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ORIGINAL ARTICLE

Magnetic Resonance Imaging of Neonates with Hypoxic Ischaemic Encephalopathy

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ABSTRACT

Objectives: *To review magnetic resonance imaging (MRI) of the brain of neonates who underwent cerebral hypothermia for hypoxic ischaemic encephalopathy (HIE) and to correlate the MRI findings with neurodevelopmental outcomes.*

Methods: *Records of all neonates who underwent cerebral hypothermia for moderate-to-severe HIE between May 2010 and October 2014 were reviewed. Signal abnormalities of the basal ganglia and thalami (BGT), posterior limb of the internal capsule (PLIC), cortex at central fissure, cortex at interhemispheric fissure, and white matter were graded. Long-term neurodevelopmental outcomes (overall, gross motor, fine motor, speech and language, and social) were assessed using the Griffiths Mental Development Scales.*

Results: *In 11 male and 4 female neonates, signal abnormality in the PLIC was associated with adverse overall outcome (p = 0.02) and adverse fine motor outcome (p = 0.011). Signal abnormalities in both the PLIC and BGT were associated with adverse fine motor outcome (p = 0.03) and borderline adverse overall outcome (p = 0.06).*

Conclusion: *Signal abnormalities in the PLIC and BGT are predictive of adverse long-term overall and fine motor neurodevelopmental outcomes.*

Key Words: *Hypothermia, induced; Hypoxia-ischemia, brain; Infant, newborn; Magnetic resonance imaging*

中文摘要

新生兒低氧缺血性腦病的磁共振成像

張棨壹、葉精勤、高利源、羅惠明、林慧文

目的：回顧分析接受腦低溫治療低氧缺血性腦病（HIE）的新生兒腦磁共振成像（MRI），並將其與神經發育結果相關聯。

方法：回顧分析從2010年5月至2014年10月所有接受腦低溫治療中至重度HIE的新生兒。將基底神經節和丘腦（BGT）、內囊後肢（PLIC）、中樞裂隙皮質、大腦半球裂隙皮質和白質的信號異常分級。並使用格里菲斯心理發展量表評估長期神經發育（總體、大肌肉運動、精細運動、言語和語言、社交）結果。

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This study has been presented at the International Pediatric Radiology 2016.

結果：在11例男性和4例女性新生兒中，PLIC信號異常與總體結果（p = 0.02）和精細運動結果（p = 0.011）負相關。PLIC和BGT的信號異常與精細運動結果負相關（p = 0.03），和總體結果趨向負相關（p = 0.06）。

結論：PLIC和BGT的信號異常能預測不利的整體和精細運動神經發育結果。

INTRODUCTION

Hypoxic ischaemic encephalopathy (HIE) is a potentially lethal sequela from perinatal insult, accounting for about 20% of all cerebral palsy in childhood.[1] Treatment with cerebral hypothermia may improve neurological outcomes up to 18 months of age, with selective head or whole-body cooling being an increasingly used adjunct treatment.[2,3] Magnetic resonance imaging (MRI) is useful to assess the damage in various brain regions and their neurodevelopmental outcome.[4-6] Nonetheless, the predictive value of MRI for subsequent neurological impairment is not affected by cerebral hypothermia.[7] We reviewed MRI of the brain of neonates who underwent cerebral hypothermia for HIE and correlated the MRI findings with neurodevelopmental outcomes.

METHODS

The research protocol was conducted in compliance with Declaration of Helsinki. Records of all neonates who underwent cerebral hypothermia for moderate-to-severe HIE between May 2010 and October 2014 were reviewed.

Severity of HIE was assessed clinically by neonatologists. Gestational age, Apgar score, cause of antenatal asphyxia, time to start of cooling, presence of clinical or electrical seizures, and age at MRI were recorded. Conventional T1-weighted, T2-weighted, inversion recovery, and echo-planar diffusion-weighted imaging at 1.5 or 3 T were performed to quantify the extent of hypoxic damage.[8] Additional sequences were included if additional complications were suspected. Signal abnormalities of the basal ganglia and thalami (BGT), posterior limb of the internal capsule (PLIC), cortex at central fissure, cortex at interhemispheric fissure, and white matter were graded by a paediatric radiologist and a paediatric neurologist, using the Martinez-Biarge classification.[6,9]

A normal PLIC extends about halfway towards the genu of the internal capsule and is defined as high signal intensity on T1-weighted imaging or inversion recovery sequences and low signal intensity on T2-weighted sequences. An equivocal PLIC is defined as reduced or asymmetrical signal intensity. An abnormal PLIC is defined as loss, reversed, or abnormal signal intensity on

Table 1. MRI findings and neurodevelopmental outcomes of 15 neonates with moderate-to-severe hypoxic ischaemic encephalopathy.

