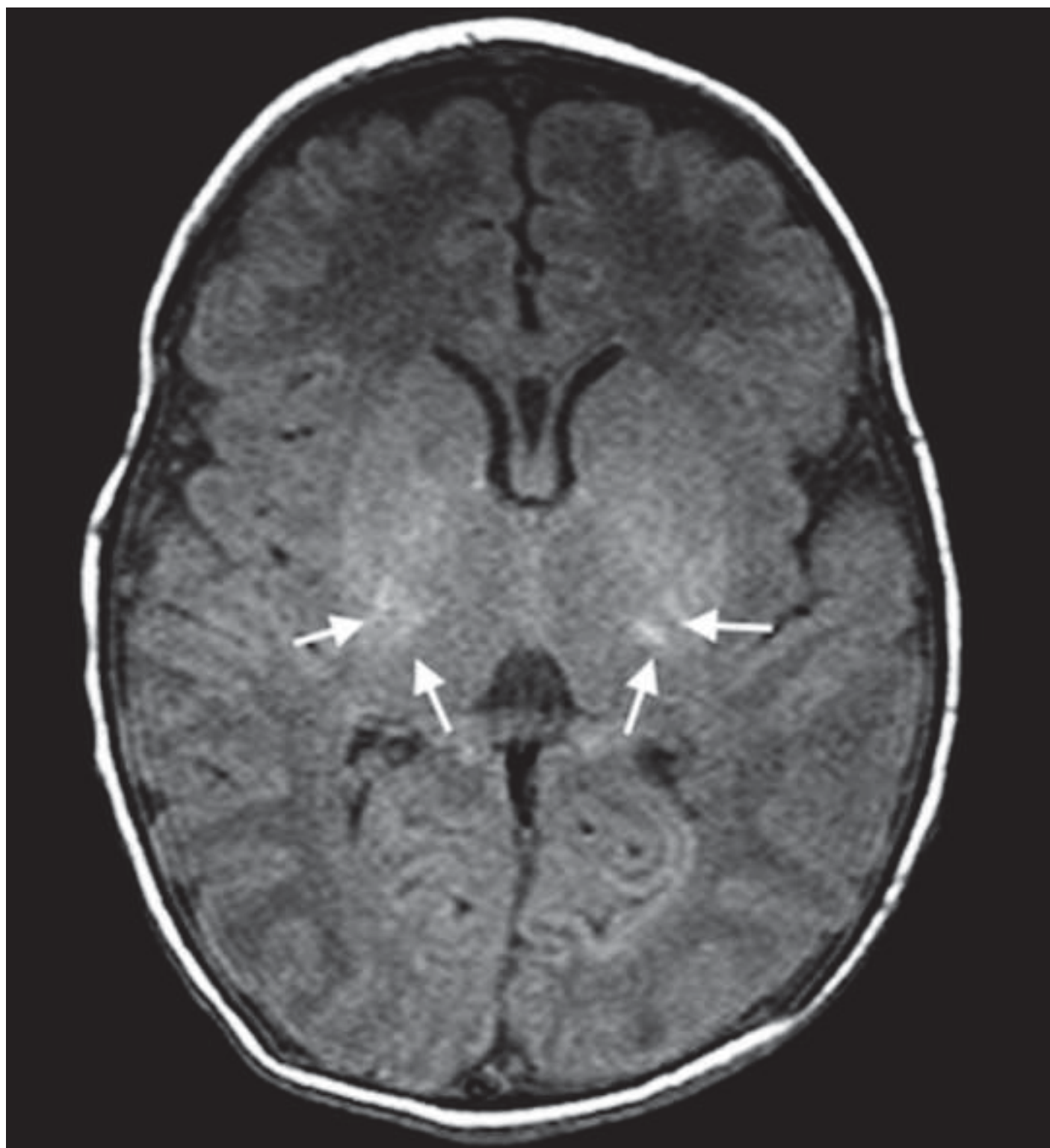


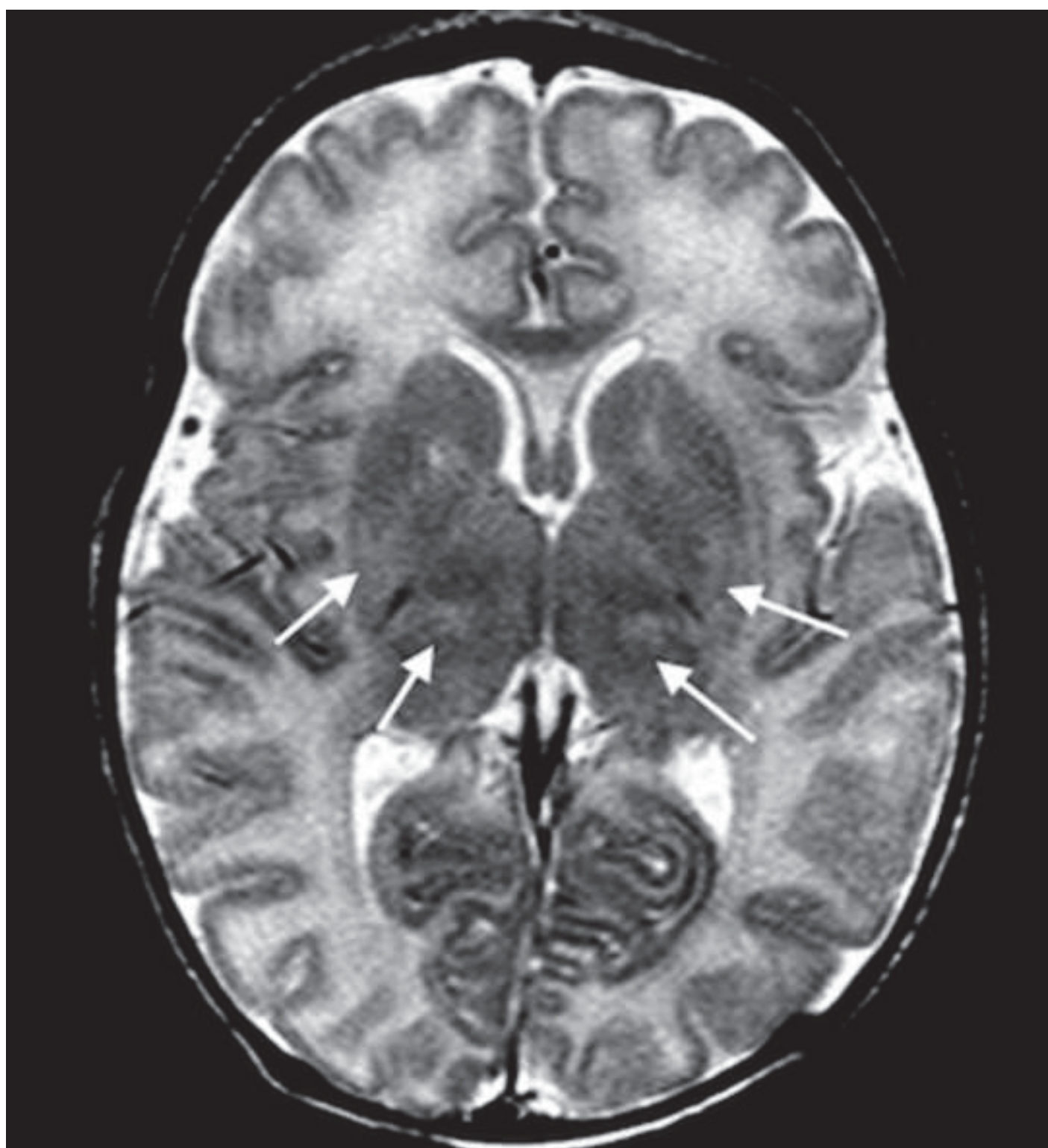












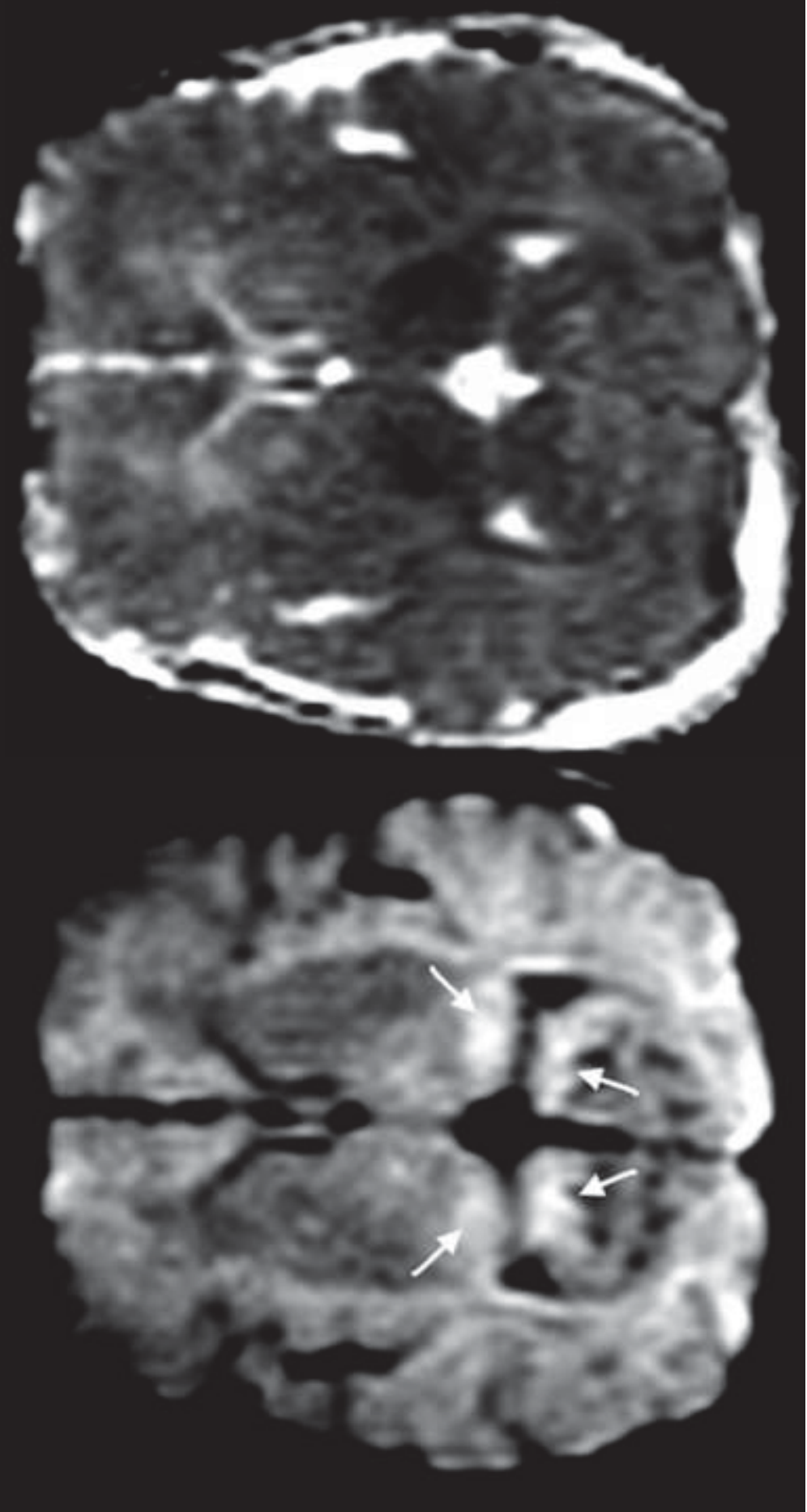


Figure 3a

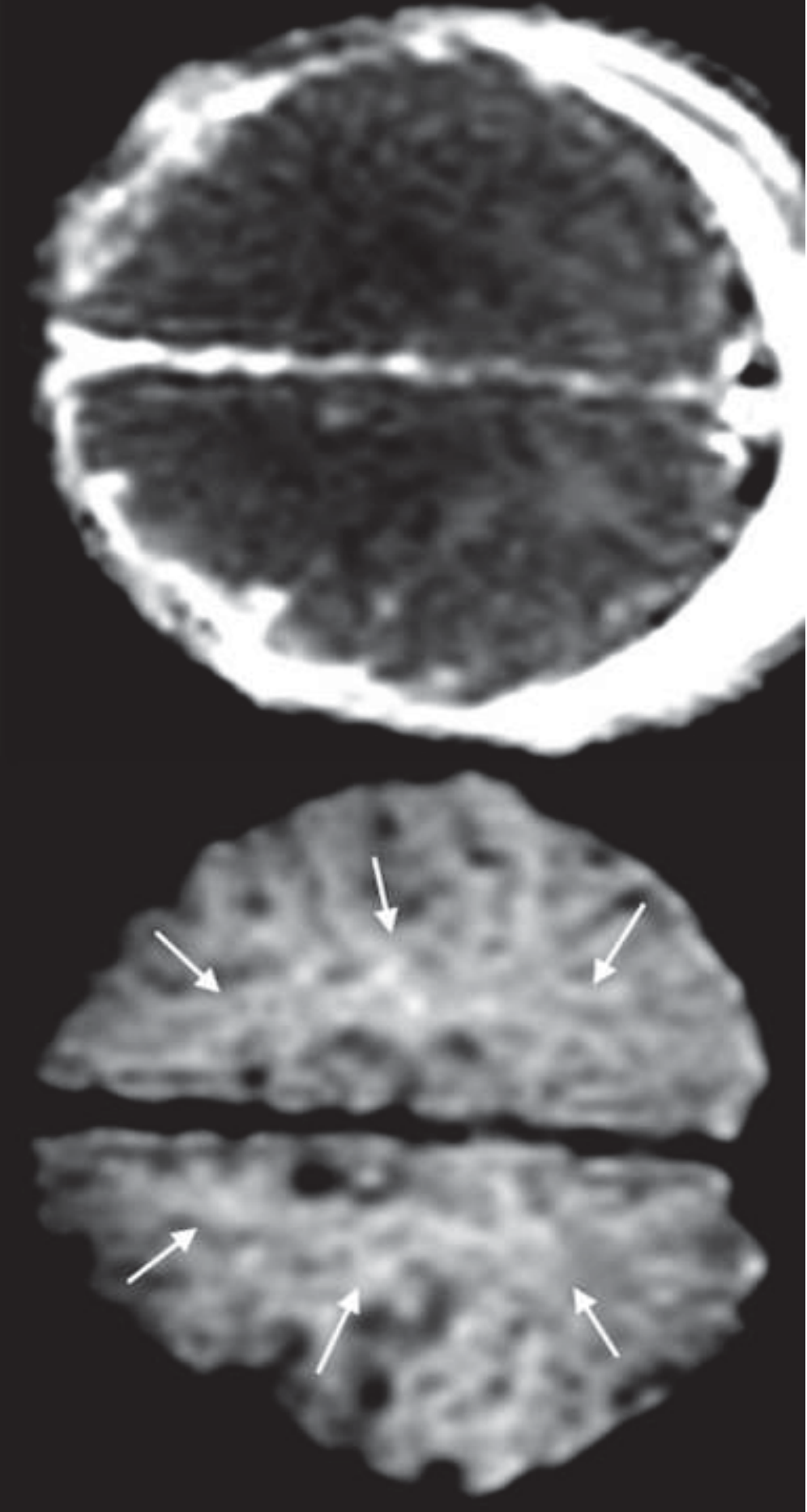


Figure 3b

APPENDIX

Description of the simplified classification and patterns of injury

Normal/ subnormal MRI	Normal MRI	No signal abnormality in the entire brain
	Punctate periventricular white matter injuries	Punctate or small confluent periventricular <1cm white matter signal abnormalities
	Watershed injuries with a W score •2	Single infarction or abnormal signal in anterior or posterior white matter (except punctate periventricular) in the intravascular boundary zones, without central or diffuse pattern criteria
Abnormal MRI	Watershed injuries with a W score >2	More extensive watershed injuries, involving anterior and posterior white matter or white matter and cortex in the intravascular boundary zones (except single infarction, central and diffuse patterns)
	Central injuries	Signal abnormalities in at least one of the following regions: lentiform nucleus, caudate nucleus, thalamus, perirolandic cortex, cerebral peduncle, hippocampus, without diffuse pattern criteria
	Diffuse injuries	Diffuse white matter signal abnormalities involving at least 4 lobes and/or cortical injuries involving more than the perirolandic cortex or watershed cortex, and/or watershed and central pattern criteria