



HAL
open science

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

Valerie Charon, Maia Proisy, Gilles Bretaudeau, Bertrand Bruneau, Patrick Pladys, Alain Beuchee, Gladys Burnouf-Rose, Jean-Christophe Ferré, Celine Rozel

► To cite this version:

Valerie Charon, Maia Proisy, Gilles Bretaudeau, Bertrand Bruneau, Patrick Pladys, et al.. Early MRI in neonatal hypoxic-ischaemic encephalopathy treated with hypothermia: Prognostic role at 2-year follow-up. *European Journal of Radiology*, 2016, 85 (8), pp.1366-1374. 10.1016/j.ejrad.2016.05.005 . hal-01361507

HAL Id: hal-01361507

<https://univ-rennes.hal.science/hal-01361507>

Submitted on 7 Oct 2016

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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

10
11
12
13 Neonates - Hypoxia-Ischaemia, Brain - Diffusion Magnetic Resonance Imaging -
14
15 Hypothermia, Induced - Patient Outcome Assessment
16
17

ABBREVIATIONS

18
19
20
21
22
23 HIE Hypoxic-Ischaemic Encephalopathy
24
25 MRI Magnetic Resonance Imaging
26
27 ADC Apparent Diffusion Coefficient
28
29 PLIC Posterior Limb of Internal Capsule
30
31 RBL Revised Brunet-Lezine
32
33 GMFCS Gross Motor Function Classification System
34
35 DQ Developmental Quotient
36
37 DWI Diffusion Weighted Imaging
38
39 PPWMI Punctate Periventricular White Matter Injuries
40
41 ROI Region Of Interest
42
43 ROC Receiver Operating Characteristic
44
45 AUC Area Under Curve
46
47 OR Odds Ratio
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000

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

1
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).
5
6

7
8
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.
16
17
18
19
20
21

Analysis of PLIC signal abnormalities

22
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.
28
29
30
31
32
33

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].
37
38
39

Statistical analysis

40
41 Data were analysed using MedCalc statistical software (version 12.5, Ostend, Belgium).
42
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.
45
46
47
48

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.
54
55
56
57

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
60
61
62
63
64
65

1
2 were presented as areas under curves (AUCs) and odds ratios (ORs) with 95% confidence
3 intervals (CIs) using logistic regression.
4

5 Finally, we calculated the predictive values for adverse outcome at 2 years of age for
6 PLIC signal abnormalities on both MRIs.
7

8 We considered $p < 0.05$ as indicating a significant difference.
9

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.
20
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.
39

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.
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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

1
2
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

10
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%).
18

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].
26

27
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.
35

36
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.
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
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

9
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.
35

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.
41

42
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
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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.
6

7
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.
26

27
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].
32

33
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.
37

38
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
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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.
12
13
14
15
16
17
18
19
20

21 CONCLUSION

22
23
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.
31
32
33
34
35

36
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.
44
45
46
47
48

49
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.
53
54
55
56
57
58
59
60
61
62
63
64
65

REFERENCES

- 1
2
3 [1] G. Dixon, N. Badawi, J.J. Kurinczuk, J.M. Keogh, S.R. Silburn, S.R. Zubrick, et al.,
4 Early Developmental Outcomes After Newborn Encephalopathy, *Pediatrics*. 109 (2002)
5 26–33.
6
7
8 [2] S.E. Jacobs, M. Berg, R. Hunt, W.O. Tarnow-Mordi, T.E. Inder, P.G. Davis, Cooling for
9 newborns with hypoxic ischaemic encephalopathy, *Cochrane Database Syst. Rev.* 1
10 (2013) CD003311.
11
12 [3] A.J. Gunn, J.S. Wyatt, A. Whitelaw, J. Barks, D. Azzopardi, R. Ballard, et al.,
13 Therapeutic hypothermia changes the prognostic value of clinical evaluation of neonatal
14 encephalopathy, *J. Pediatr.* 152 (2008) 55–58, 58.e1.
15
16 [4] M. Rutherford, L.A. Ramenghi, A.D. Edwards, P. Brocklehurst, H. Halliday, M. Levene,
17 et al., Assessment of brain tissue injury after moderate hypothermia in neonates with
18 hypoxic–ischaemic encephalopathy: a nested substudy of a randomised controlled trial,
19 *Lancet Neurol.* 9 (2010) 39–45.
20
21 [5] J.L.Y. Cheong, L. Coleman, R.W. Hunt, K.J. Lee, L.W. Doyle, T.E. Inder, et al.,
22 Prognostic utility of magnetic resonance imaging in neonatal hypoxic-ischemic
23 encephalopathy: substudy of a randomized trial, *Arch. Pediatr. Adolesc. Med.* 166
24 (2012) 634–640.
25
26 [6] S. Shankaran, P.D. Barnes, S.R. Hintz, A.R. Laptook, K.M. Zaterka-Baxter, S.A.
27 McDonald, et al., Brain injury following trial of hypothermia for neonatal hypoxic-
28 ischaemic encephalopathy, *Arch. Dis. Child. Fetal Neonatal Ed.* 97 (2012) F398–404.
29
30 [7] P. Wintermark, A. Hansen, J. Soul, M. Labrecque, R.L. Robertson, S.K. Warfield, Early
31 versus late MRI in asphyxiated newborns treated with hypothermia, *Arch. Dis. Child.*
32 *Fetal Neonatal Ed.* 96 (2011) F36–44. doi:10.1136/adc.2010.184291.
33
34 [8] T. Agut, M. León, M. Rebollo, J. Muchart, G. Arca, A. Garcia-Alix, Early identification
35 of brain injury in infants with hypoxic ischemic encephalopathy at high risk for severe
36 impairments: accuracy of MRI performed in the first days of life, *BMC Pediatr.* 14
37 (2014) 177. doi:10.1186/1471-2431-14-177.
38
39 [9] J.H. Skranes, F.M. Cowan, T. Stiris, D. Fugelseth, M. Thoresen, A. Server, Brain
40 imaging in cooled encephalopathic neonates does not differ between four and 11 days
41 after birth, *Acta Paediatr. Oslo Nor.* 1992. (2015). doi:10.1111/apa.13016.
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
- [10] E. Boudes, X. Tan, C. Saint-Martin, M. Shevell, P. Wintermark, MRI obtained during versus after hypothermia in asphyxiated newborns, *Arch. Dis. Child. Fetal Neonatal Ed.* 100 (2015) F238–242.
- [11] V. Charon, M. Proisy, J.-C. Ferré, B. Bruneau, C. Tréguier, A. Beuchée, et al., Comparison of early and late MRI in neonatal hypoxic-ischemic encephalopathy using three assessment methods, *Pediatr. Radiol.* 45 (2015) 1988–2000.
- [12] E. Saliba, T. Debillon, Neuroprotection par hypothermie contrôlée dans l'encéphalopathie hypoxique-ischémique du nouveau-né à terme, *Arch. Pédiatrie.* 17, Supplement 3 (2010) S67–S77.
- [13] H.B. Sarnat, M.S. Sarnat, Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study, *Arch. Neurol.* 33 (1976) 696–705.
- [14] O. Brunet, I. Lézine, D. Josse, Brunet-Lézine révisé: échelle de développement psychomoteur de la première enfance, Etablissements d'Applications Psychotechniques, Issy-Les-Moulineaux, France, 1997.
- [15] A.J. Barkovich, B.L. Hajnal, D. Vigneron, A. Sola, J.C. Partridge, F. Allen, et al., Prediction of neuromotor outcome in perinatal asphyxia: evaluation of MR scoring systems, *AJNR Am. J. Neuroradiol.* 19 (1998) 143–149.
- [16] J.S. Coats, A. Freeberg, E.G. Pajela, A. Obenaus, S. Ashwal, Meta-analysis of apparent diffusion coefficients in the newborn brain, *Pediatr. Neurol.* 41 (2009) 263–274.
- [17] L. Liauw, G. van Wezel-Meijler, S. Veen, M.A. van Buchem, J. van der Grond, Do apparent diffusion coefficient measurements predict outcome in children with neonatal hypoxic-ischemic encephalopathy?, *AJNR Am. J. Neuroradiol.* 30 (2009) 264–270.
- [18] M.A. Rutherford, J.M. Pennock, S.J. Counsell, E. Mercuri, F.M. Cowan, L.M. Dubowitz, et al., Abnormal magnetic resonance signal in the internal capsule predicts poor neurodevelopmental outcome in infants with hypoxic-ischemic encephalopathy, *Pediatrics.* 102 (1998) 323–328.
- [19] M. Martinez-Biarge, J. Diez-Sebastian, O. Kapellou, D. Gindner, J.M. Allsop, M.A. Rutherford, et al., Predicting motor outcome and death in term hypoxic-ischemic encephalopathy, *Neurology.* 76 (2011) 2055–2061.
- [20] C. Kuenzle, O. Baenziger, E. Martin, L. Thun-Hohenstein, M. Steinlin, M. Good, et al., Prognostic value of early MR imaging in term infants with severe perinatal asphyxia, *Neuropediatrics.* 25 (1994) 191–200.
- [21] C. Boichot, P.M. Walker, C. Durand, M. Grimaldi, S. Chapuis, J.B. Gouyon, et al., Term neonate prognoses after perinatal asphyxia: contributions of MR imaging, MR

spectroscopy, relaxation times, and apparent diffusion coefficients, *Radiology*. 239 (2006) 839–848.

