Specific white matter lesions related to motor dysfunction in spastic cerebral palsy: A meta-analysis of diffusion tensor imaging studies

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Abstract

Background: Assessing motor impairment in spastic cerebral palsy (SCP) is a key factor in the treatment and rehabilitation of patients. We intend to investigate the correlation between diffusion tensor imaging properties of sensorimotor pathways and motor function in SCP using meta-analysis, and to determine specific white matter lesions that are closely related to motor dysfunction in SCP.

Methods: We conducted a literature search of PubMed, Embase, Scopus, and Web of Science databases to identify trials published from January 1999 to January 2019, that had evaluated the correlation between fractional anisotropy (FA) and motor function scores in SCP. Correlation coefficient (r) values were extracted for each study, and the extent of r was quantitatively explored. The r values between FA within different sensorimotor pathways and motor function scores were pooled respectively.

Results: Nineteen studies involving 504 children with SCP, were included. FA in both sensory and motor pathways significantly correlated with motor function scores. However, compared with the corticospinal tract and thalamic radiation, FA in the posterior limb of the internal capsule (PLIC) correlated more strongly with gross motor function classification system and upper limb motor function (r = -0.71, 95% CI -0.80--0.60; r = 0.73, 95% CI 0.60-0.82, respectively; P < 0.05).

Conclusions: FA within the PLIC is more closely related to motor dysfunction, and can potentially be a biomarker for evaluating the degree of motor impairment in SCP.

Keywords: cerebral palsy; diffusion tensor imaging; fractional anisotropy; sensorimotor pathways; motor function

Introduction

Cerebral palsy (CP) is a childhood-onset motor and posture disorder resulting from an early non-progressive brain lesion, the most common subtype of which is spastic CP (SCP).[1,2] Assessing the degree of motor impairment allows development of management and treatment strategy, and is therefore a key factor in the rehabilitation of patients.[3]

In previous studies, the Gross Motor Function Classification System (GMFCS) and assessments of upper limb motor function (ULMF), such as the Assisting Hand Assessment (AHA) have been frequently used to assess the degree of motor impairment in children with bilateral and unilateral SCP because of good inter-rater reliability.[4-7] However, it is important to note that an individual's performance will vary across the different assessment systems, which pose a problem for the integrated analysis of motor function. Furthermore, the accuracy of evaluation relies on the experience of assessors and the state of the assessed children. It may be difficult to perform detailed clinical assessments during infancy.

As a non-invasive imaging technique, magnetic resonance imaging (MRI) can reveal general anatomical positions and severity of brain lesions, as well as study the underlying pathogenesis in SCP.[3] However, conventional MRI cannot be used to comprehensively analyze variations in microscopic structure and is limited in the quantitative assessment of motor impairment.[8] A more sensitive method is diffusion tensor imaging (DTI), which detects microscopic structural white matter changes. As DTI metrics, fractional anisotropy (FA) correlates significantly with the structural integrity of white matter, such as reduced myelin, axonal count, and/or axonal integrity; and mean diffusivity (MD) reflects changes in cell density and extracellular space.[9] In studies of SCP using DTI, FA is the most frequently used

metric. Decreased FA reflects the severity of white matter damage.[10]

Further, several studies have explored the relationship between FA of sensorimotor pathways and motor function. Some studies reveal that decreased FA of motor pathways such as the corticospinal tract (CST) and posterior limb of the internal capsule (PLIC), is associated with motor function scores.[7,11-23] However, other studies have reported that sensory pathways including the posterior thalamic radiation (PTR) and superior thalamic radiation (STR), are more associated with motor function than are motor pathways in SCP.[8,24-26] However, several other studies did not find a significant correlation between FA of sensorimotor pathways and motor outcomes.[27-29] These conflicting findings may result from underlying differences in types of CP and heterogeneous methodology. Thus, the tracts associated with motor impairment have not been definitively identified, and it is not yet known whether specific white matter tract lesions are more likely to be associated with clinical motor deficits.

Therefore, in this study, we investigate the correlation between FA of sensorimotor pathways and motor function scores through a meta-analysis. We also aim to determine if specific white matter lesions are closely related to motor dysfunction in SCP.

