Grey matter injury patterns in cerebral palsy: associations between structural involvement on MRI and clinical outcomes

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ABBREVIATION
GMI Grey matter injury

AIMS In a population cohort of children with grey matter injury (GMI) and cerebral palsy (CP), we aimed to describe and classify magnetic resonance imaging characteristics specific to GMI, and to identify key structure–function associations that serve as a basis for rating GMI in clinically relevant ways.
METHOD Symmetry, extent of cerebral injury, and pathological pattern for 54 children (37 males, 17 females) with CP and a predominant GMI pattern on chronic-phase magnetic resonance imaging were related to gross motor function, motor type and topography, epilepsy, intellectual disability, blindness, and deafness.
RESULTS Relative to mild GMI where there was no pallidal abnormality, severe GMI, comprising pallidal abnormality alone or in conjunction with other deep nuclear and generalized cortical–subcortical involvement, was strongly associated with Gross Motor Function Classification System levels IV to V (OR 35.7 [95% CI 3.5, 368.8]). Involvement of the basal ganglia was associated with non-spastic/mixed motor types, but predominantly where cortical–subcortical grey and white matter involvement was not extensive. The prevalence of epilepsy was highest where there was diffuse cortical–subcortical involvement and white matter loss.
INTERPRETATION Better understanding of structure–function relationships in CP and GMI, and how to rate the severity of GMI, will be helpful in the clinical context and also as a basis for investigation of causal pathways in CP.

Various patterns of cerebral abnormality have been identified on magnetic resonance imaging (MRI) of children with cerebral palsy (CP). A pattern of bilateral injury primarily affecting the deep grey nuclei, cortex, and subcortex is classified under the general heading of grey matter injury (GMI) and occurs in approximately 14% to 22% of children with CP.[1] Particular topographical distributions of GMI are indicative of the likely pathogenesis.

GMI is commonly associated with perinatal hypoxia–ischaemia/hypotension in term newborn infants, but may also occur in preterm neonates and may be the result of infection/inflammation, haemorrhage, toxins, or acquired conditions such as kernicterus and hypoglycaemia. There is frequently interplay between these pathogenic pathways. Hypoxia–ischaemia/hypotension in the term newborn infant results in distinctive patterns of GMI that are believed to be determined by the abruptness, severity, and duration of insult. Experimental studies show two classic patterns that can also be seen pathologically or detected on MRI in the human infant – a deep nuclear-cortical pattern and a parasagittal watershed pattern.[2–5] A deep nuclear-cortical pattern follows moderate to profound hypoxia/hypotension where the insult is severe, abrupt, and/or prolonged. Although variable, the brain regions reported to be most affected in the term infant include the ventrolateral thalami, posterior putamina, the sensory-motor (rolandic) cortex, and the subrolandic white matter.[3,5–10] Severe or abrupt insults may cause additional injury to the globus pallidus, hippocampus, brainstem, or all supratentorial structures.[3,11,12] In contrast, a mild-to-moderate insult, or a more gradual onset over at least 1 or more hours, enables a relative redistribution of blood flow to protect the brainstem, sensory-motor cortex, and central grey matter.[13,14] The burden of injury then falls on the parasagittal regions of the cortex and subcortical white matter in the arterial watershed territories, predominantly resulting in discrete, often multicystic, infarctions that in severe injury may involve the entire cortex and underlying white matter.[3,5,13,15] In human neonates, a mixed pattern of injury is commonly seen where parasagittal watershed injury co-exists with a deep nuclear-cortical pattern.[5] In contrast to these patterns of hypoxic–ischaemic/hypotensive injury,

kernicterus is typically associated with bilateral insults isolated to the globus pallidus or subthalamic nucleus,[16,17] and hypoglycaemia with injury localized to the parietal and occipital lobes, with possible extension into the frontal lobes and globus pallidi.[18]

Broad MRI patterns are preferentially associated with different clinical outcomes in children with CP,[19–21] but we are only just beginning to better understand the particular imaging characteristics within each pattern that predict outcome.[7–9,22–29] More detailed information on structure–function relationships from population CP cohorts will assist clinicians in understanding and explaining the results of MRI studies to families, and will facilitate research aimed at a more in-depth exploration of causal pathways to CP. In a large population cohort of children with GMI and CP, we aimed to describe and classify MRI characteristics specific to GMI, and to identify key structure–function relationships that would serve as a basis for rating the severity of GMI in clinically relevant ways.