- [22] V. Jadas, M. Brasseur-Daudruy, C. Chollat, L. Pellerin, A.M. Devaux, S. Marret, et al., [The contribution of the clinical examination, electroencephalogram, and brain MRI in assessing the prognosis in term newborns with neonatal encephalopathy. A cohort of 30 newborns before the introduction of treatment with hypothermia], *Arch. Pédiatrie Organe Off. Société Fr. Pédiatrie*. 21 (2014) 125–133.
- [23] E. Twomey, A. Twomey, Stephanie Ryan, J. Murphy, V.B. Donoghue, MR imaging of term infants with hypoxic-ischaemic encephalopathy as a predictor of neurodevelopmental outcome and late MRI appearances, *Pediatr. Radiol.* 40 (2010) 1526–1535.
- [24] B.J.M. van Kooij, M. van Handel, R.A.J. Nivelstein, F. Groenendaal, M.J. Jongmans, L.S. de Vries, Serial MRI and neurodevelopmental outcome in 9- to 10-year-old children with neonatal encephalopathy, *J. Pediatr.* 157 (2010) 221–227.e2.
- [25] P.-L. Khong, C. Tse, I.Y.C. Wong, B.C.C. Lam, P.-T. Cheung, W.H.S. Goh, et al., Diffusion-weighted imaging and proton magnetic resonance spectroscopy in perinatal hypoxic-ischemic encephalopathy: association with neuromotor outcome at 18 months of age, *J. Child Neurol.* 19 (2004) 872–881.
- [26] A.J. Barkovich, S.P. Miller, A. Bartha, N. Newton, S.E.G. Hamrick, P. Mukherjee, et al., MR imaging, MR spectroscopy, and diffusion tensor imaging of sequential studies in neonates with encephalopathy, *AJNR Am. J. Neuroradiol.* 27 (2006) 533–547.
- [27] R.L. Robertson, L. Ben-Sira, P.D. Barnes, R.V. Mulkern, C.D. Robson, S.E. Maier, et al., MR line-scan diffusion-weighted imaging of term neonates with perinatal brain ischemia, *AJNR Am. J. Neuroradiol.* 20 (1999) 1658–1670.
- [28] R.C. McKinstry, J.H. Miller, A.Z. Snyder, A. Mathur, G.L. Schefft, C.R. Almlie, et al., A prospective, longitudinal diffusion tensor imaging study of brain injury in newborns, *Neurology*. 59 (2002) 824–833.
- [29] M. Rutherford, S. Counsell, J. Allsop, J. Boardman, O. Kapellou, D. Larkman, et al., Diffusion-weighted magnetic resonance imaging in term perinatal brain injury: a comparison with site of lesion and time from birth, *Pediatrics*. 114 (2004) 1004–1014.
- [30] S. Thayyil, M. Chandrasekaran, A. Taylor, A. Bainbridge, E.B. Cady, W.K.K. Chong, et al., Cerebral magnetic resonance biomarkers in neonatal encephalopathy: a meta-analysis, *Pediatrics*. 125 (2010) e382–395.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
- [31] F. Cavalleri, L. Lugli, M. Pugliese, R. D'Amico, A. Todeschini, E. Della Casa, et al., Prognostic value of diffusion-weighted imaging summation scores or apparent diffusion coefficient maps in newborns with hypoxic-ischemic encephalopathy, *Pediatr. Radiol.* 44 (2014) 1141–1154.
- [32] S.K. Goergen, H. Ang, F. Wong, E.A. Carse, M. Charlton, R. Evans, et al., Early MRI in term infants with perinatal hypoxic-ischaemic brain injury: interobserver agreement and MRI predictors of outcome at 2 years, *Clin. Radiol.* 69 (2014) 72–81.
- [33] T. Alderliesten, L.S. de Vries, M.J.N.L. Benders, C. Koopman, F. Groenendaal, MR imaging and outcome of term neonates with perinatal asphyxia: value of diffusion-weighted MR imaging and ^1H MR spectroscopy, *Radiology.* 261 (2011) 235–242.
- [34] R.J. Vermeulen, P.E.M. van Schie, L. Hendrikx, F. Barkhof, M. van Weissenbruch, D.L. Knol, et al., Diffusion-weighted and conventional MR imaging in neonatal hypoxic ischemia: two-year follow-up study, *Radiology.* 249 (2008) 631–639.
- [35] O. Brissaud, M. Amirault, F. Villega, O. Periot, J.F. Chateil, M. Allard, Efficiency of fractional anisotropy and apparent diffusion coefficient on diffusion tensor imaging in prognosis of neonates with hypoxic-ischemic encephalopathy: a methodologic prospective pilot study, *AJNR Am. J. Neuroradiol.* 31 (2010) 282–287.
- [36] N. Bednarek, A. Mathur, T. Inder, J. Wilkinson, J. Neil, J. Shimony, Impact of therapeutic hypothermia on MRI diffusion changes in neonatal encephalopathy, *Neurology.* 78 (2012) 1420–1427.

FIGURES LEGENDS

1
2
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)
7
8
9

10
11
12
13 **Fig. 2** Flow chart of patients
14
15
16
17

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)
28
29
30
31
32
33
34
35

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)
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2 **TABLES LEGENDS**
3
4
5
6

7 **Table 1.** Eligibility criteria for whole body hypothermia (French Society of Neonatology)
8
9

10 **Table 2** Neonates' characteristics for the two outcome groups
11
12

13 **Table 3** Results of early and late MRIs in favourable and adverse outcome groups
14
15
16

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
20
21
22
23

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)
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Jennifer Chauvel for her contribution to data collection and Mrs. Tracey Westcott for her editorial assistance.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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

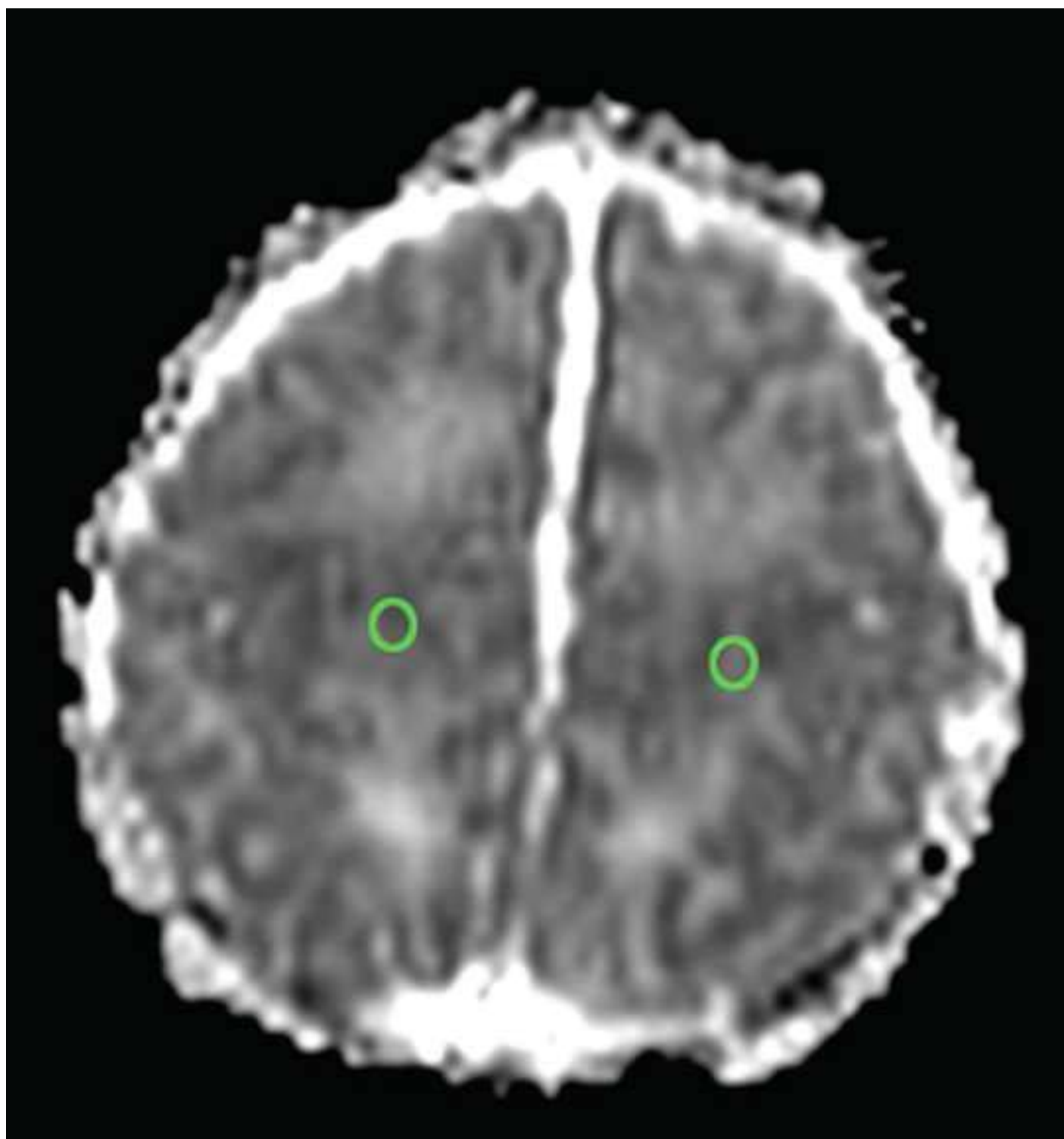
	All neonates with available follow-up data		Neonates who had both MRIs sequentially	
	Early MRI	Late MRI	Early MRI	Late MRI
	N = 32	N = 35	N = 29	N = 29
Se	100 (47.8-100)	100 (59-100)	100 (39.8-100)	100 (39.8-100)
Sp	96.3 (81-99.9)	89.3 (71.8-97.7)	96 (79.6-99.9)	88 (68.8-97.5)
PPV	83.3 (35.9-99.6)	70 (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)