Sex / gestational age (weeks)	Birth weight (kg)	Time to start cooling (hours)	Grading of HIE	Age at MRI (days)	Signal abnormality				
					Basal ganglia and thalami	Posterior limb of the internal capsule	Central fissure	Interhemispheric fissure	White matter (extent)
M / 39	4.06	3	Moderate	4	Mild	Equivocal	Mild	Mild	Severe (focal)
F / 40	2.70	3	Moderate	7	Moderate	Equivocal	Mild	Normal	Severe (diffuse)
M / 41	3.54	>5	Moderate	17	Mild	Normal	Mild	Mild	Severe (diffuse)
M / 40	4.00	4	Moderate	7	Normal	Normal	Normal	Normal	Normal
M / 41	3.29	4.5	Moderate	15	Normal	Normal	Mild	Normal	Normal
F / 38	2.94	1	Moderate	35	Mild	Equivocal	Normal	Normal	Normal
F / 38	3.65	4	Moderate	21	Mild	Equivocal	Normal	Normal	Mild (diffuse)
M / 40	3.44	2	Severe	5	Severe	Abnormal	Mild	Mild	Mild (diffuse)
F / 39	2.82	1.5	Moderate	11	Normal	Normal	Normal	Normal	Normal
M / 40	3.55	1	Moderate	9	Mild	Equivocal	Mild	Normal	Severe (diffuse)
M / 39	3.33	1	Moderate	12	Normal	Normal	Mild	Mild	Moderate (focal)
M / 40	3.24	4	Moderate	11	Mild	Equivocal	Moderate	Moderate	Mild (diffuse)
M / 40	3.40	1.5	Severe	12	Severe	Abnormal	Moderate	Moderate	Moderate (diffuse)
M / 38	3.83	1	Severe	7	Moderate	Abnormal	Moderate	Moderate	Severe (diffuse)
M / 37	2.40	2.5	Moderate	12	Mild	Equivocal	Mild	Mild	Mild (diffuse)

Abbreviation: HIE = hypoxic ischaemic encephalopathy; MRI = magnetic resonance imagining

T1-weighted and/or T2-weighted sequences (Figure 1).

Mild BGT lesions are defined as subtle focal abnormalities, most frequently seen in the ventrolateral nuclei of the thalami and / or posterior putamen. Moderate BGT lesions are defined as multifocal discrete areas of damage or more diffuse abnormal signal intensity in different areas. Severe BGT lesions are defined as widespread abnormal signal intensity in the entire area, with or without caudate nuclei involvement (Figure 2).

Cortical injuries are graded at the central and interhemispheric fissures, with abnormality defined as loss of grey-white matter differentiation (more common during the first week of life) and cortical highlighting (more common after the first week). Abnormality is classified as mild (involving one to two sites), moderate

