Correlating magnetic resonance imaging characteristics with motor outcome in cerebral palsy children with white matter injury

Nilima Ananda Narkhede[1], **Sushma Save**[2]

[1] Department of Pediatrics, Bharatratna Dr Babasaheb Ambedkar Hospital, Mumbai

[2] Department of Pediatrics, TN Medical college & B Y L Nair hospital, Mumbai.

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Abstract

Introduction: Cerebral palsy (CP) is the term used to describe individuals with a movement disorder resulting from non-progressive disturbance to the developing brain[1]. The diagnosis of CP is based on the presence of a motor deficit, and they manifest with reduced motor capacity. The most widely utilized classification system for the severity of motor limitations is the gross motor function classification system (GMFCS)[2].

Material and Methods: We tried to describe the white matter injury on Magnetic Resonance Imaging (MRI) in children with cerebral palsy irrespective of clinical subtype. We also studied if there was association between white matter injury on MRI in children with cerebral palsy and motor outcomes-gross motor function classification system Expanded and Revised(GMFCS E &R). It was an observational, Cross sectional Descriptive study with analytical wing aged between 6 months to 12 years of age carried out for 8 months. Children diagnosed to have cerebral palsy on history and clinical examination were enrolled in the study.

Results: A total of 50 children diagnosed with cerebral palsy were enrolled in our study. Majority of the study sample were <5years old (29) and males (31). We found that symmetrical involvement, severe white matter loss in the hemisphere and callosal thinning were the strongest predictors of poor gross motor function. Bilateral, extensive WM (white matter) loss was more likely to result in quadriplegia, whereas volume loss in the posterior-mid WM more frequently resulted in diplegia. Asymmetrical involvement was associated with less extensive hemispheric involvement than symmetrical WMI (White matter injury). Cysts, deep grey abnormality, and Wallerian change in the PLIC (Posterior limb of Internal Capsule) and cerebral peduncles were all more commonly seen in association with unilateral and asymmetric patterns of WMI.

All children with unilateral WMI functioned at GMFCS levels I or II or III whereas bilateral involvement was associated with wheeled mobility (GMFCS levels IV–V). Motor outcomes for children with asymmetrical WMI fell between those with symmetrical and unilateral WMI on MRI.

Conclusion: Laterality/ symmetry of WMI along with extent and location of WM loss can predict gross motor function in Cerebral palsy.

Key words: Cerebral palsy, white matter, MRI.

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Address for correspondence:

Dr. Nilima Ananda Narkhede

Department of Pediatrics, Bharatratna Dr Babasaheb Ambedkar Hospital, Mumbai

E-mail: nilimanarkhede12@gmail.com

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Introduction

Cerebral palsy (CP) is the term used to describe individuals with a movement disorder resulting from non-progressive disturbance to the developing brain[1].

CP is the most common motor disability in childhood.[4] The diagnosis of CP necessitates the presence of a motor deficit, and the most common presenting problem is reduced motor capacity. The severity of CP is related to motor outcomes, and the ability to predict motor and functional outcomes is vital for coordination of optimal therapy and rehabilitation.[5]

The most widely utilized classification system for the severity of motor limitations in children with CP is the gross motor function classification system (GMFCS).[2] The revised and expanded version of the GMFCS describes

the movement ability of children with CP in one of five ordinal levels across five age bands, with emphasis on the child's typical performance in different settings.

Magnetic resonance imaging (MRI) provides an in vivo view of brain structure and plays a pivotal role in identification of timing of disturbance and the most likely pathogenic mechanism. Traditional structural brain MRI is recommended by the American Academy of Neurology in the evaluation of all children with CP where the aetiology has not been established and is currently much more clinically accessible [5].

White matter injury (WMI) is the most common MRI pattern (45%), followed by grey matter injury (14%), normal imaging (13%), malformations (10%), focal vascular insults (9%) and miscellaneous patterns (7%) [6,7].