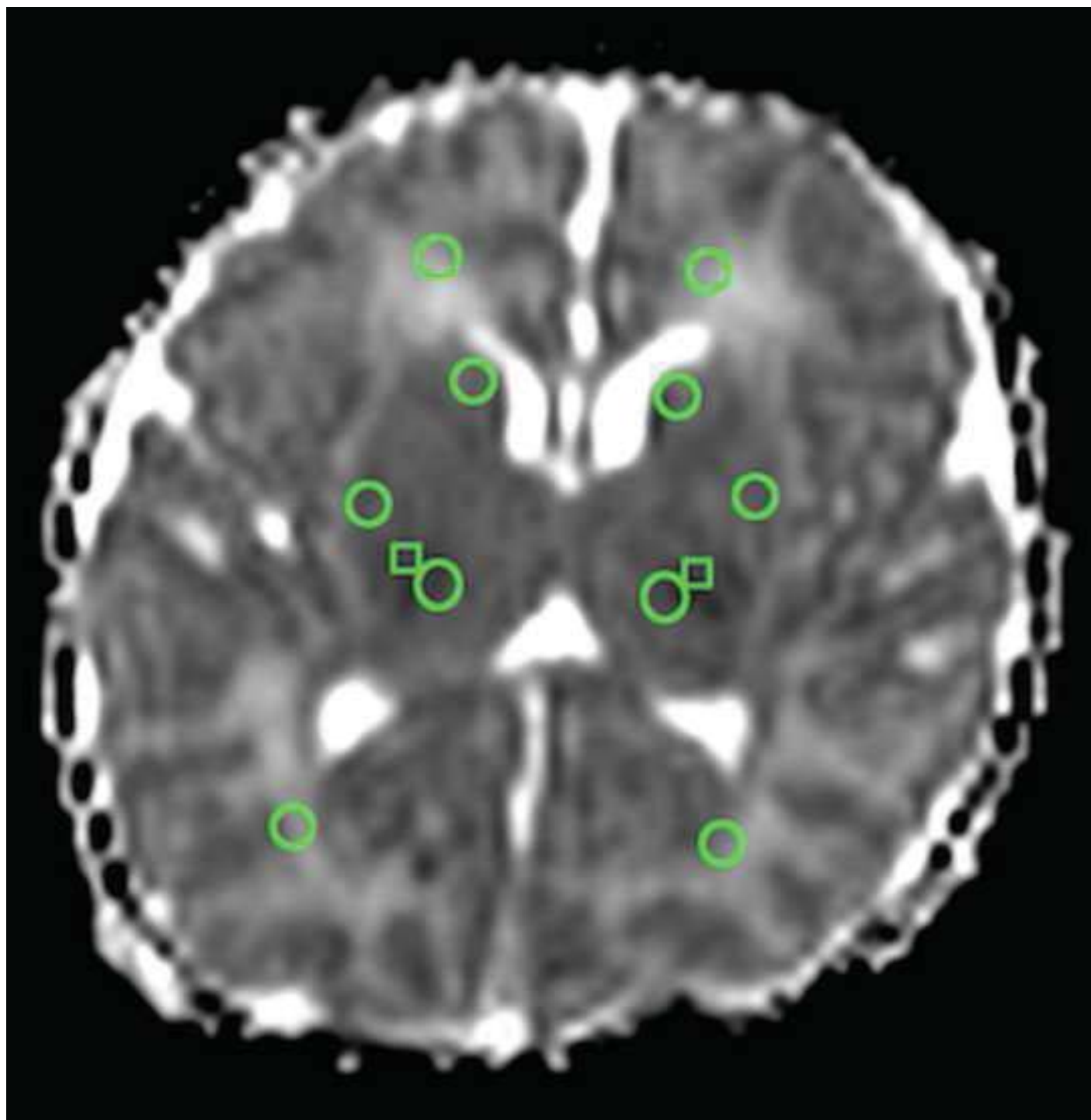
Data are percentages (95% confidence interval)

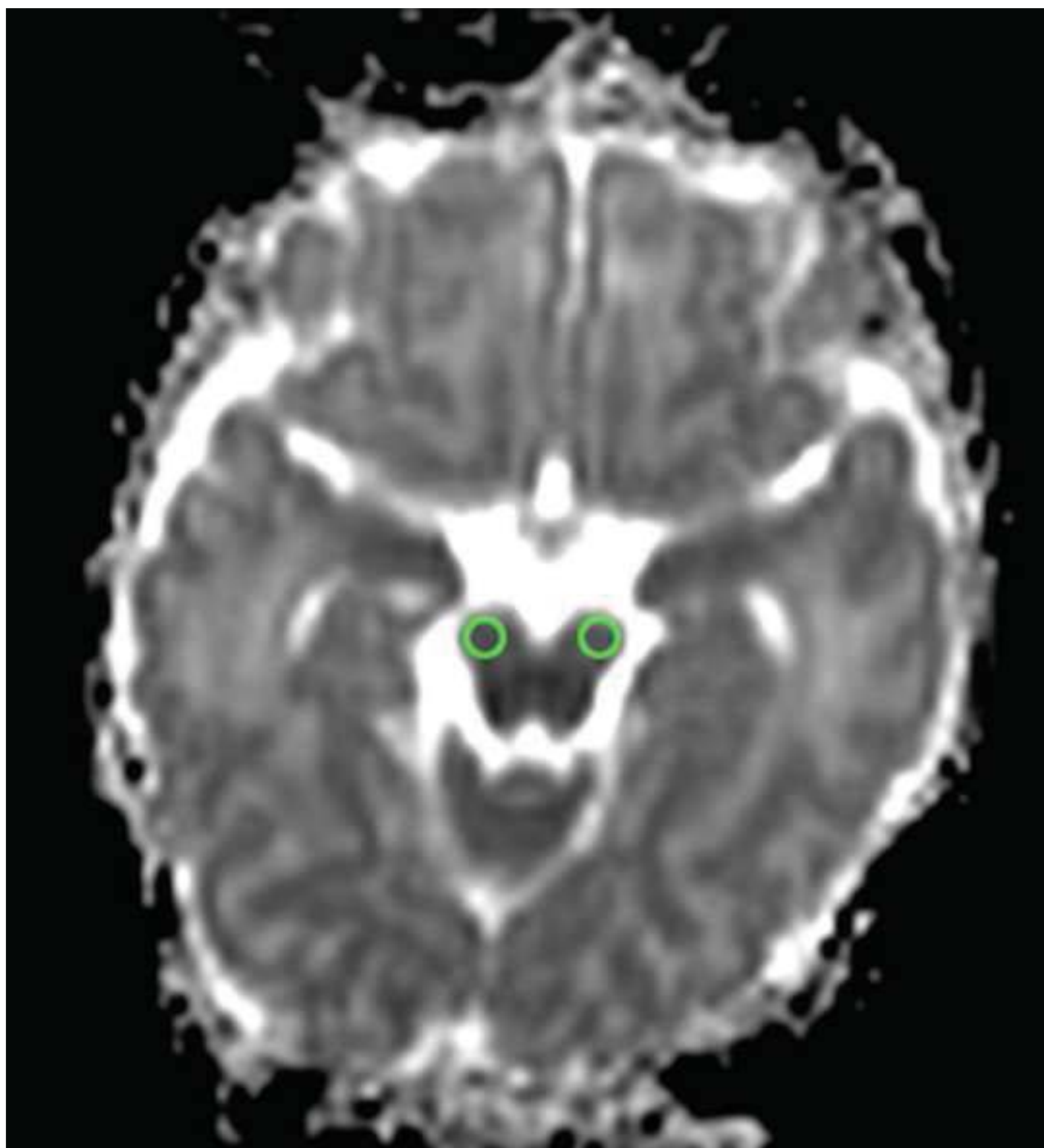
N = number of neonates, Se = sensitivity, Sp = specificity, PPV = positive predictive value, NPV = negative predictive value