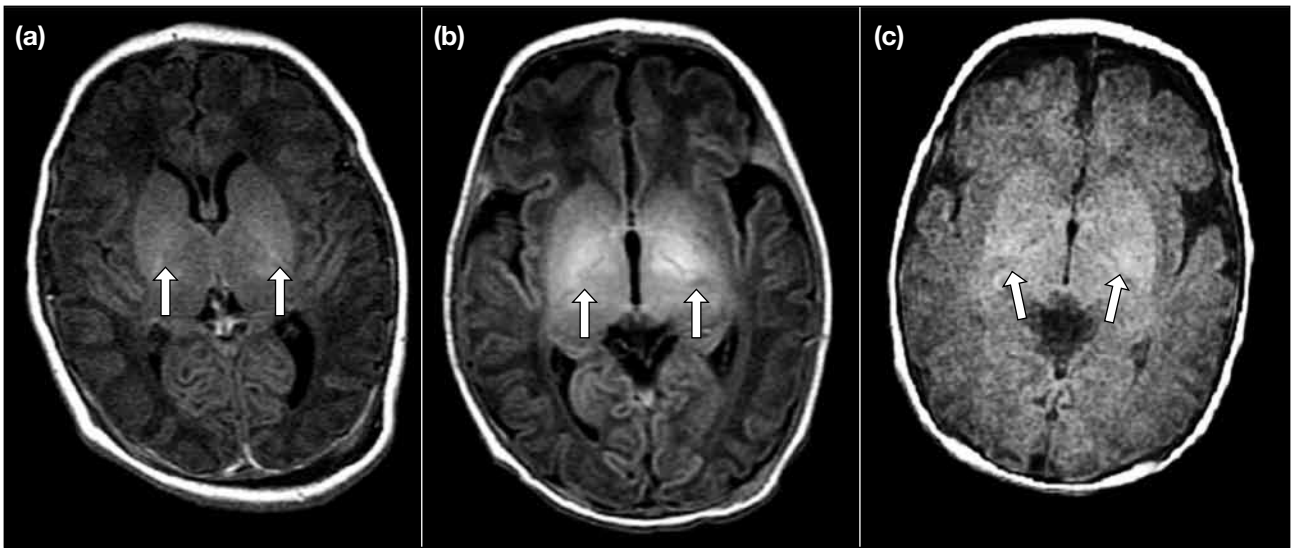

Figure 1. Magnetic resonance imaging of the posterior limb of the internal capsule (arrows) showing (a) normal signal (preserved symmetrical T1 hyperintensity), (b) equivocal signal (preserved but asymmetrical T1 hyperintensity), and (c) abnormal signal (loss of T1 hyperintensity).

Neurodevelopmental outcome					Development
Overall	Gross motor	Fine motor	Speech and language	Social	
Good	Good	Good	Good	Good	Normal
Good	Good	Good	Good	Good	Normal
Poor	Poor	Poor	Poor	Poor	Global delay, mixed spastic dystonic cerebral palsy
Good	Good	Good	Good	Good	Normal
Good	Good	Good	Good	Good	Normal
Good	Good	Good	Delayed	Delayed	Mild speech and social delay
Good	Good	Good	Good	Good	Normal
Poor	Poor	Poor	Poor	Poor	Spastic quadriplegic cerebral palsy
Good	Good	Good	Delayed	Good	Expressive speech delay
Poor	Poor	Delayed	Delayed	Delayed	Autistic spectrum disorder, right hemiparesis
Good	Good	Good	Good	Good	Normal
Good	Good	Good	Good	Good	Normal
Poor	Good	Poor	Good	Good	Unilateral dystonic posturing, gross motor delay
Poor	Poor	Poor	Poor	Poor	Spastic quadriplegia
Good	Good	Good	Good	Good	Normal

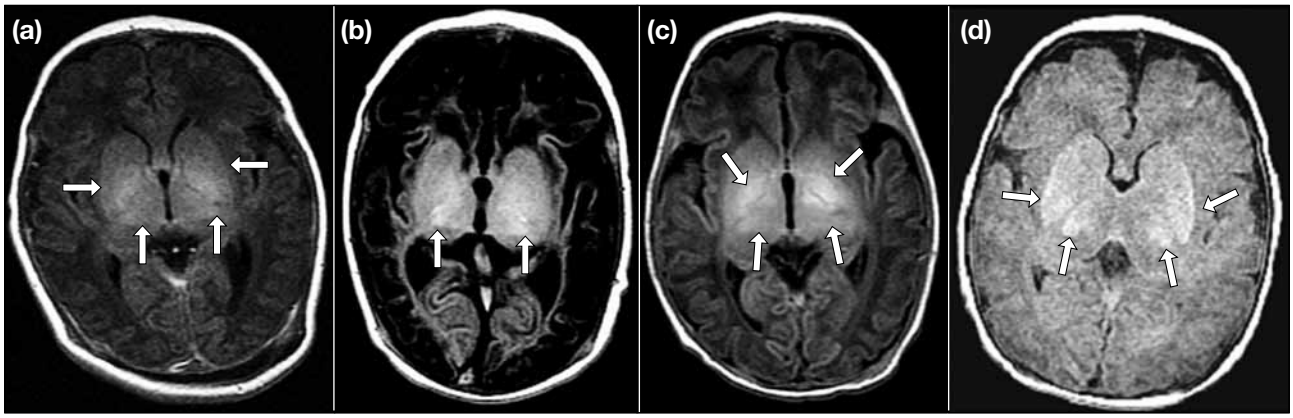

Figure 2. Spin-echo T1-weighted magnetic resonance imaging of the basal ganglia and thalami (arrows) showing (a) normal signal, (b) mild change (subtle focal abnormality, most frequently in the ventrolateral nuclei of the thalami and / or posterior putamen), (c) moderate change (multifocal discrete areas of damage or more diffuse abnormal signal intensity involving different regions), and (d) severe change (widespread abnormal signal intensity involving the entire region, with or without caudate nuclei involvement).