What this paper adds

- Pallidal abnormality was common and, combined with generalized cortical–subcortical injury, was the strongest predictor of poor gross motor function in children with CP and grey matter injury (GMI).
- A non-spastic motor type was associated with non-diffuse cortical–subcortical injury, no white matter loss, and involvement of the basal ganglia.
- The prevalence of epilepsy was highest in the context of diffuse cortical–subcortical involvement and white matter loss.

METHOD

The study was undertaken at the Melbourne Children's campus, Australia. Ethics approval was granted by the Royal Children's Hospital Human Research Ethics Committee.

Participants

Eligible participants were identified from the Victorian CP Register, an ongoing population register of individuals with CP born or living in the Australian state of Victoria since 1970. Brain MRI was sought for a 1999 to 2008 Victorian birth cohort of children with presumed pre/perinatally acquired CP. For 84% of scans, a MAGNETOM Avanto 1.5T (Siemens AG, Erlangen, Germany) was used. The scanning protocol was dependent on clinical indication, but all scans included T1- and T2-weighted axial sequences, and most included sagittal sequences. Fluid-attenuated inversion recovery and diffusion-weighted imaging sequences were available in 88% and 50% of scans respectively. Children were included if they had available MRI performed after the first 6 months of life and imaging classified to a single pattern of GMI, defined as increased T2 and FLAIR signal and/or volume loss affecting the deep grey matter alone or both deep grey matter and cortical–subcortical regions. Classification was made through standardized assessment of the most recent, good quality, clinical MRI by one of two paediatric radiologists (CDD, MRD), blind to clinical information and previously generated reports. Scans were deemed of insufficient quality if they were degraded by movement artefact to the extent that assessment of abnormality was not possible. Difficulties with classification were resolved by consensus.

MRI data

Structural involvement in terms of signal abnormality and/or volume loss was categorized as symmetrical (R=L) or asymmetrical (L>R or R>L). In the deep grey matter, signal abnormality and volume loss were recorded separately for the thalamus, putamen, and globus pallidus. Extent of deep grey involvement was categorized as (1) thalamus only; (2) thalamus and putamen; (3) thalamus, putamen, and globus pallidus; and (4) globus pallidus only. In the cerebral cortex–subcortex, signal abnormality and volume loss were recorded for the sensory-motor cortex, hippocampus, and for each of the four lobes. Extent of involvement was categorized as (1) none/focal/parasagittal; (2) central sulcus; (3) central sulcus and hippocampus; and (4) diffuse. Additional assessments were made of the degree of white matter loss (none, mild, moderate, or severe) and involvement of the cerebellum.

Clinical and demographic data

Clinical and demographic data extracted from the Victorian CP Register comprised motor types (spastic, spastic-dyskinetic, dyskinetic, other), topographical pattern (bilateral symmetric, bilateral asymmetric, unilateral), Gross Motor Function Classification System (GMFCS) level (dichotomized as levels I–III and IV–V to represent ambulant and non-ambulant groups), and presence of epilepsy, intellectual impairment, blindness, and bilateral deafness. Clinical data are updated for the register from the child's medical record after each child turns 5 using previously published definitions.[30–32]

Statistical analysis

Relationships between MRI characteristics were investigated using Cuzick's nonparametric test for trend across ordered groups.[33] Extent of involvement in the deep grey matter, cortex–subcortex, white matter, and cerebellum was tabulated by dichotomized GMFCS, motor type, motor topography, and each comorbidity. Fisher's exact tests were used to investigate the strength of evidence for a true association between MRI characteristics and clinical domains. Logistic regression analysis with factor terms was used to assess the odds and 95% confidence intervals of classification to GMFCS levels IV to V relative to levels I to III for each imaging variable category or level. Based on the strength of these associations, a simple rating scale was proposed and logistic regression analysis was used to assess the odds of classification to GMFCS levels IV to V for each rating. Statistical analysis was conducted using Stata 13.1 (Stata Corp 2013, College Station, TX, USA).

RESULTS

The study group comprised 54 children (37 males [68%] and 17 females [32%]) born between 1999 and 2008 with

GMI on MRI performed after 6 months of age. Additional characteristics of the cohort are shown in Table I.

MRI characteristics

Cerebral abnormalities were symmetrical in 45 children (83%). Of the nine children with asymmetrical lesions, eight had greater involvement of the left hemisphere. Frequency distributions for extent of involvement in the deep grey matter, cortex–subcortex, white matter, and cerebellum are shown for the entire group in the final columns of Table II. The most common category of deep nuclear involvement, seen in 32 scans (59%), was bilateral involvement of the thalamus, putamen, and globus pallidus. Cortical–subcortical involvement was fairly evenly distributed between the four categories. Twenty children (37%) had severe white matter loss in all lobes, and ten (18%) had abnormality detected in the cerebellum.