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







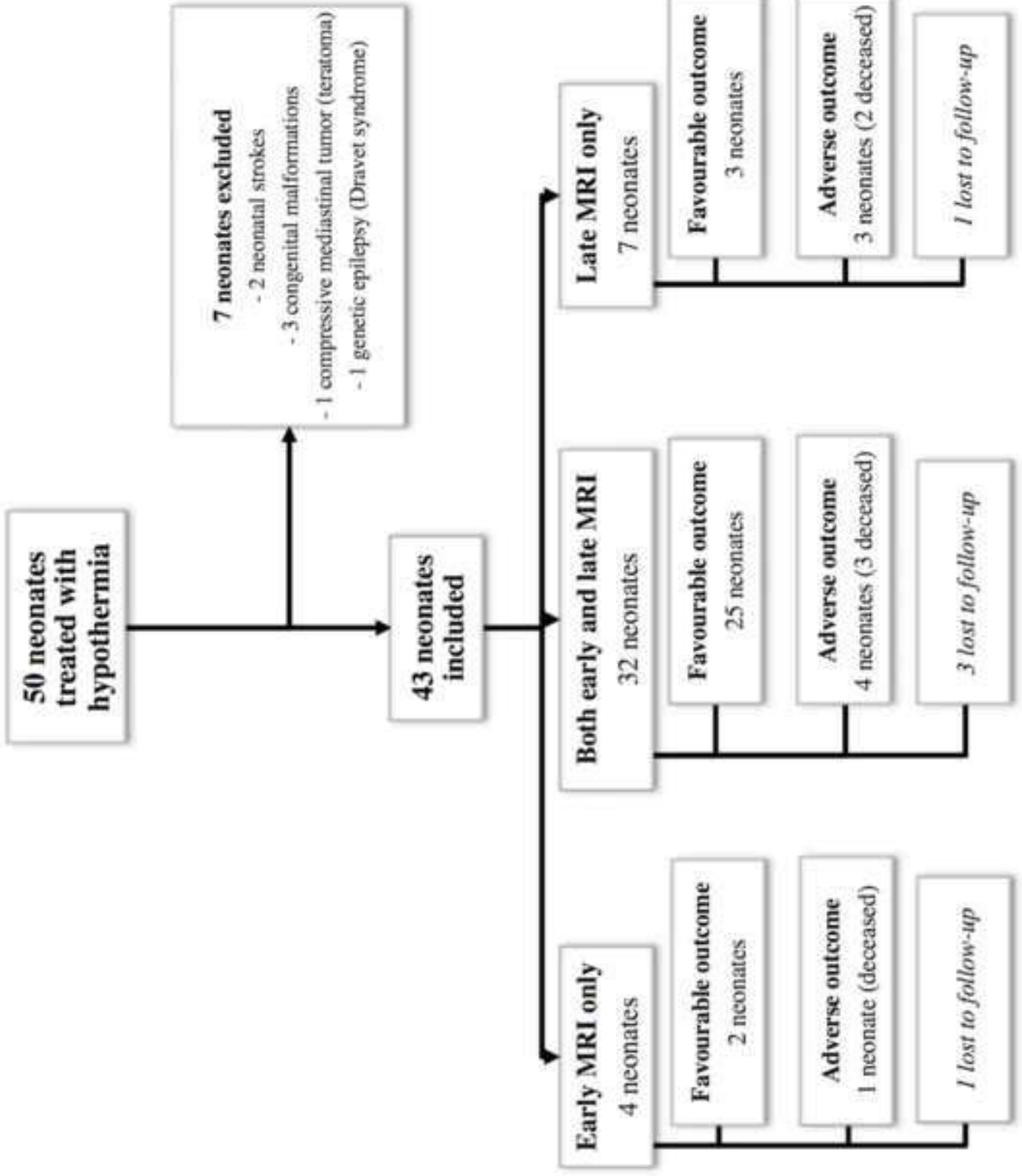
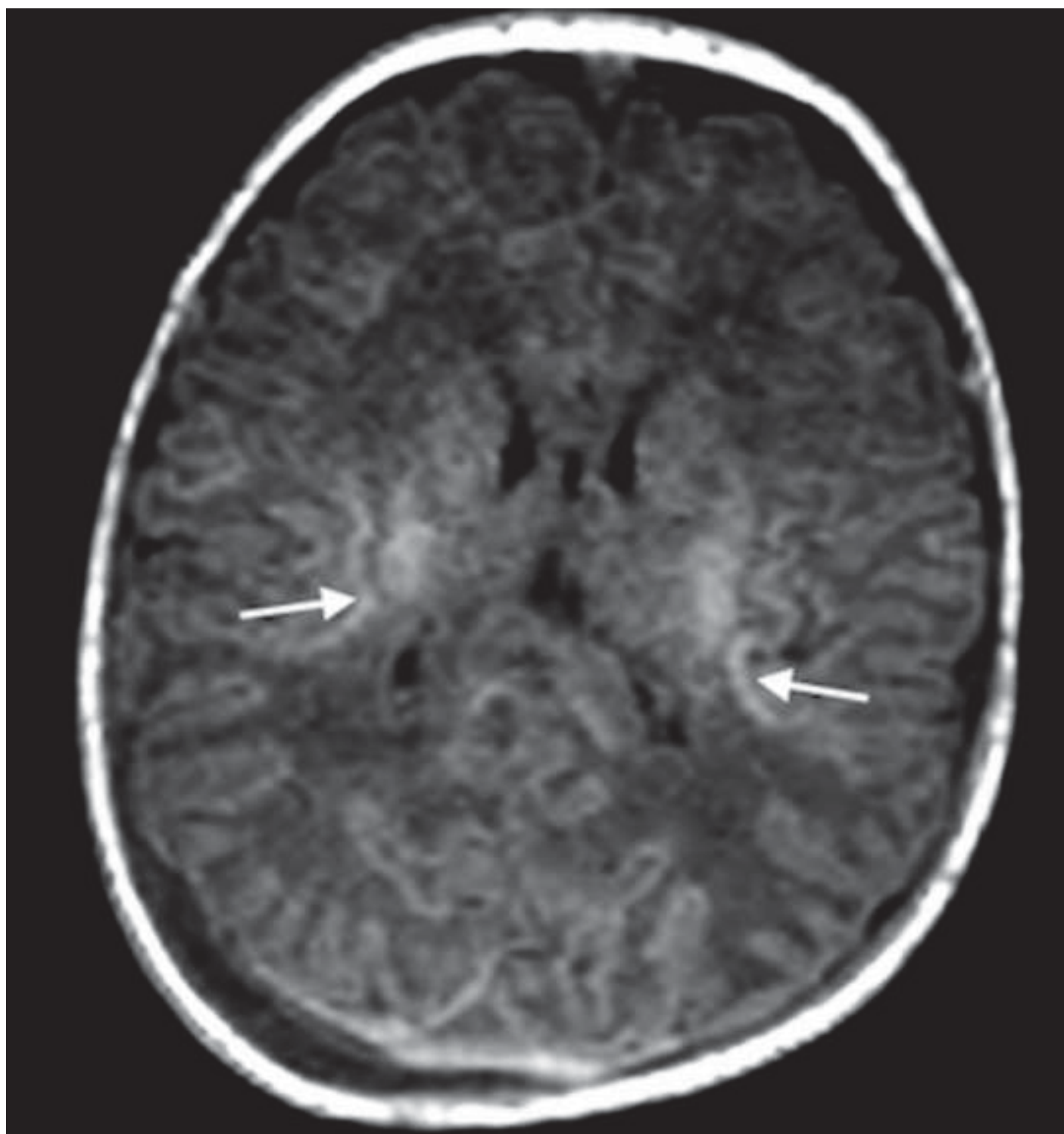