As CP originates from an interference, lesion, or abnormality of the developing brain, it can be assumed that MRI has the potential to identify the lesion or abnormality and, thus, can help us to understand the timing of CP origin.[8]

A focus of current research is the prevention of CP, which requires clinical outcomes to be correlated with the presumed timing and etiology of lesions in the developing brain. This can be achieved by brain magnetic resonance imaging (MRI), which also provides information about the location and extent of brain injuries.[5]

Aim and Objective: To describe white matter injury on Magnetic Resonance Imaging (MRI) and to study association between white matter injury on MRI and motor outcomes- gross motor function classification system Expanded & Revised (GMFCS E& R) in children with cerebral palsy [3].

Secondary Objective: To study association between white matter injury on MRI and motor topography.

Material and Methods

It was an observational, Cross sectional Descriptive study with an analytical wing aged between 6 months to 12 years and carried out for 8 months (March 2019 to October 2019). Children diagnosed to have cerebral palsy on history and clinical examination attending the Paediatric Outpatient Department (OPD), Paediatric Neurology and Epilepsy Clinic or Paediatric inpatient department (IPD) satisfying the inclusion and exclusion criteria were enrolled in the study after obtaining written informed consent from parent/ guardian. Ethical committee approval was taken.

Children aged between 6 months to 12 years of age diagnosed to have cerebral palsy as determined by review of previous records or OPD/IPD document of the participant and confirmed on clinical examination. MRI Brain performed any time after six months of corrected age and parent/guardian willing to give consent for participation in the study were included in the study.

Patients who has undergone surgical intervention or Botox injection for disability, on intensive physiotherapy, children with comorbid neurological or chronic systemic illnesses were excluded from the study.

Abnormal MRI findings were assessed as unilateral (one normal hemisphere), asymmetrical or symmetrical. MRI features like Signal abnormality, Volume loss, Cysts (recorded for anterior, mid and posterior region) noted. Other features noted- ventricular dilatation, basal ganglia involvement, cerebellar involvement, callosal thinning, posterior limb of internal capsule affected or not, cerebral peduncles affected or not. These features were recorded for each hemisphere separately.

Qualitative data represented in form of frequency and percentage. Quantitative data represented using Mean ± Standard Deviation and Median & Interquartile range. Association among various study parameters was assessed with the help of chi-square test (Fisher exact test for 2*2 table). Results were graphically represented where deemed necessary. Appropriate statistical software, including but not restricted to MS Excel, PSPP version 1.0.1 was used for statistical analysis. Graphical representation was done in MS Excel 2010.

Result

A total 50 children diagnosed with cerebral palsy were enrolled. Majority of study population was less than 5 year old. 62% were males whereas 38% were females.70% of children were born term while 4% were born < 28 weeks. Mean corrected age at imaging was 35.26 ± 20.05 months.

Abnormalities were symmetrical in 74% of scans, asymmetrical in 12%, and unilateral in 14%. The majority showed signal abnormality (94%), WM loss (90%), enlarged ventricles (72%), and Callosal thinning (74%), whereas relatively few had cysts (16%), deep grey matter involvement (31% thalamus; 18% basal ganglia), cerebellar involvement (7%), and involvement of the PLIC (28%) or cerebral peduncles (20%).

Extent of signal abnormality in the hemisphere was strongly associated with laterality/symmetry of WMI ($p < 0.05$). Symmetrical WMI was associated with extensive signal abnormality than unilateral WMI (97 % vs 71%). Location of signal abnormality was also clearly associated with laterality/symmetry ($p < 0.05$). Extent and location of WM loss were both strongly associated with laterality/symmetry (both $p < 0.05$). Symmetrical WM loss was extensive than unilateral loss (95% vs 42%) and involved the posterior + middle+ anterior WM (45% vs 0%), whereas unilateral WM loss was focal and confined to the mid and/or anterior or posterior WM.

Cysts, deep grey abnormality, Wallerian change in the PLIC and cerebral peduncles were more common with unilateral and asymmetric patterns of WMI. Cyst, Callosal thinning, PLIC affection were strongly associated with MRI laterality/symmetry ($p < 0.05$).

GMFCS and motor topography were both strongly associated with MRI laterality/symmetry (p <0.05). All children with unilateral WMI functioned at GMFCS levels I or II or III whereas bilateral involvement was associated with wheeled mobility (GMFCS levels IV–V) in 33% of children with asymmetrical WMI and 75% with symmetrical WMI. Motor outcomes for children with asymmetrical WMI fell between those with symmetrical and unilateral WMI on MRI. There is strong association between MRI symmetry and motor topography ($p < 0.05$). Unilateral WMI resulted in contralateral CP in all children while bilateral CP had bilateral WMI. Asymmetry on MRI was associated with 50% children having quadriplegia and another 50% with diplegia.