Table I: Characteristics of 54 children born between 1999 and 2008 with cerebral palsy and grey matter injury on magnetic resonance imaging performed after 6 months of age

	Participants with GMI *n*=54 (%)
Year of birth	
1999–2003	33 (61.1)
2004–2008	21 (38.9)
Sex	
Male	37 (68.5)
Female	17 (31.5)
Birth gestation	
Preterm (<37)	5 (9.6)
Term (37+)	47 (90.4)
Unknown	2
5min Apgar score	
7–10	23 (45.1)
4–6	16 (31.4)
0–3	12 (23.5)
Unknown	3
Neonatal seizures	
No	8 (16.7)
Yes	40 (83.3)
Unknown	6
Neonatal care	
None	4 (7.6)
NICU	36 (67.9)
SCN	13 (24.5)
Unknown	1
Motor type	
Spastic	21 (38.9)
Spastic-dyskinetic	21 (38.9)
Dyskinetic	7 (13.0)
Other	5 (9.3)
Unknown	0
GMFCS	
Level I–II	11 (20.4)
Level III	7 (13.0)
Level IV	13 (24.1)
Level V	23 (42.6)
Unknown	0
Epilepsy	
No	24 (44.4)
Yes	30 (55.6)
Unknown	0

GMI, grey matter injury; NICU, neonatal intensive-care unit; SCN, special care nursery; GMFCS, Gross Motor Function Classification System.

Relationships between MRI characteristics

Five children with pallidal lesions had no cortical–subcortical involvement. Excluding these five children, more extensive involvement of the deep grey nuclei was associated with more extensive cortical–subcortical injury (p=0.008 for trend across ordered groups) but not with more severe white matter loss (p=0.907) or cerebellar involvement (p=0.231). Severity of white matter loss was strongly associated with extent of cortical–subcortical involvement (p<0.001); 12 out of 14 children with diffuse cortical–subcortical involvement also had severe white matter loss.

Associations between MRI characteristics and clinical outcomes

Gross motor function

Symmetrical lesions were relatively more likely to be associated with poor gross motor function (GMFCS levels IV–V) than asymmetrical lesions (OR 5.5 [95% CI 1.2, 25.5]; Table III). As symmetry was a potential confounder in the association between MRI characteristics and GMFCS, the other associations were examined for symmetrical lesions only. GMFCS level was strongly associated with extent of deep nuclear involvement (p=0.001). Compared to two out of nine (22%) children with thalamic involvement only, 25 out of 28 (89%) children with symmetrical involvement of the thalamus, putamen, and globus pallidus were classified as GMFCS levels I to V (OR 35.0 [95% CI 5.5, 221.4]), as were four out of five children with isolated pallidal involvement (OR 20.0 [95% CI 1.4, 287.6]). Although gross motor function was less strongly associated with cortical–subcortical involvement (p=0.041), all 10 children with diffuse cortical–subcortical injury functioned at GMFCS level IV to V compared to only half of those with none/focal/parasagittal involvement (OR 5.1 [95% CI 0.8, 32.8]).

Proposed GMI severity rating scale

An overall severity rating was created based on the observed strong associations between dichotomized GMFCS level, pallidal involvement, and diffuse cortical–subcortical involvement. GMI was deemed mild where there was no pallidal abnormality regardless of the extent of cortical–subcortical involvement. Moderate and severe GMI were both associated with discernible pallidal abnormality, but a severe rating also involved diffuse cortical–subcortical abnormality (Table IV). Examples of imaging classified to these three severity ratings are shown in Figures 1 to 3.

The scale was strongly associated with the level of gross motor function (p<0.001; Table III). Compared to mild GMI, the odds of moderate injury being associated with GMFCS levels IV to V was 17.1 (95% CI 3.6, 80.3) and the odds of severe injury was 35.7 (95% CI 3.5, 368.8). Very similar odds ratios were seen when scans showing isolated pallidal lesions were excluded.