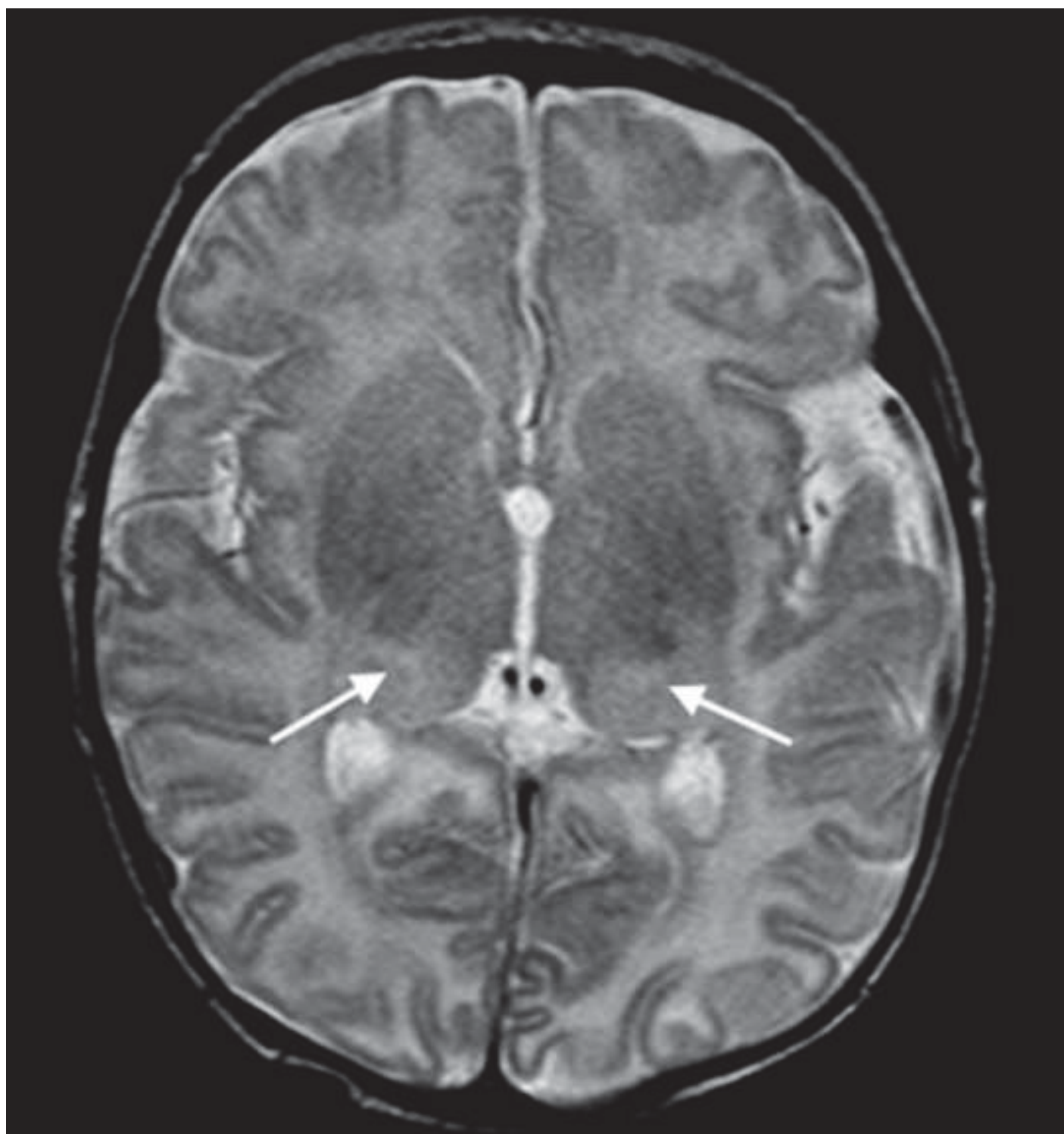
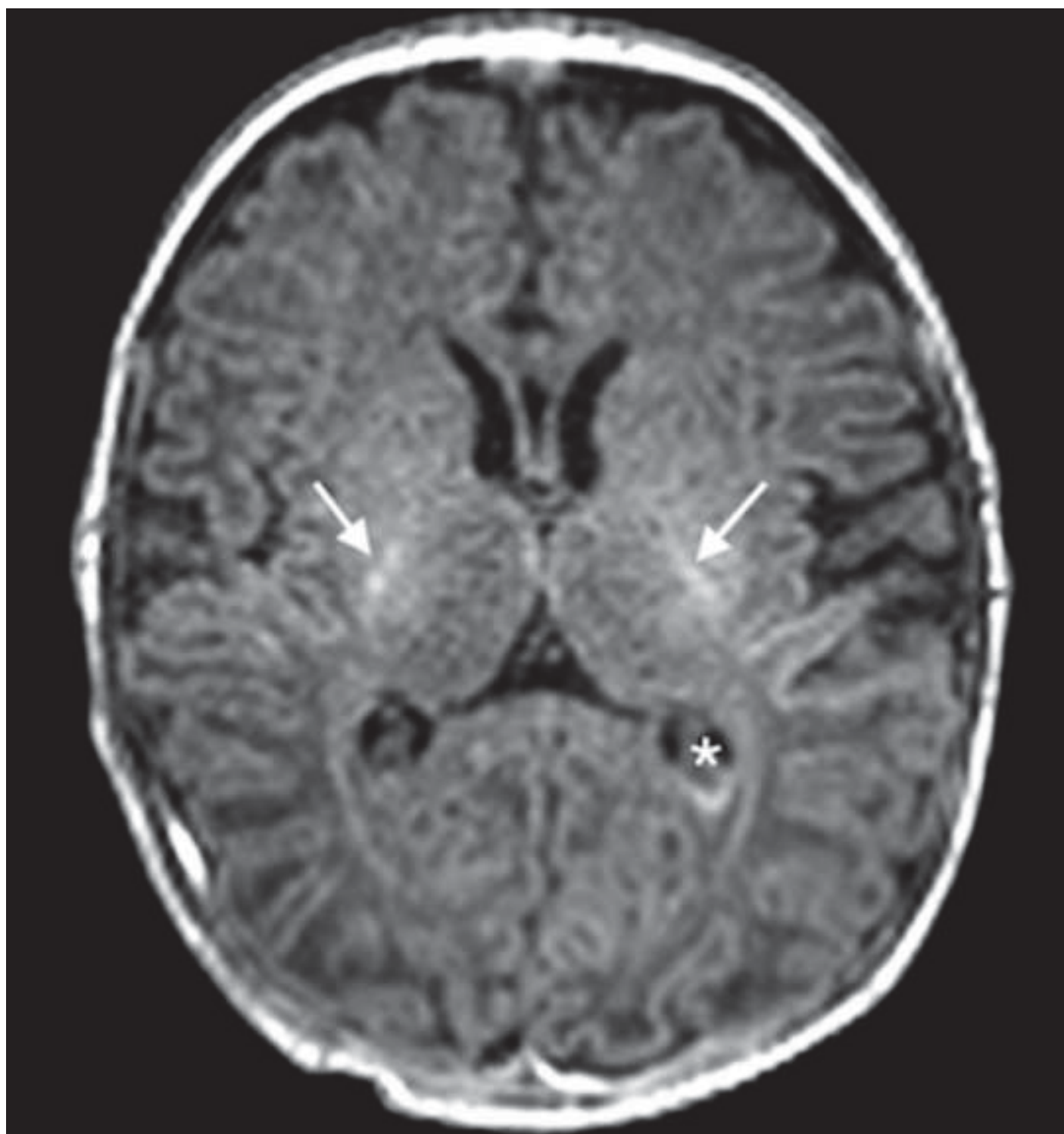
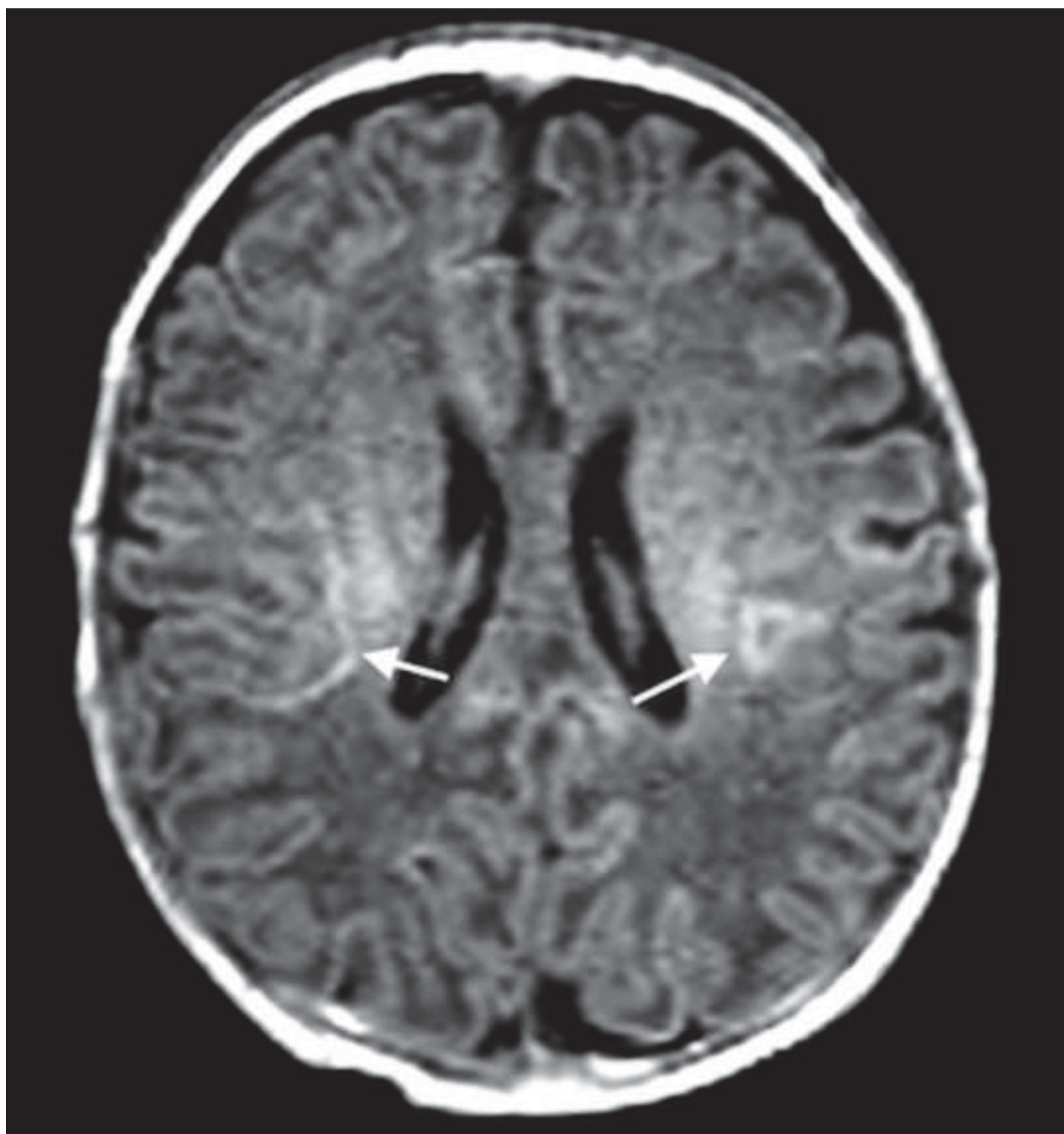