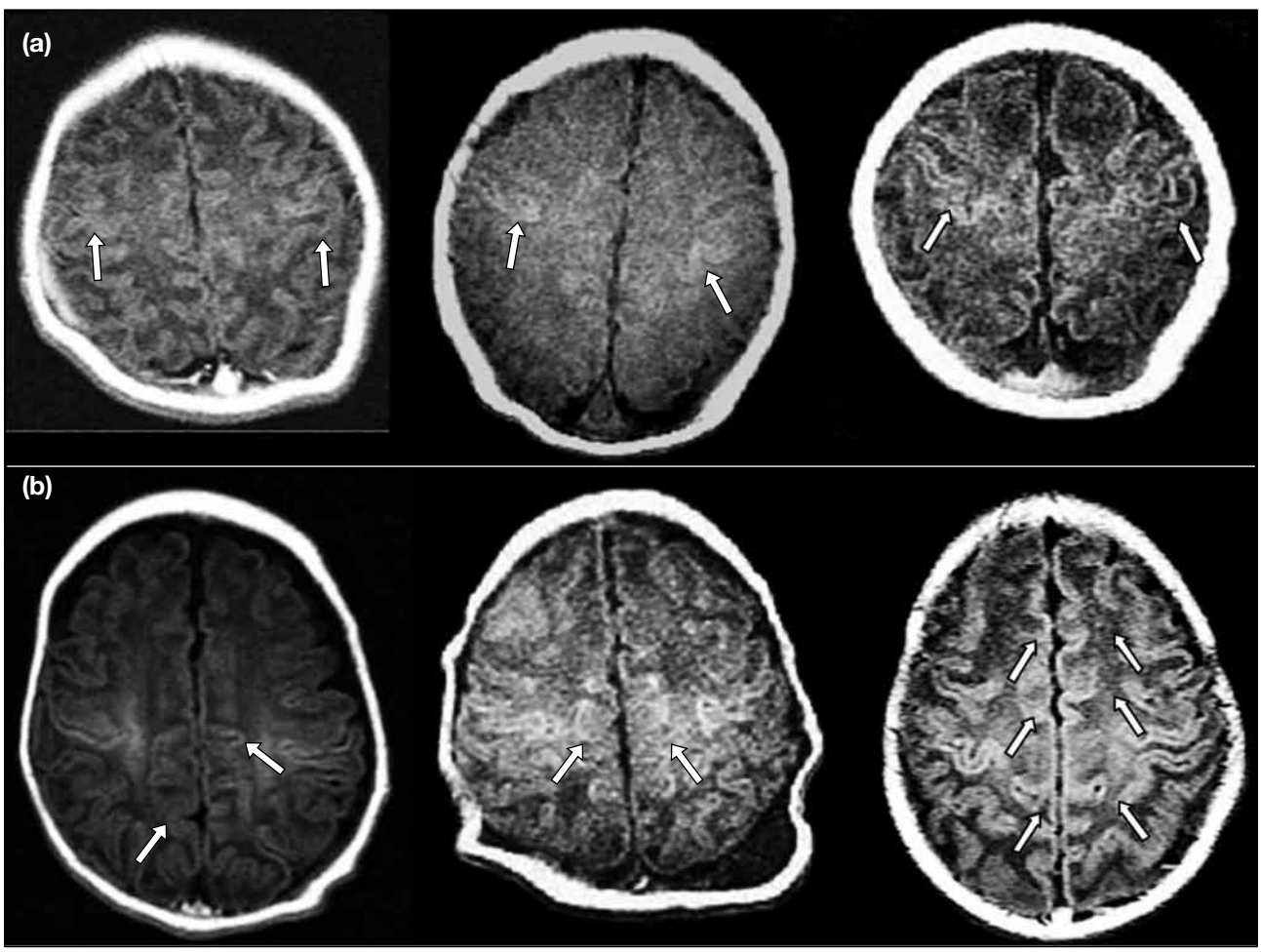

Figure 3. Spin-echo T1-weighted magnetic resonance imaging showing normal signal, mild signal abnormality, and moderate signal abnormality (arrows) of the (a) central fissure and (b) interhemispheric fissure.

(involving three to four sites), and severe (widespread involvement) [Figure 3].

White matter abnormality is defined as increased T2-weighted signal intensity. It is defined as mild when only periventricular white matter is involved, moderate when the abnormality is more marked or when there are discrete areas within the subcortical white matter, and severe when there is widespread abnormality, overt infarction, haemorrhage, and / or loss of grey-white matter differentiation (Figure 4).

Other MRI findings may include epidural haematoma and parenchymal haemorrhage (Figure 5).

Long-term neurodevelopmental outcomes (overall, gross motor, fine motor, speech and language, and social) were assessed using the Griffiths Mental Development Scales by the paediatric neurology team.[10] Fisher's exact test was used to determine the association between MRI signal abnormalities and long-term neurodevelopmental outcomes. A p value of <0.05 was considered statistically significant.

RESULTS

11 male and 4 female neonates born after 37 to 41 (mean, 39) weeks of gestation were included (Table 1). One of them underwent cerebral hypothermia after 5 hours due to logistic reasons. MRI of the brain was performed at the age of 4 to 35 (mean, 11) days. Among the 15 neonates, signal abnormalities were noted in the BGT (n = 11; 7 mild, 2 moderate, 2 severe), PLIC (n = 10; 7 equivocal, 3 abnormal), central fissure (n = 11; 8 mild, 3 moderate), interhemispheric fissures (n = 8; 5 mild, 3 moderate), and white matter (n = 11; 4 mild, 2 moderate, and 5 severe, with 3 focal and 8 diffuse abnormalities).