Motor type

The extent of cortical–subcortical involvement was strongly associated with motor type (p=0.001) whereas the

Table II: Magnetic resonance imaging characteristics for 54 children with cerebral palsy and grey matter injury across motor types and for the entire cohort

MRI characteristic	Motor type: Spastic *n*=21 *n* (row %)	Spastic-dyskinetic *n*=21 *n* (row %)	Dyskinetic *n*=7 *n* (row %)	Other *n*=5 *n* (row %)	*p*-value for difference[a]	Relative odds of non-spastic/ mixed motor type OR (95% CI)	Entire cohort *n*=54 *n* (col %)
Symmetry							
Symmetrical	16 (35.6)	17 (37.8)	7 (15.6)	5 (11.1)	0.465	Reference	45 (83.3)
Asymmetrical	5 (55.6)	4 (44.4)	0 (0.0)	0 (0.0)		0.4 (0.1, 1.9)	9 (16.7)
Extent of involvement							
Deep grey matter							
Thalamus only	7 (58.3)	3 (25.0)	1 (8.3)	1 (8.3)	0.228	Reference	12 (22.2)
Globus pallidus only	0 (0.0)	3 (60.0)	0 (0.0)	2 (40.0)		Predicts perfectly	5 (9.3)
Thalamus+putamen	1 (20.0)	3 (60.0)	1 (20.0)	0 (0.0)		5.6 (0.5, 66.4)	5 (9.3)
Thalamus+putamen+GP	13 (40.6)	12 (37.5)	5 (15.6)	2 (6.3)		2.0 (0.5, 7.9)	32 (59.3)
Cortical–subcortical involvement							
None/focal/parasagittal	3 (23.1)	4 (13.8)	3 (23.1)	3 (23.1)	0.001	20.0 (2.8, 144.3)	13 (24.1)
Central sulcus	4 (36.4)	4 (36.4)	1 (9.1)	2 (18.2)		10.5 (1.5, 72.8)	11 (20.4)
Central sulcus+hippocampus	2 (12.5)	11 (68.8)	3 (18.7)	0 (0.0)		42.0 (5.1, 345.1)	16 (29.6)
Diffuse	12 (85.7)	2 (14.3)	0 (0.0)	0 (0.0)		Reference	14 (25.9)
White matter loss							
None	2 (12.5)	7 (43.8)	3 (18.7)	4 (25.0)	0.029	13.0 (2.3, 74.3)	16 (29.6)
Mild	4 (36.4)	5 (45.4)	2 (18.2)	0 (0.0)		3.2 (0.7, 15.1)	11 (20.4)
Moderate	2 (28.6)	4 (57.1)	0 (0.0)	1 (14.3)		4.6 (0.7, 30.4)	7 (13.0)
Severe	13 (65.0)	5 (25.0)	2 (10.0)	0 (0.0)		Reference	20 (37.0)
Cerebellum							
Unaffected	15 (34.1)	18 (40.9)	7 (15.9)	4 (9.1)	0.405	Reference	44 (81.5)
Affected	6 (60.0)	3 (30.0)	0 (0.0)	1 (10.0)		0.3 (0.1, 1.4)	10 (18.5)

[a]Fisher's exact test. MRI, magnetic resonance imaging; GP, globus pallidus.

Table III: Magnetic resonance imaging characteristics for 54 children with cerebral palsy and grey matter injury across dichotomized Gross Motor Function Classification Systems levels and for the entire cohort

MRI characteristic	GMFCS level: I–III *n*=18 *n* (row %)	IV–V *n*=36 *n* (row %)	*p*-value for difference[a]	Relative odds of GMFCS IV–V OR (95% CI)[b]	Entire cohort *n*=54 *n* (col %)
Symmetry					
Symmetrical	12 (26.7)	33 (73.3)	0.047	5.5 (1.2, 25.5)	45 (83.3)
Asymmetrical	6 (66.7)	3 (33.3)		Reference	9 (16.7)
Extent of symmetrical involvement					
Deep grey matter					
Thalamus only	7 (77.8)	2 (22.2)	0.001	Reference	9 (20.0)
Globus pallidus only	1 (20.0)	4 (80.0)		20.0 (1.4, 287.6)	5 (11.1)
Thalamus+putamen	1 (33.3)	2 (66.7)		7.0 (0.32, 34.8)	3 (6.7)
Thalamus+putamen+globus pallidus	3 (10.7)	25 (89.3)		35.0 (5.5, 221.4)	29 (62.2)
Cortical–subcortical					
None/focal/parasagittal	6 (50.0)	6 (50.0)	0.041	Reference	12 (26.7)
Central sulcus	3 (37.5)	5 (62.5)		0.7 (0.1, 3.6)	8 (17.8)
Central sulcus+hippocampus	3 (20.0)	12 (80.0)		2.6 (0.5, 12.4)	15 (33.3)
Diffuse	0 (0.0)	10 (100.0)		5.1 (0.8, 32.8)	10 (22.2)
White matter loss					
None	5 (31.2)	11 (68.8)	0.673	Reference	16 (35.6)
Mild	1 (11.1)	8 (88.9)		1.2 (0.2, 6.6)	9 (20.0)
Moderate	1 (33.3)	2 (66.7)		0.2 (0.0, 1.3)	3 (6.7)
Severe	5 (29.4)	12 (70.6)		1.4 (0.3, 5.9)	17 (37.8)
Cerebellum					
Unaffected	12 (32.4)	25 (67.6)	0.087	Reference	37 (82.2)
Affected	0 (0.0)	8 (100.0)		5.7 (0.7, 48.8)	8 (17.8)
Proposed overall severity rating					
Mild: no GP	13 (76.5)	4 (23.5)	<0.001	Reference	17 (31.5)
Moderate: GP+non-diffuse CSC	4 (16.0)	21 (84.0)		17.1 (3.6, 80.3)	25 (46.3)
Severe: GP alone or GP+diffuse CSC	1 (8.3)	11 (91.7)		35.7 (3.5, 368.8)	12 (22.2)