No associations were observed between GMFCS levels and extent and location of signal abnormality, ventricular dilatation, cystic change, thalamic involvement, basal ganglia involvement, cerebellar involvement and Callosal thinning, PLIC, and peduncles. There was no association of MRI characteristics with motor topography.

Table 1: Demographic characteristics pertaining to the most affected hemisphere, and clinical characteristics across groups based on laterality/symmetry of white matter injury (WMI) and for the entire cohort.

Demographic characteristics		Symmetrical n= 37	Asymmetrical n= 6	Unilateral n= 7	Total n=50	p#
Age (years)	<5	20	5	4	29	0.40
	>5	17	1	3	21	Not significant
Gender	Males	25	3	3	31	0.37
	Females	12	3	4	19	Not significant
Gestational age(weeks)	<28	2	0	0	2	0.47 Not significant
	28-31	5	1	0	6	
	32-36	5	2	0	7	
	37+	25	3	7	35	
Corrected age at imaging	0.5 to <1	1	1	0	2	0.85 Not significant
	1 to <2	10	2	3	15	
	2 to <3	8	1	1	10	
	3 to <4	10	1	2	13	
	5+	8	1	1	10	

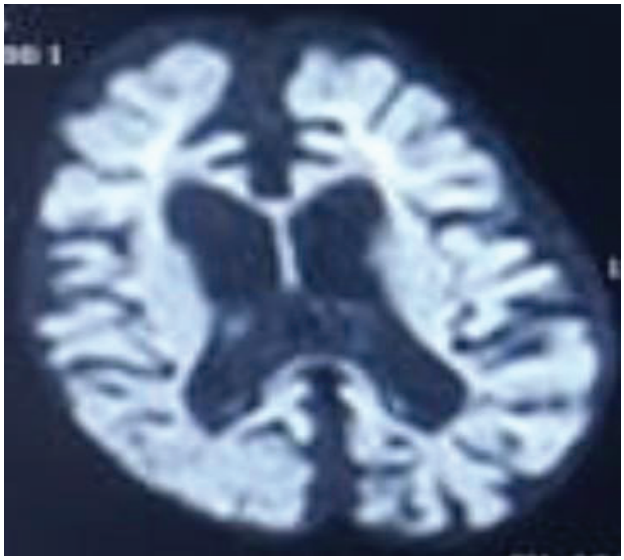
Table 2: MRI characteristics pertaining to the most affected hemisphere, and clinical characteristics across groups based on laterality/symmetry of white matter injury (WMI) and for the entire cohort.

MRI characteristics		Symmetrical n= 37	Asymmetrical n= 6	Unilateral n= 7	Total n=50	p#
Signal abnormality	Absent	1	0	2	3	0.02* Significant
	Present	36	6	5	47	
Extent of signal abnormality	None	1	0	2	3	0.00* Significant
	One region	0	0	2	2	
	Two region	18	3	3	24	
	Three region	18	3	0	21	
Location of signal abnormality	NA	1	0	2	3	0.00* Significant
	Posterior+mid	12	3	2	17	
	Posterior+mid+anterior	18	3	0	21	
	Mid only	0	0	0	0	
	Anterior+mid	6	0	1	7	
	Ant only	0	0	2	2	
WM loss	Absent	2	1	2	5	0.14 Not significant
	Present	35	5	5	45	