Among the 15 neonates, overall neurodevelopmental outcome was good in 10 and poor in 5; gross motor outcome was good in 11 and poor in four; fine motor outcome was good in 10 and delayed / poor in five;

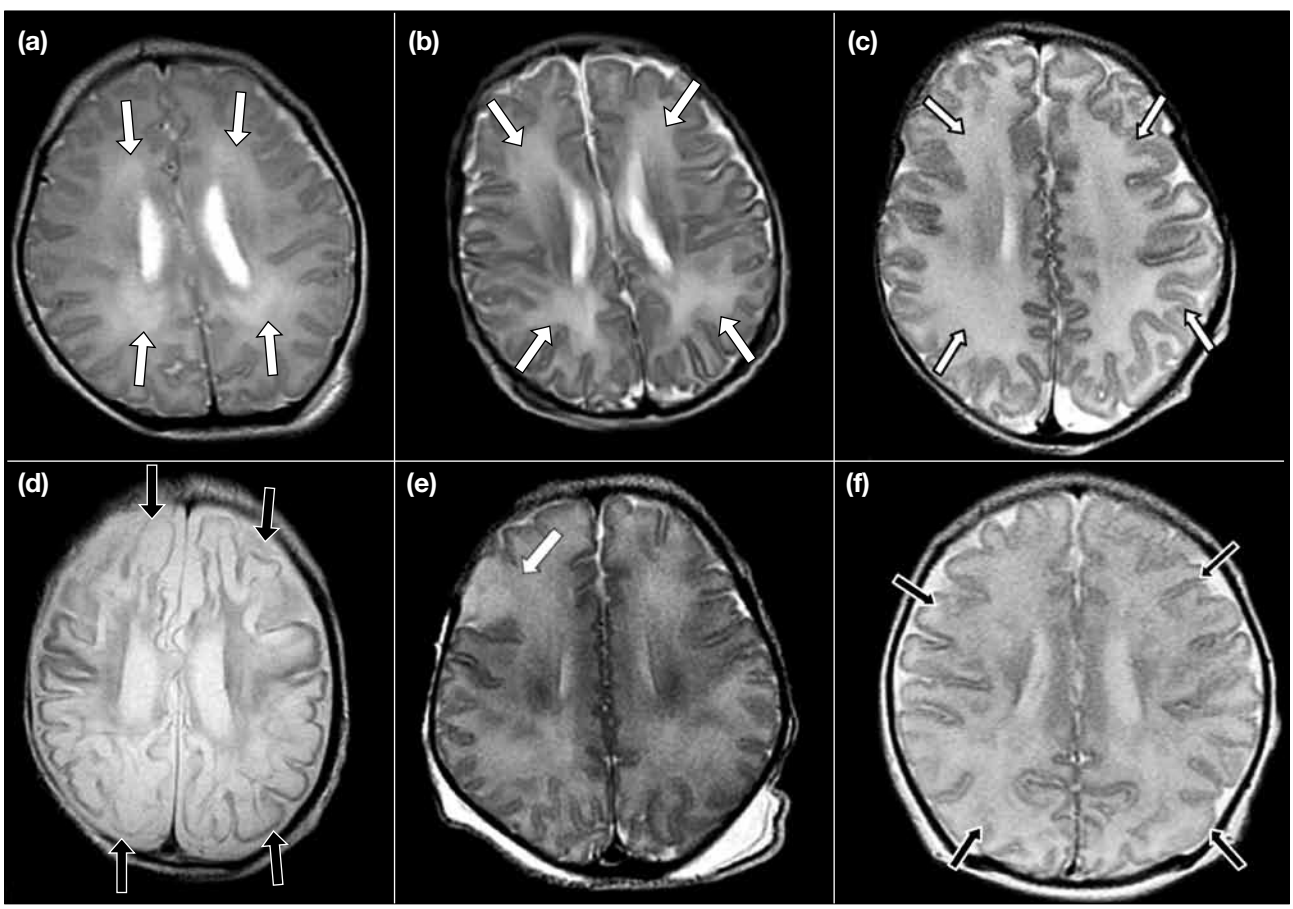

Figure 4. Fast spin-echo T2-weighted magnetic resonance imaging of the white matter (arrows) showing (a) normal signal, (b) mild, (c) moderate, (d) severe, (e) focal, and (f) diffuse signal abnormalities.