[a]Fisher's exact test. [b]Logistic regression with factor terms. GMFCS, Gross Motor Function Classification System; OR, odds ratio; CI, confidence interval; GP, globus pallidus involved; CSC, cortical–subcortical involvement.

Table IV: Proposed scale for classification of severity of grey matter injury with respect to gross motor function based on extent of deep grey and cortical/subcortical involvement

	Deep grey matter involvement			
	Thal only	GP only	Thal+put	Thal+put+GP
Cortical–subcortical involvement				
None/focal/ parasagittal	Mild	Moderate	Mild	Moderate
Central sulcus	Mild	Moderate	Mild	Moderate
Central sulcus+ hippocampus	Mild	Moderate	Mild	Moderate
Diffuse	Mild	Severe	Mild	Severe

Thal, thalamus; GP, globus pallidus; put, putamen.

extent of deep nuclear involvement was not (p=0.228; Table II). Diffuse cortical–subcortical injury resulted in a spastic motor type in 12 out of 14 children. The strongest predictors of a non-spastic or mixed motor type were isolated pallidal involvement (perfect prediction), non-diffuse cortical–subcortical injury (OR 20.8 [95% CI 3.9, 109.9]), and no white matter loss (OR 13.0 [95% CI 2.3, 74.3]).

Motor topography

As expected, a strong association was seen between motor topography and lesion symmetry on MRI (p<0.001). All 45 children with symmetrical lesions had bilateral CP. Of the nine children with asymmetrical lesions, six had unilateral or asymmetric motor impairment with greater impairment on the side contralateral to the more severely affected cerebral hemisphere.

Comorbidities

The prevalence of epilepsy varied according to extent of cortical–subcortical involvement (p=0.035) and severity of white matter loss (p<0.001), with more extensive lesions associated with higher frequencies of epilepsy (see Table V). These data did not suggest any strong associations between extent of involvement on MRI and blindness, deafness, or intellectual disability. However, although only four out of 52 children (8%) were bilaterally deaf, deafness was seen in two out of five children with MRI abnormality confined to the globus pallidus bilaterally.

Pathogenic pattern

The lesion pattern was suggestive of a history of severe hypoglycaemia in four children and kernicterus in five children. The pathology was assumed to be hypoxia–ischaemia/hypotension for the remaining 45 children. Of these, 35 had MRI findings consistent with a deep nuclear-cortical pattern and 10 with a mixed deep nuclear-cortical and parasagittal watershed pattern.

DISCUSSION

This study adds to existing knowledge about patterns of GMI in children with CP and our understanding of relationships between abnormal findings on chronic-phase MRI and clinical outcomes. The important findings were: (1) pallidal abnormality was common and, combined with extent of cortical–subcortical injury, was a strong predictor of poor gross motor function; (2) a non-spastic motor type was associated with extensive deep GMI and non-diffuse cortical–subcortical injury; and (3) the likelihood of epilepsy was highest in the context of generalized cortical–subcortical involvement and white matter loss.