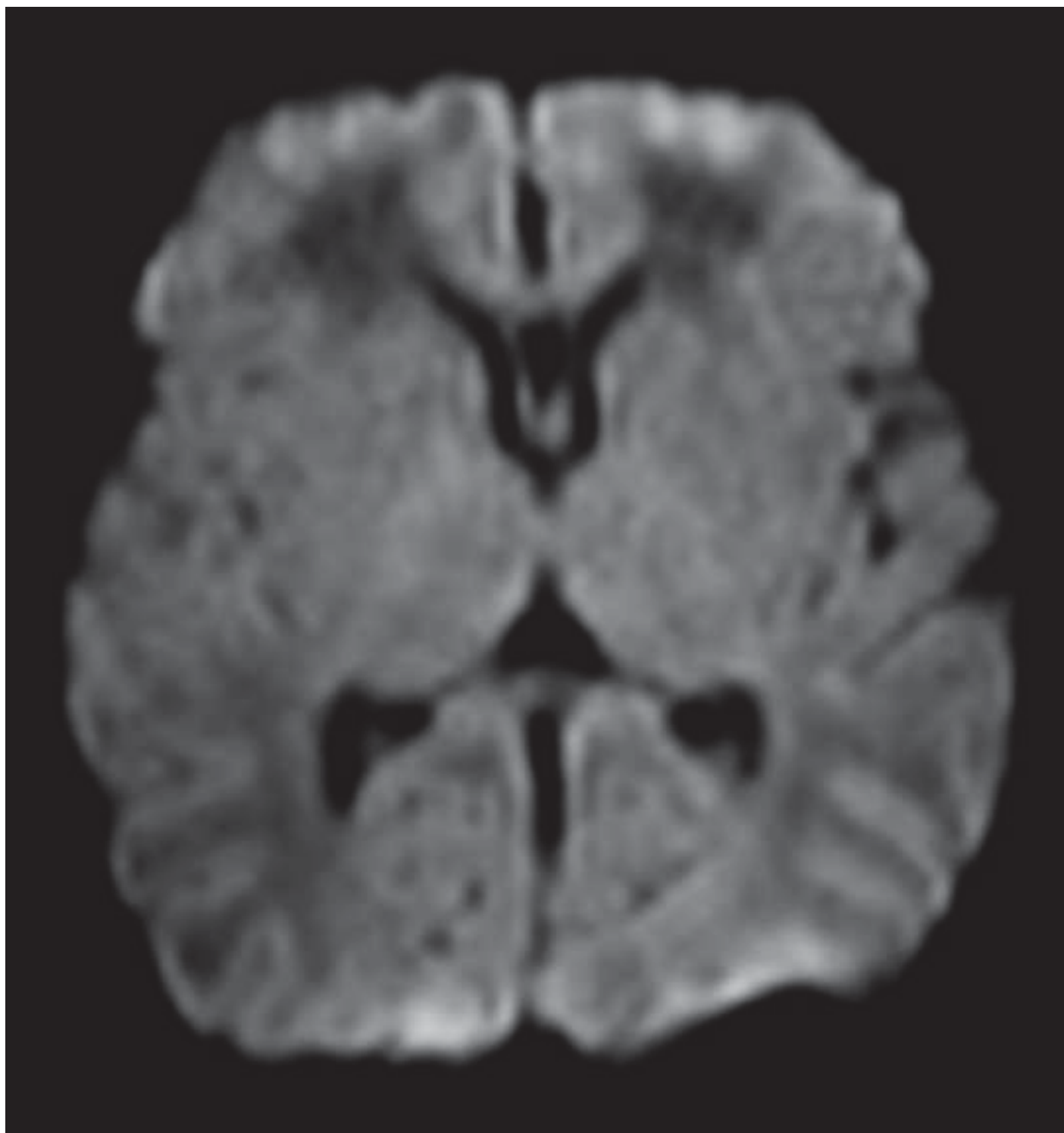
Figure 2

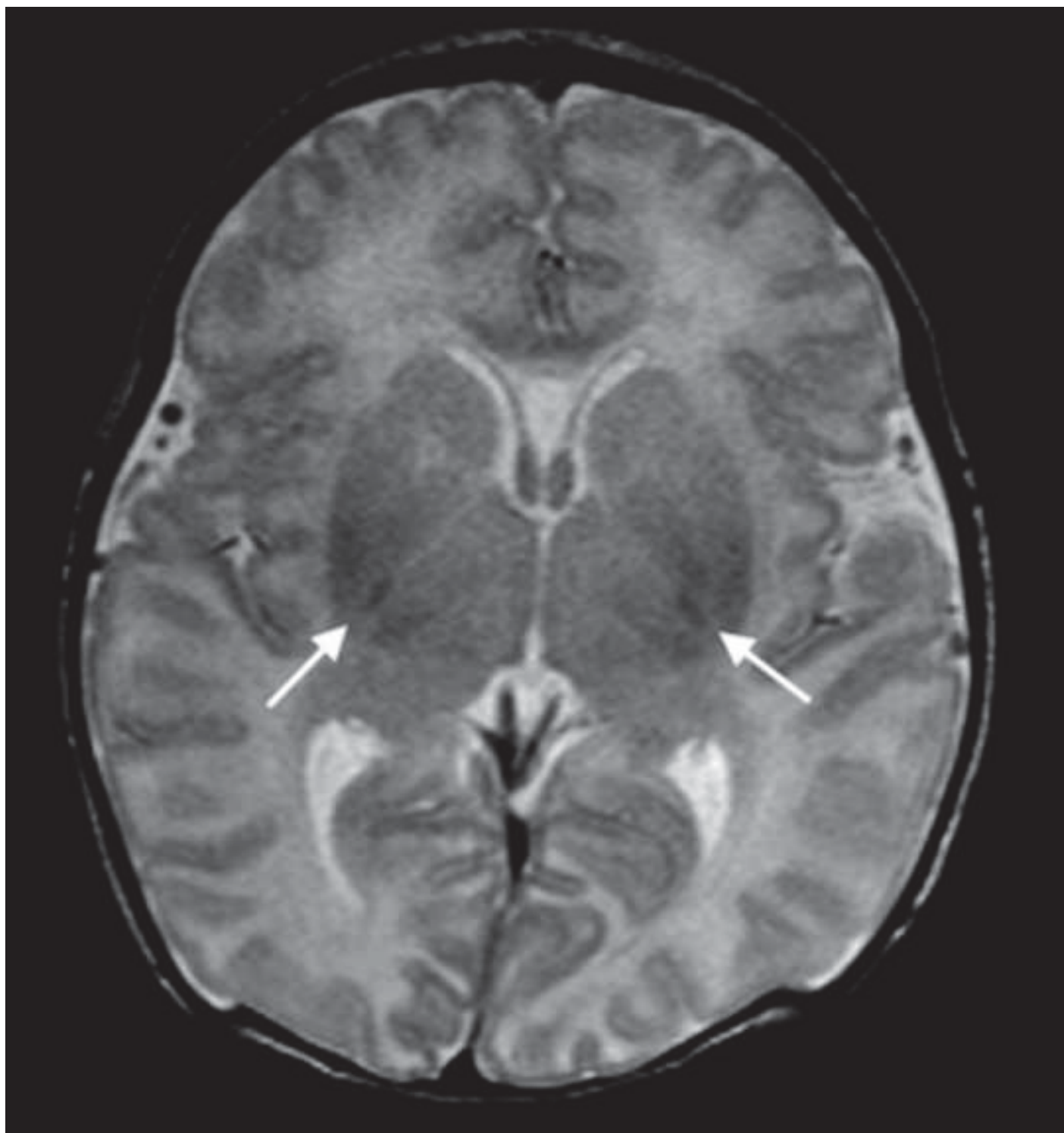


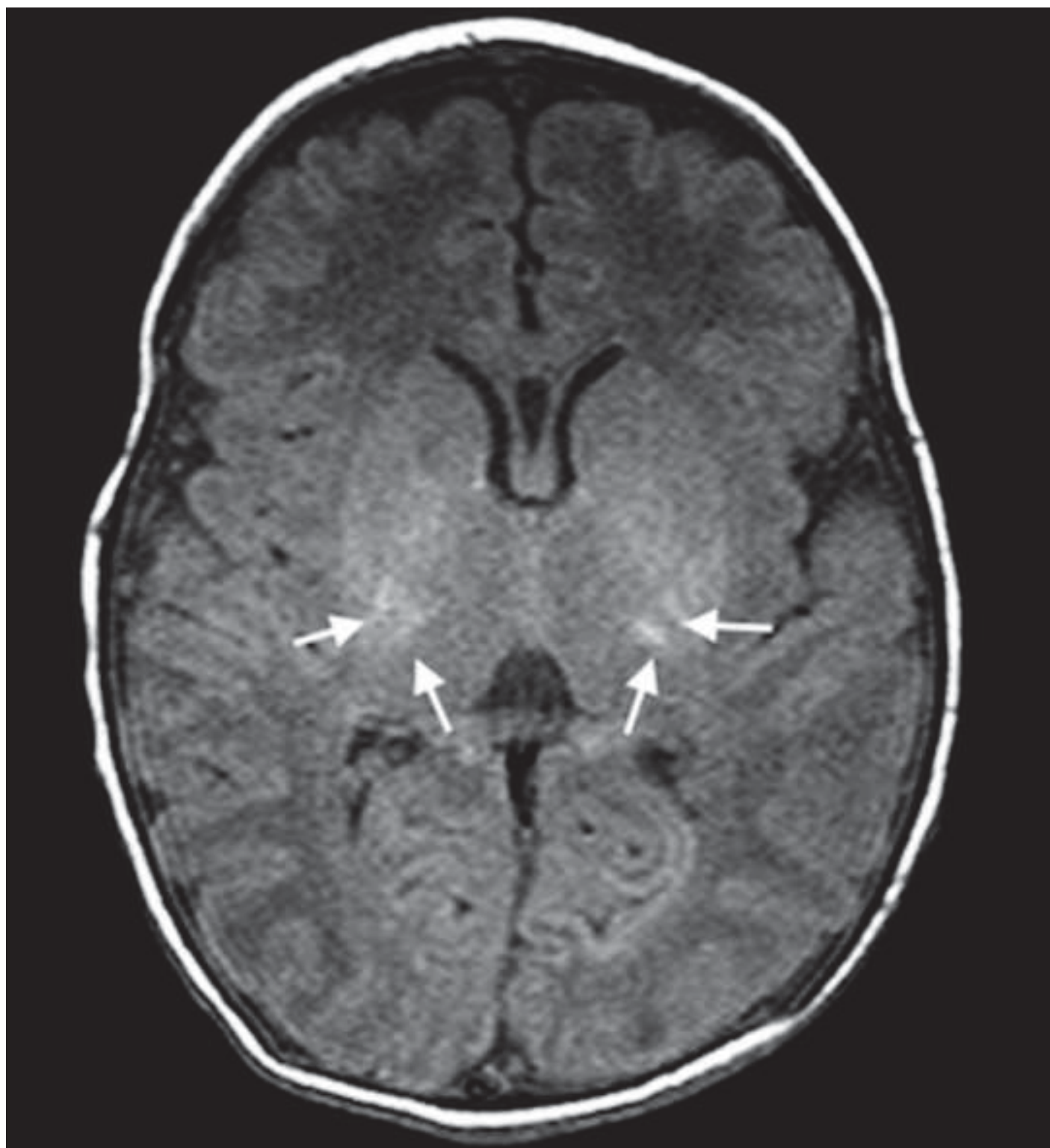