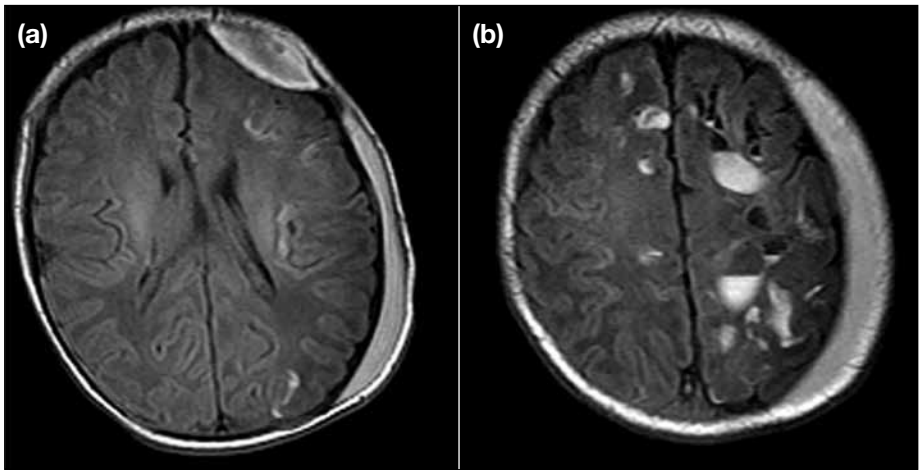

Figure 5. Spin-echo T1-weighted magnetic resonance imaging showing (a) left epidural haematoma, and (b) parenchymal haemorrhage.