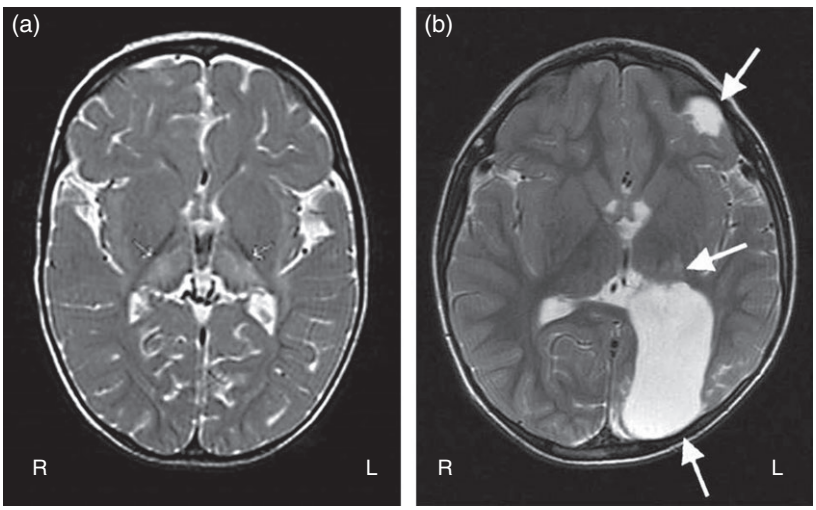

Figure 1: Mild grey matter injury. (a) Brain MRI in a 17-month-old male with history of hypoxic encephalopathy. Axial T2-weighted image demonstrates bilateral, symmetric signal abnormality, and mild volume loss affecting the thalami (arrows). The basal ganglia are spared. (b) Brain MRI in a 3-year-old male with right-sided seizures and right hemiplegia. Axial T2-weighted image demonstrates areas of cystic encephalomalacia in the left frontal and parieto-occipital regions due to parasagittal watershed infarcts (arrows) and ex-vacuo ventricular dilatation, left thalamic gliosis, and volume loss (arrow).

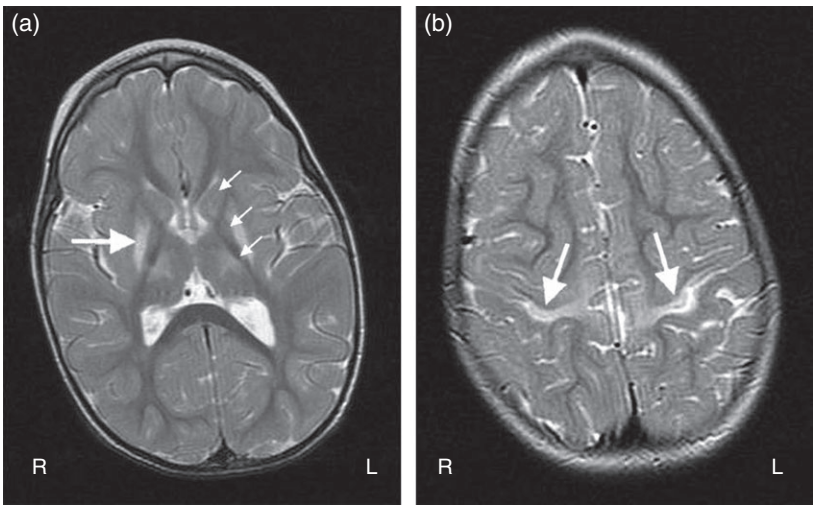

Figure 2: Moderate grey matter injury. Brain MRI in a 24-month-old male with history of meconium aspiration. (a) Axial T2-weighted image demonstrates bilateral, symmetric gliotic changes in the basal ganglia, including the putamen and globus pallidus minimally (small arrows) and thalami (long arrow). (b) Similar changes along the central sulcus bilaterally.