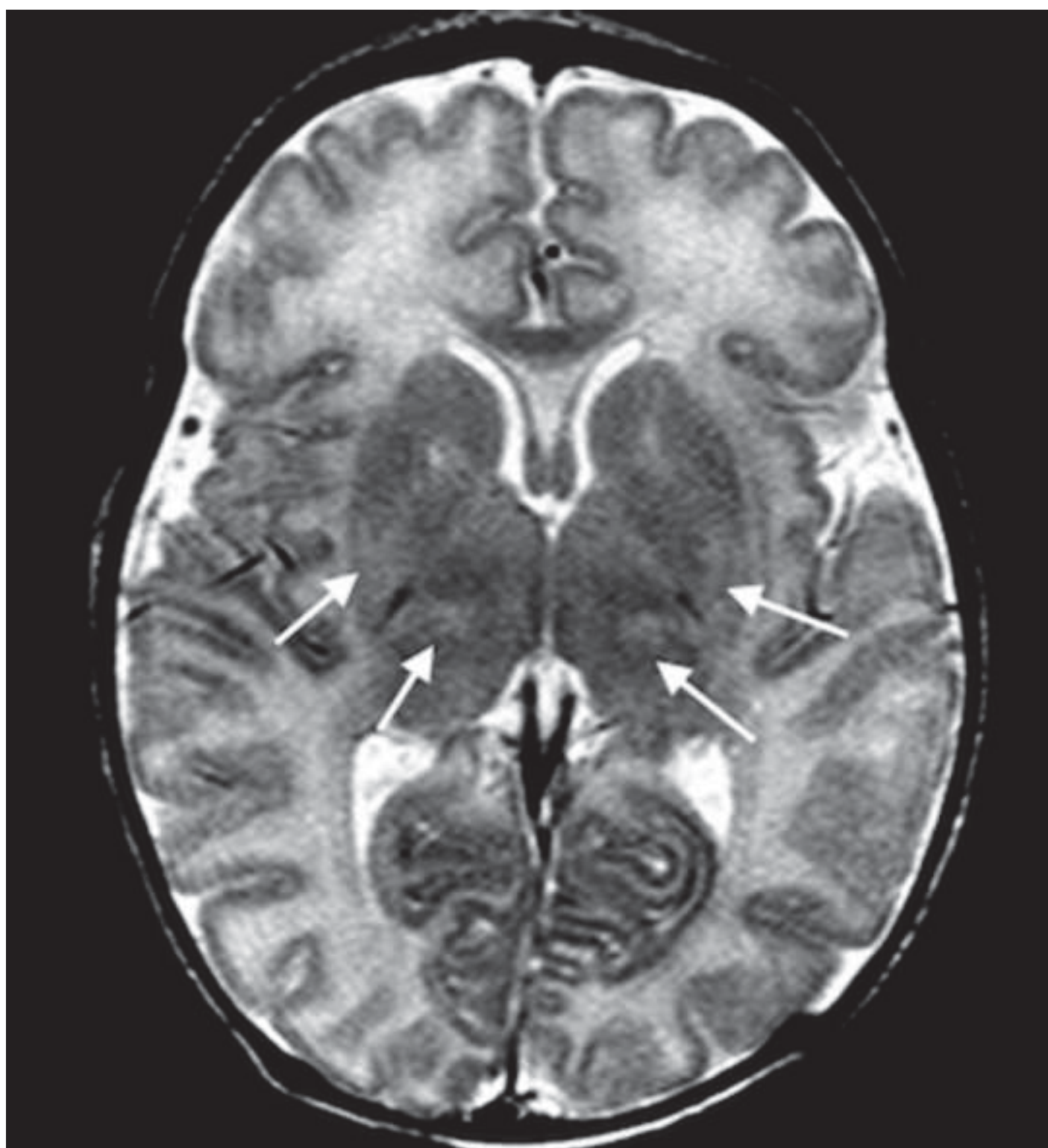












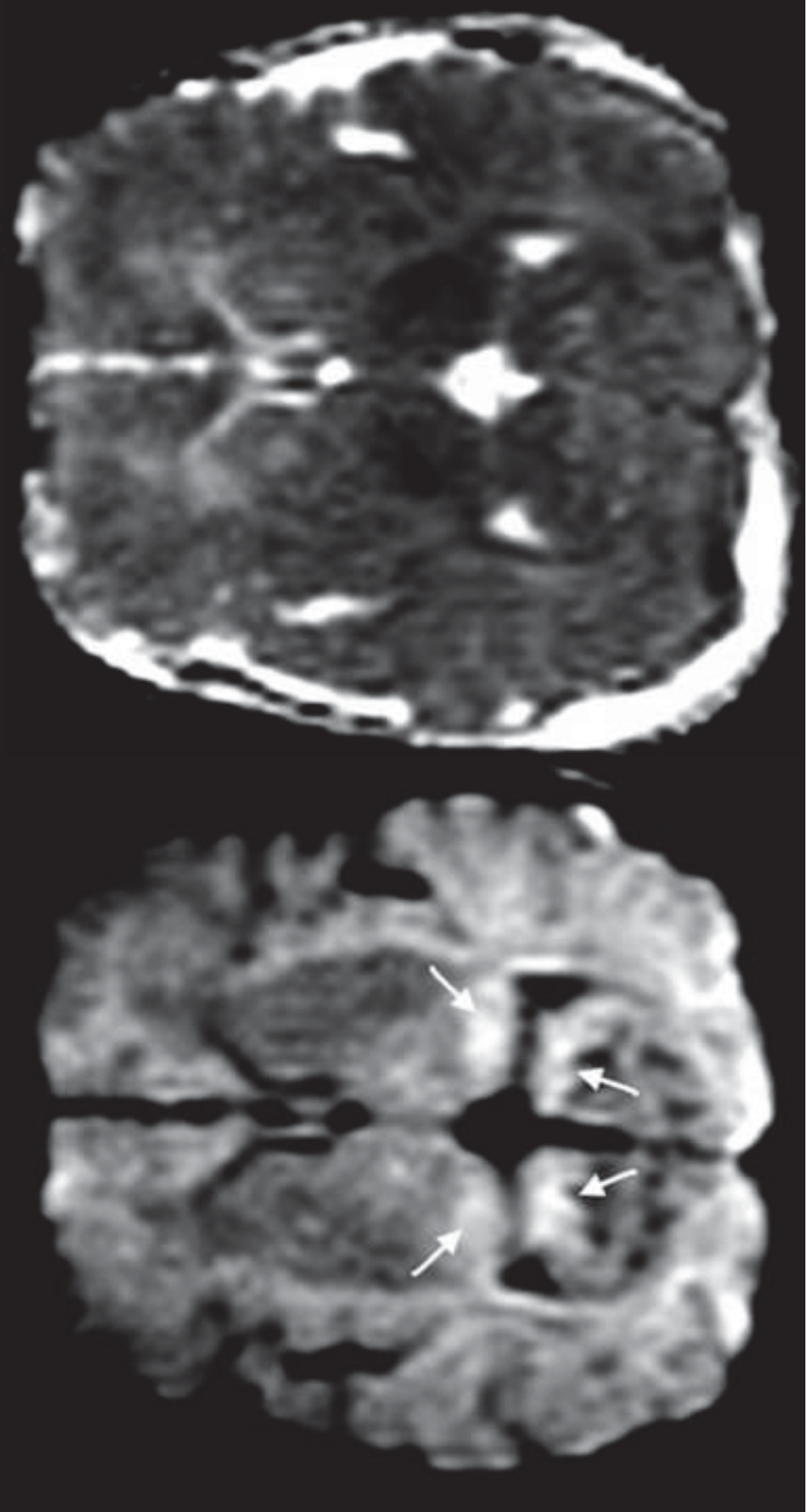