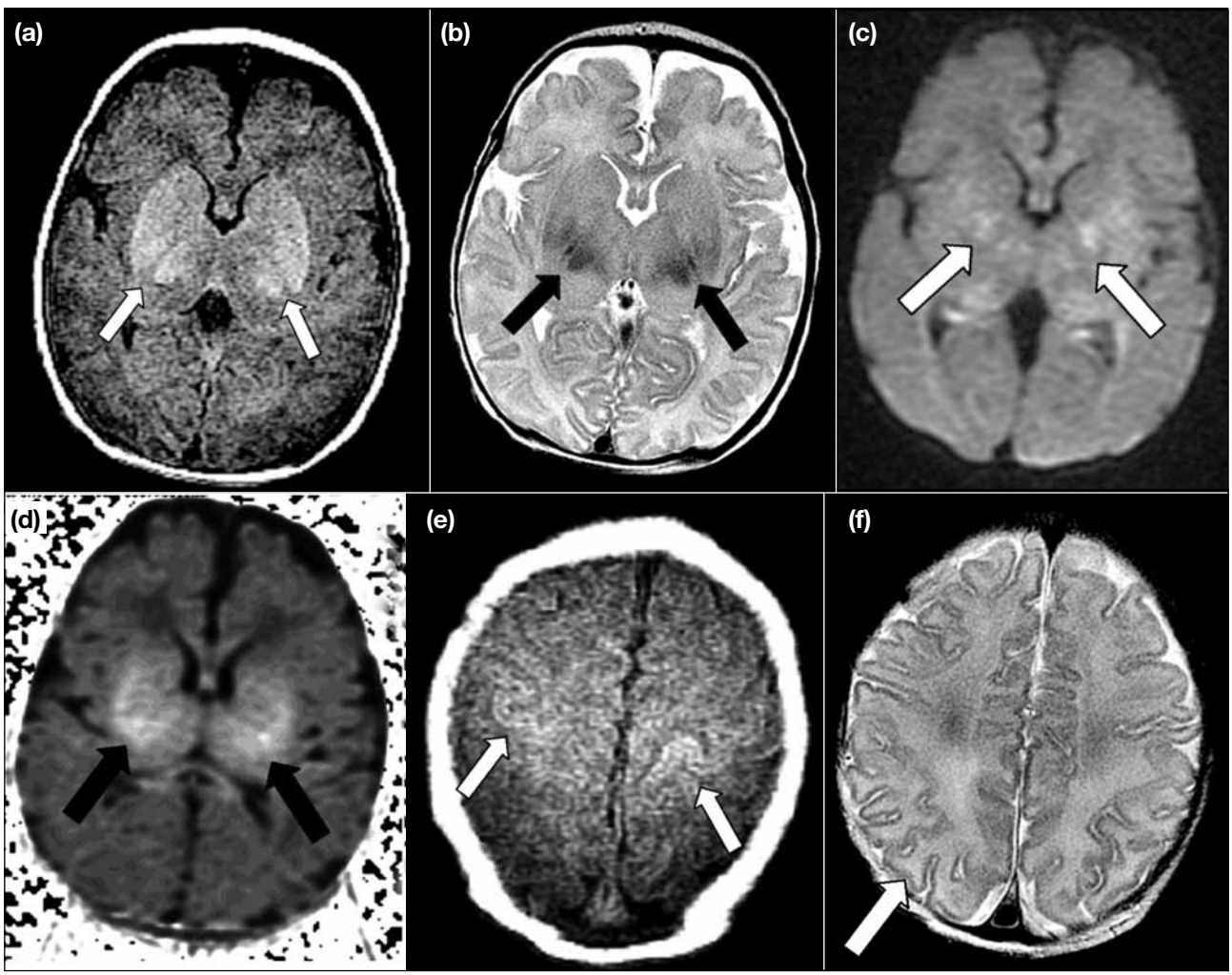

Figure 6. Magnetic resonance imaging of patient 8 with severe hypoxic ischaemic encephalopathy showing (a) T1-hyperintense and (b) T2-hypointense bilateral deep grey matter including bilateral thalami, putamina, and globus pallidi (arrows), restricted diffusion at the bilateral posterior limb of the internal capsule on (c) diffusion-weighted image and (d) apparent diffusion coefficient image (arrows), (e) mild signal abnormality at central and interhemispheric fissures on T1-weighted image (arrows), and (f) mild signal abnormality of diffuse white matter with increased T2-weighted signal at the bilateral frontoparietal regions (arrow).