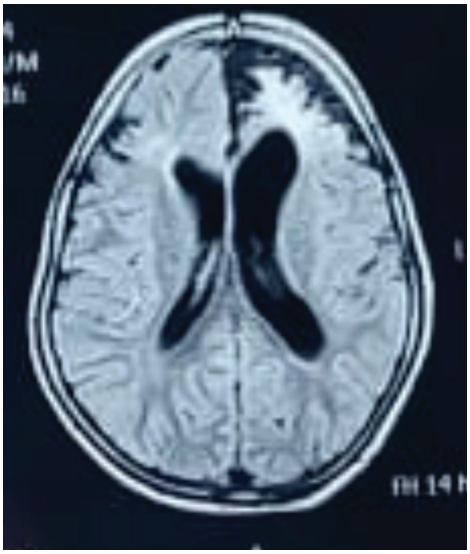
Extent of WM loss	None	2	1	2	5	0.00* Significant
	One region	0	0	2	2	
	Two region	18	2	3	23	
	Three region	17	3	0	20	
Location of WM loss	NA	2	1	2	5	0.01* Significant
	Posterior only	0	0	0	0	
	Posterior+mid	12	2	2	16	
	Posterior+mid+anterior	17	3	0	20	
	Mid only	0	0	0	0	
	Ant+mid	6	0	1	7	
	Ant only	0	0	2	2	
Ventricular dilatation	Not affected	22	2	2	26	0.20 Not significant
	Affected	15	4	5	24	
Cysts	Not affected	34	4	2	40	0.00* Significant
	Affected	3	2	5	10	
Thalamus	Not affected	34	5	5	44	0.29 Not significant
	Affected	3	1	2	6	
Basal ganglia	Not affected	34	6	5	45	0.17 Not significant
	Affected	3	0	2	5	
Cerebellum	Not affected	34	6	7	47	0.57 Not significant
	Affected	3	0	0	3	
Callosal thinning	Not affected	12	2	7	21	0.00* Significant
	Affected	25	4	0	29	
PLIC	Not affected	36	6	5	47	0.02* Significant
	Affected	1	0	2	3	
Peduncles	Not affected	33	6	7	46	0.46 Not significant
	Affected	4	0	0	4	

Table 3: Clinical characteristics pertaining to the most affected hemisphere, and clinical characteristics across groups based on laterality/symmetry of white matter injury (WMI) and for the entire cohort.

Clinical characteristics		Symmetrical n= 37	Asymmetrical n= 6	Unilateral n= 7	Total n=50	p#
GMFCS level	I	0	0	2	2	0.00* Significant
	II	2	1	2	5	
	III	7	3	3	13	
	IV	17	1	0	18	
	V	11	1	0	12	
Motor topography	Quadriplegia	25	3	0	28	0.00* Significant
	Diplegia	12	3	0	15	
	Hemiplegia	0	0	7	7	



Severe, diffuse white matter is damaged with extreme enlargement of lateral ventricle (white matter adjacent to lesions from anterior horns [open arrows] to trigones [solid arrows] is lost).



Asymmetric white matter involvement

Discussion

The worldwide prevalence of CP ranges from 1.5 to more than 4 per 1000 live births or children of a defined age range [9]. There are about 25 lakhs CP children in India as per the last statistical information [10]. The prevalence and pattern of Cerebral Palsy varies between different geographical regions, probably because of different etiological factors and different classifications used. Abnormal neuroanatomical findings are found in 80% to 90% of children with cerebral palsy, more often with MRI than with Computed Tomography scan. White matter damage is the most common finding, especially in children with bilateral spasticity, whereas isolated grey matter damage is rare [5,6,11]. Neuroimaging has suggested that about a third of cerebral palsy results from prenatal insults, and about 40% to insults around the time of birth, with the remainder occurring postnatally. The American Academy of Neurology now recommends that all cases of cerebral palsy of unknown origin undergo neuroimaging[12].

The revised and expanded version of the GMFCS describes the movement ability of children with CP in one of five ordinal levels across five age bands, with emphasis on the child's typical performance in different settings. Children at level I perform the same activities as their age-matched peers but with some difficulty in speed, balance, and coordination, while children at level V have difficulty controlling their head and trunk posterior in most positions and achieving any voluntary control of movement. The GMFCS has subsequently been widely adopted as the prime method for describing the severity of the motor disability in children with CP in both research and clinical contexts [13].

Extent and location of signal abnormality and volume loss in the hemisphere were strongly associated with laterality/symmetry of WMI Symmetrical WMI was associated with extensive signal abnormality. This finding was consistent with the study done by Reid et al ($p=0.004$) A possible explanation is that the three laterality/symmetry groups comprise different proportions of periventricular leukomalacia and intraventricular hemorrhage as the predominant pathologic mechanism. PVL is usually bilateral and symmetrical and, because of the typical location of the lesions, commonly results in spastic diplegia [14].