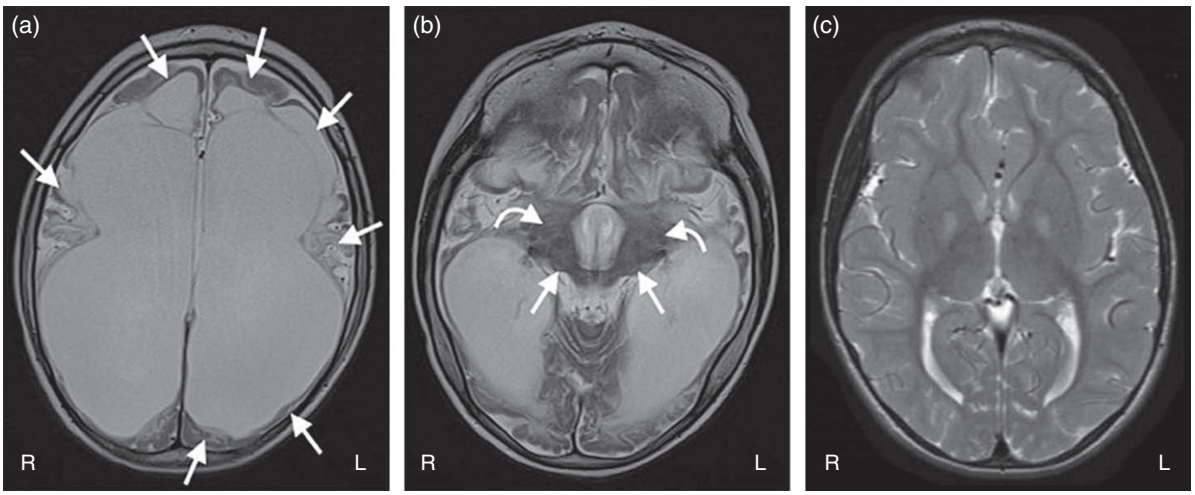

Figure 3: Severe grey matter injury. T2-weighted axial images demonstrating (a) severe bilateral cortical and subcortical cystic encephalomalacia (arrows) with secondary gross ex-vacuo dilatation of the lateral ventricles and (b) severe volume loss and gliosis of the thalami (straight arrows) and basal ganglia (curved arrows). (c) axial T2-weighted image demonstrates bilaterally symmetric, abnormal increased signal in the globus pallidi indicative of neonatal kernicterus.

The high rate of pallidal abnormality in our CP cohort was a somewhat unexpected finding because it has been previously reported that abnormality seen in the globus pallidi in acute scans are often not seen in imaging performed later in life.[34] Bilateral injury to the putamen and thalamus has been previously reported on later MRI to be accompanied by pallidal abnormality in approximately 33% of cases of asphyxia, and 50% of cases have been reported to have additional lesions in the cortical and subcortical areas bordering the central sulcus and in the hippocampus.[11] The corresponding figures for our cohort of 86% and 76% are likely explained by the fact that our CP cohort excludes children with milder injury without motor sequelae but includes five children with isolated pallidal injury suggestive of kernicterus.

Signal abnormality and/or volume loss in the globus pallidi, either alone or as indicator of extensive involvement, was the strongest MRI predictor of gross motor function in our study. Previous groups have suggested that children with severe gross motor impairment (GMFCS IV–V) are likely to have more widespread involvement within the deep grey nuclei, plus involvement of the sensory-motor

Table V: Magnetic resonance imaging characteristics for children with cerebral palsy, grey matter injury, and comorbid epilepsy, blindness, deafness, and/or intellectual disability

	Epilepsy *n*=30/54		Functional blindness *n*=16/53		Bilateral deafness *n*=4/52		Intellectual disability *n*=33/47	
	n (%)	*p*	*n* (%)	*p*	*n* (%)	*p*	*n* (%)	*p*
Symmetry								
Symmetrical	24 (53.3)	0.715	14 (31.8)	0.706	4 (9.3)	1.000	27 (67.5)	0.657
Asymmetrical	6 (66.7)		2 (22.2)		0 (0.0)		6 (85.7)	
Extent of involvement								
Deep grey matter								
Thalamus only	8 (66.7)	0.393	5 (41.7)	0.388	0 (0.0)	0.099	7 (63.6)	1.000
Globus pallidus only	1 (20.0)		2 (40.0)		2 (40.0)		4 (80.0)	
Thalamus+putamen	3 (60.0)		0 (0.00		0 (0.0)		4 (80.0)	
Thalamus+putamen+GP	18 (56.2)		9 (29.0)		2 (6.7)		18 (69.2)	
Cortical–subcortical involvement								
None/focal/parasagittal	5 (38.5)	0.035	4 (30.8)	0.439	3 (23.1)	0.140	9 (69.2)	0.123
Central sulcus	4 (36.4)		3 (27.3)		0 (0.0)		6 (54.6)	
Central sulcus+hippocampus	9 (56.2)		7 (43.8)		1 (6.2)		9 (64.3)	
Diffuse	12 (85.7)		2 (15.4)		0 (0.0)		9 (100.0)	
White matter loss								
None	2 (12.5)	<0.001	5 (31.2)	0.825	3 (18.8)	0.208	8 (53.3)	0.320
Mild	5 (45.4)		3 (27.3)		1 (9.1)		6 (66.7)	
Moderate	4 (57.1)		1 (14.3)		0 (0.0)		6 (85.7)	
Severe	19 (95.0)		7 (36.8)		0 (0.0)		13 (81.2)	
Cerebellum								
Unaffected	23 (52.3)	0.483	13 (30.2)	1.000	3 (6.7)	0.544	22 (56.4)	1.000
Affected	7 (70.0)		3 (30.0)		1 (11.1)		5 (62.5)	