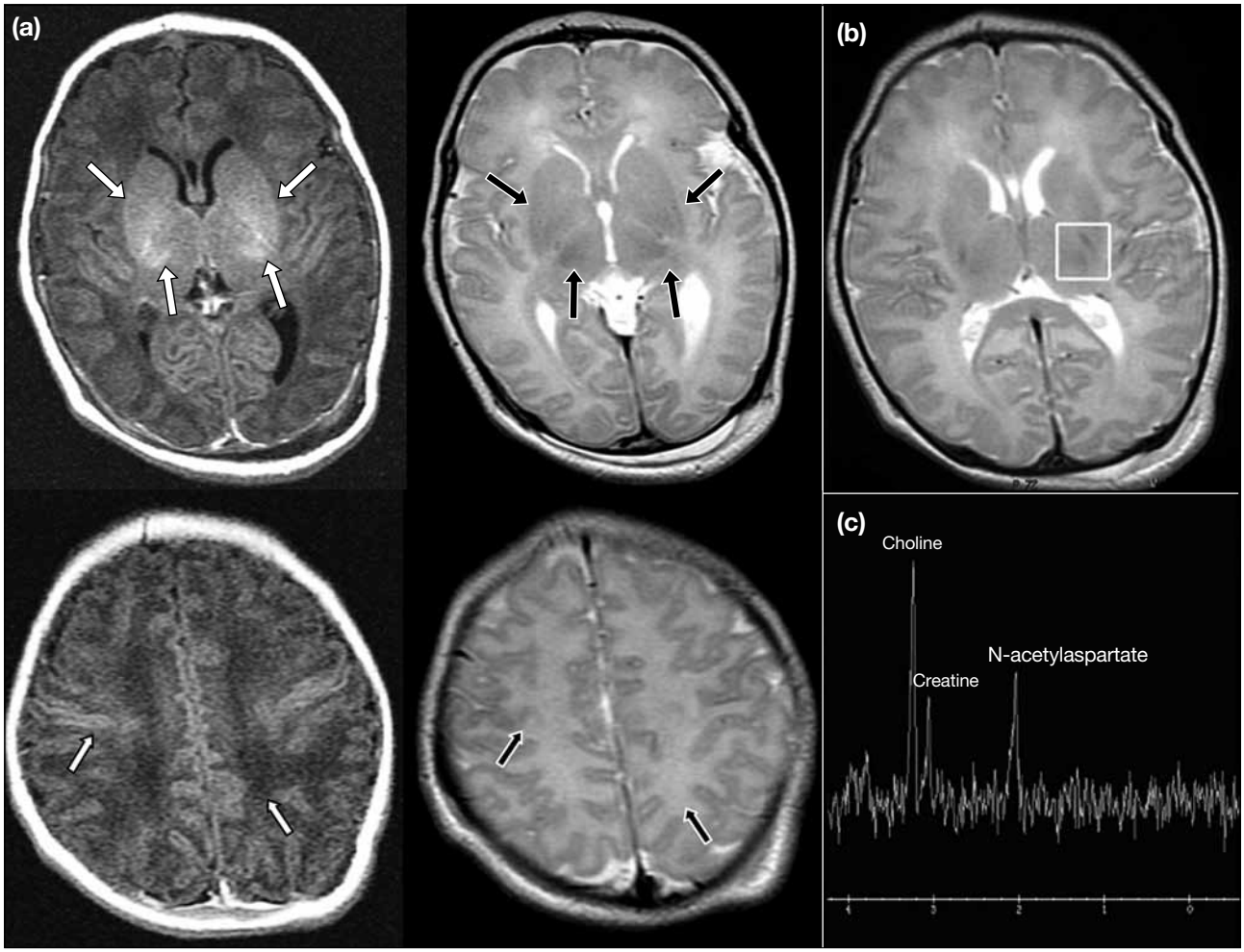

Figure 7. (a) Spin-echo T1-weighted magnetic resonance imaging of patient 4 with moderate hypoxic ischaemic encephalopathy showing normal basal ganglia and thalami, posterior limb of the internal capsule, and cortical grey and white matter (arrows). (b) Single-voxel proton magnetic resonance spectroscopy at the left basal ganglia (box) with echo time of 144 ms showing (c) normal N-acetylaspartate, choline, and creatine peaks for neonates.

Table 2. Correlation of signal abnormalities in various regions of the brain and neurodevelopmental outcomes.

Signal abnormality	Neurodevelopmental outcome				
	Overall	Gross motor	Fine motor	Speech and language	Social
PLIC	0.022	0.528	0.011	0.127	0.108
BGT	0.237	0.516	0.251	0.509	0.497
Central fissure	0.231	0.516	0.251	0.251	0.528
Interhemispheric fissure	0.282	0.569	0.085	0.491	0.231
White matter	0.231	0.516	0.251	1.000	0.528
Both PLIC and BGT	0.06	0.49	0.03	0.18	0.22

Abbreviations: BGT = basal ganglia and thalami; PLIC = posterior limb of the internal capsule.

speech and language outcome was good in nine and delayed / poor in six; and social outcome was good in 10 and delayed / poor in five. Adverse motor outcomes included dystonic cerebral palsy (n = 1), mixed spastic dystonic cerebral palsy (n = 1), spastic quadriplegic cerebral palsy (n = 2), and right hemiparesis (n = 1). Other adverse outcomes included mild speech and social delay (n = 1), expressive speech delay (n = 1), and autistic spectrum disorder (n = 1). MRI findings of patients 8 and 4 are illustrated in Figures 6 and 7,

respectively.

Signal abnormality in the PLIC was associated with adverse overall outcome (p = 0.02) and adverse fine motor outcome (p = 0.011). Signal abnormalities in both the PLIC and BGT were associated with adverse fine motor outcome (p = 0.03) and borderline adverse overall outcome (p = 0.06) [Table 2].

DISCUSSION

HIE is associated with high morbidity and mortality.[1] Expedient cerebral hypothermia can improve neurological outcome.[2] Clinical course, electrophysiological study, cranial sonography, MRI, and MRI spectroscopy have been used to predict outcome. MRI of the brain in the first 2 weeks of life is most sensitive and specific to assess severity of injury and potential reversible complications.[11] Signal abnormality in the PLIC is a predictor of adverse neurodevelopmental outcome.[12,13] However, the predictive value of MRI for subsequent neurological impairment is not affected by therapeutic hypothermia.[7] More severe signal abnormalities in the PLIC and BGT infer a poorer prognosis. Axial T1- and T2-weighted and diffusion-weighted images are useful in assessing PLIC and BGT injuries. Restricted diffusion often implies more severe injuries. At 1 to 4 days after delivery, diffusion-weighted sequence can better observe signal abnormality, compared with conventional imaging.[11] Nonetheless, optimal timing of MRI and the time of appearance of restricted diffusion remain unknown, as images do not differ between 4 and 11 days after birth.[14] Deep grey matter injury as a result of prolonged partial asphyxia is most prevalent in patients with HIE, followed by white matter and cortical injuries.[15,16] Severe white matter and cortical injuries are associated with various adverse developmental outcomes, including cognitive, visual, language, behaviour, and seizure problems.[10,17,18] Children with normal or solitary white matter lesions were at increased risk of motor and cognitive impairment at 9 to 10 years compared with controls.[19,20] Social and speech and language skills are more advanced neurodevelopmental milestones, and long-term follow-up is needed to detect adverse outcomes. In patients with no or minimal brain injury, MRI has a negative predictive value of 74% for subsequent normal neurodevelopment at the mean age of 22 (standard deviation, 7) months.[21] Conventional MRI sequences may not be sensitive enough to detect subtle brain injury; MRI spectroscopy, fractional anisotropy, and diffusion tensor imaging may enable more accurate prediction of neurodevelopmental outcomes.[22]

Our study was limited by its small sample size. The patient who underwent cerebral hypothermia after 5 hours may have confounded the outcome.

CONCLUSION

Signal abnormality in the PLIC and BGT are predictive of adverse long-term overall and fine motor neurodevelopmental outcome.

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