Symmetrical WM loss was extensive and involved the posterior + middle+ anterior WM whereas unilateral WM loss focal and confined to the mid and/or anterior or posterior WM. This finding was consistent with study done by Reid etal ($p<0.001$) [1]. Consistent with our findings, the only association found in a Japanese study of 34 children with spastic diplegia was positive correlation between degree of WM loss and severity of motor disability [15].

GMFCS and motor topography were both strongly associated with MRI laterality/symmetry. This finding was consistent with study done by Reid etal ($p<0.001$) All children with unilateral WMI functioned at GMFCS levels I or II or III whereas bilateral involvement was associated with wheeled mobility (GMFCS levels IV–V) in 33% of children with asymmetrical WMI and 75% with symmetrical WMI. Motor outcomes for children with asymmetrical WMI fell between those with symmetrical and unilateral WMI on MRI[1].

Unilateral WMI resulted in contralateral CP in all children while bilateral CP had bilateral WMI. Asymmetry

on MRI was associated with 50% children having quadriplegia and another 50% with diplegia.

The key finding of the study was that, after controlling for laterality/symmetry, extensive volume loss was the most important predictor of gross motor function(p=0.02].

Yokochi (1991) and Holmstrom et al. (2010) reported that in subjects with athetoid and hemiplegic CP, respectively, motor disabilities were more severe when lesions involved both grey and white matter on MRI as opposed to grey or white matter involvement alone[15,16].

Future studies could better assess the relationship between brain structure and motor outcomes in CP by considering a standardized, quantitative measure of MRI classification which includes detailed information about the location and extent of brain lesions [12,13]. A relationship was reported between specific MRI findings and two motor outcomes in CP, namely the severity of functional disability (according to GMFCS level) and motor type (referring to CP subtype and neurology). These findings could aid in predicting the type of treatment that children with CP should receive and assist with the tailoring of early interventions such as spasticity management, hip surveillance, lower limb arthroses for walking and orthopedic involvement for hip displacement [5].

Amongst children with symmetrical WMI, the proportion with quadriplegia was higher. MRI showed extensive WM loss across the posterior, mid, ands anterior in quadriplegia. Compared to no abnormality, quadriplegia was also more common in association with abnormality in the cerebellum, basal ganglia and thalamus.

Metz c etal (2022) found that children with cerebral palsy due to a genetic cause had higher GMFCS levels (P = .004) and more often presented with epilepsy (P = .04). They correlated the clinical phenotype, abnormalities during pregnancy, and delivery with the cause of cerebral palsy. Higher GMFCS is more common in children with chromosomal aberration, brain malformation, and hypoxic-ischemic encephalopathy and less common in children with neonatal stroke and cerebral hemorrhage[20].

Jystad KP etal reported that children with congenital anomalies have more severe motor impairments [21].

Conclusion

laterality/ symmetry of WMI along with extent and location of WM loss can predict gross motor function in Cerebral palsy.

Limitation

Conventional MRI technique is not sensitive to detect subtle white matter injury and it is also difficult to identify individual white matter tract injury particularly corticospinal tract injury. Diffusion tensor imaging with tractography enables correct localization of individual tract injury.However, these techniques are not routinely available clinically and mainly used in the research context.

Summary

Symmetrical involvement , severe white matter loss in the hemisphere and callosal thinning were the strongest predictors of poor gross motor function.

Bilateral, extensive WM (white matter) loss was more likely to result in quadriplegia, whereas volume loss in the posterior-mid WM more frequently resulted in diplegia.

Asymmetrical involvement was associated with less extensive hemispheric involvement than symmetrical WMI (White matter injury).

Cysts, deep grey abnormality, and Wallerian change in the PLIC (Posterior limb of Internal Capsule) and cerebral peduncles were all more commonly seen in association with unilateral and asymmetric patterns of WMI.

All children with unilateral WMI functioned at GMFCS levels I or II or III whereas bilateral involvement was associated with wheeled mobility (GMFCS levels IV–V). Motor outcomes for children with asymmetrical WMI fell between those with symmetrical and unilateral WMI on MRI.

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