GP, globus pallidus.

cortex, hippocampus, and posterior limbs of internal capsules, whereas mild impairment (GMFCS levels I–III) is more likely to result from focal and subtle abnormalities in the ventrolateral nuclei of the thalami and/or posterior putamen, and parasagittal watershed lesions.[7,15,25] Data from our study only partly support these previously reported associations. We observed that involvement of the globus pallidus showed the strongest association with gross motor function, independent of other regions affected, even when isolated pallidal abnormality was excluded. Since the numbers in this study were quite small, the association between GMFCS and pallidal abnormality needs to be confirmed in other studies. Our finding, however, has some biological plausibility since the globus pallidus is involved in both the direct and indirect pathways from the putamen that promote volitional movement and provide background stability for the movement by a combination of stimulation and inhibition of different muscle groups.[23]

We have proposed and presented a new rating scale for severity of GMI in CP based on the strength of association between MRI variables and gross motor function. This scale comprises mild, moderate, and severe categories based on qualitative assessment of pallidal involvement and diffuse cortical–subcortical injury. Previously published rating scales did not work well in our cohort.[7,35] Firstly, we could not clearly distinguish between the two main patterns of hypoxia–ischaemia/hypotension; parasagittal watershed lesions were observed, but only in conjunction with deep nuclear-cortical patterns. Secondly, classification was difficult because of greater regional heterogeneity within the broader patterns of hypoxic–ischaemic/hypotensive injury than has previously been described from experimental and human studies.[5–10] For instance, few scans in our cohort showed signal change confined to the ventrolateral thalami.

Deep grey involvement affecting the putamen and globus pallidus was associated with a mixed or non-spastic motor type, particularly where cortical–subcortical involvement was not generalized. This finding is consistent with previous reports that bilateral deep grey matter lesions, without involvement of the pyramidal tracts, commonly result in extrapyramidal abnormalities and dyskinetic CP.[7–9,23,26–28] A small number of children in this study had hypotonia, a motor type that has been previously reported in association with GMI.[36]

The likelihood of epilepsy was highest in the context of generalized cortical–subcortical involvement and white matter loss, including the hippocampus and temporal lobes. This finding is consistent with the fact that hippocampal abnormality after hypoxia–ischaemia is known to be associated with epilepsy,[37] with previous research suggesting the likelihood of epilepsy is predominantly dependent on the severity of the cortical injury.[25]

We found no strong associations between intellectual impairment and MRI characteristics, possibly partly because the motor disorder limits assessment of cognition in severe cases.[38] In earlier studies, better cognitive function was seen in children with less severe involvement of the basal ganglia and thalami after hypoxic–ischaemic injury,[9] whereas those with additional central or

hippocampal involvement, or severe white matter involvement, had a greater likelihood of severe cognitive impairment.[6,7,27,39]

It has been postulated that injury to the deep nuclei, white matter, midbrain, optic radiations, and cortex after hypoxic–ischaemic encephalopathy can predict the likelihood of visual disorders, including strabismus, optic neuropathy, and cortical visual impairment.[25] We were unable to associate blindness with any specific region in this study. On the other hand, the few cases of deafness tended to be associated with insults involving the globus pallidus, hinting at kernicterus as the common cause. Both the cochlear nuclei in the brain stem and the auditory nerve are extremely sensitive to the toxic effects of bilirubin.

The strengths of this study are the use of a population birth cohort, clear inclusion criteria, pathogenic homogeneity based on imaging, and inclusion of several clinical outcomes. A limitation is the lack of sensitivity of MRI. Signal change and volume loss can be difficult to appreciate on chronic-phase scans, particularly where there is mild or bilateral involvement.

CONCLUSION

In a cohort of 54 children with CP and GMI on chronic-phase conventional MRI, there was a strong association between the level of gross motor function and pallidal abnormality, either alone or as an indication of extensive deep grey matter involvement. This finding has biological plausibility but needs to be substantiated in other studies. We have provided initial evidence for the constructive validity of a new scale that rates the severity of GMI in terms of its relationship to gross motor function and have demonstrated important associations between MRI characteristics and other clinical outcomes. This information will be helpful in the clinical context and also as a basis for investigation of causal pathways.

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