Figure 3a

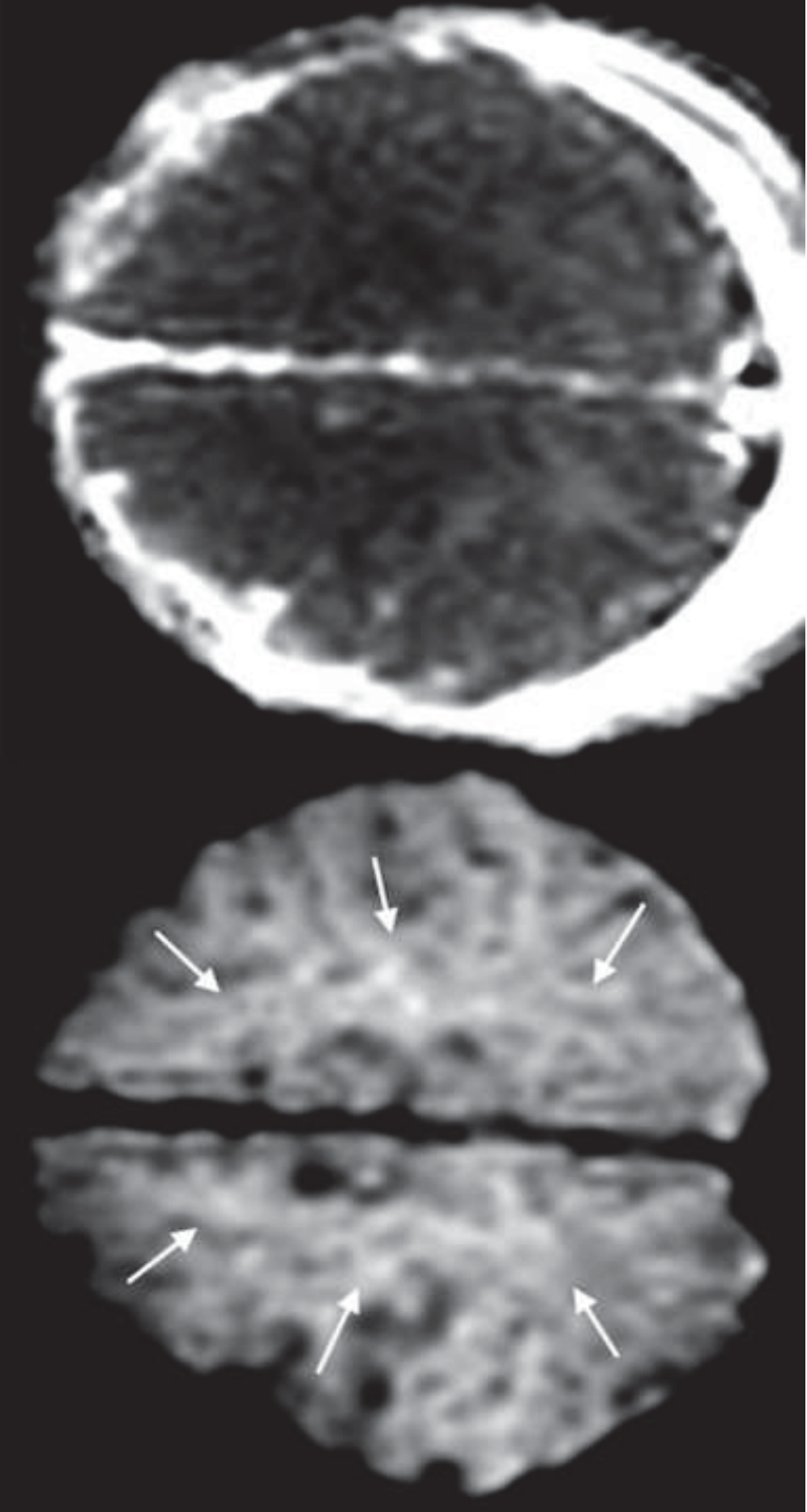


Figure 3b

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