Materials and Methods

This study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses.[30]

Literature search

A literature search of relevant databases (PubMed, Embase, Scopus, and Web of Science) was

conducted to identify trials published from January 1999 to January 2019, using the keywords "cerebral palsy" and "diffusion magnetic resonance imaging or diffusion MRI or diffusion tensor imaging or DTI or tractography" and "fractional anisotropy or FA" and "motor function". Two investigators (HJ, with 15 years of pediatric radiology experience; and HL, with 13 years of pediatric radiology experience) independently reviewed all identified studies. References in identified articles were also reviewed. Disagreements were resolved by discussion between the two review authors. If no agreement could be reached, the plan was determined by a third author (JY, with 25 years of pediatric radiology experience).

Study selection

Inclusion criteria in the present meta-analysis were as follows: (a) data were acquired from children who had been diagnosed with SCP by pediatric neurologists, following the definition of CP established by the International Executive Committee, USA, 2006[1]; (b) DTI of the brain had been performed; and (c) the relationship between FA of sensorimotor pathways and motor function scores was investigated.

The following studies were excluded: (a) review articles, letters, comments, case reports; (b) those that provided no relevant data; including studies that had analyzed the relationship between FA and motor scores with change of treatment, the correlation between FA asymmetry index and motor scores, or did not obtain the full data; and (c) studies that reported duplicate patient data.

Quality Assessment and Data Extraction

The methodological quality of the included studies was independently assessed by two observers using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)

instrument.[31] The information extracted from each publication included the following: authors, publication year, nation of origin, sample size, patient age at MRI scan, study design, MRI field, sensorimotor pathway, motor function score, and correlation coefficient. The motor function assessment scales selected for SCP were selected according to the following hierarchy of assessment scales: GMFCS > AHA > Box & Blocks test > Melbourne unilateral upper limb assessment > Jebsen-Taylor test of hand function > Children's Hand Experience Questionnaire. For bilateral SCP, the data were pooled from both right and left hemispheres. For unilateral SCP, the data were extracted from the ipsilateral hemisphere. In case of disagreements regarding quality assessment, the two observers discussed each instance until a consensus was reached.

Meta-analysis

In this meta-analysis, the r values for the correlation between FA within different sensorimotor pathways (PTR, STR, CST, and PLIC), and the motor function scores were pooled respectively. The r values were extracted for each study and the extent of r was quantitatively explored. Because the range of r values is limited from -1 to 1, Fisher transformation was used to convert r into an approximately normal distribution.[32] Subsequently, the weighted summary r values were calculated using the Hedges-Olkin method.[33] Data heterogeneity was analyzed by using the Cochran Q statistic and the inconsistency index (I^2) value. $I^2 > 50\%$ and $P < 0.1$ indicated high heterogeneity. A random effects model was used to analyze combined data from the selected studies[32]. Statistical analysis was conducted to compare differences in r values among pathways. A subgroup analysis by study design was performed to explore the extent of r. Meta-regression analysis

was performed to investigate the influence of age. Publication bias was assessed using Begg's test. All analyses were performed using the software STATA version 14 and Review Manager 5.3. $P < 0.05$ was considered statistically significant.

Results

Literature Search

The detailed steps of the literature search are shown in Figure 1. The search initially yielded 140 potential studies after removal of duplicates. From these, a total of 89 articles were excluded based on careful reading of abstracts; and these included studies of patients without SCP, no correlation analyses, reviews, case reports, and animal model studies. An additional 32 articles were excluded after careful reading of the full-text because of non-relevant data, a lack of sufficient information to calculate the correlation coefficients, and duplicate patient data. Of these excluded studies, six were focused on the relationship between FA and motor scores following changes in treatment, and 5 were focused on the relationship between FA asymmetry and motor scores. Finally, 19 articles were included in this meta-analysis.

Data Extraction and Quality Assessment

The included studies involved a total of 504 patients with SCP (bilateral SCP: n = 223; unilateral SCP: n = 281), aged 0–19 years. Five of the selected studies were prospective studies; the rest were retrospective studies. Nine studies explored the correlation between FA and the GMFCS in bilateral SCP, while 10 explored the correlation between FA and ULMF in unilateral SCP. In five studies, motor function was assessed using the AHA, as well as the Melbourne unilateral upper limb assessment and Jebsen-Taylor test of hand function - In

these studies, only the AHA data were extracted. The r values of all studies on sensory and motor pathways were extracted for the meta-analysis. For three studies, the r values were calculated using the reported r^2 values. Detailed information regarding the included studies is presented in Table 1. Evaluations of the study design characteristics based on the QUADAS-2 tool are shown in On-line Figures 1 and 2.

Meta-Analysis

The summary r values for the correlation between FA within different sensorimotor pathways and GMFCS are shown in Figure 2. After pooling 6 studies, the FA in PTR correlated with GMFCS (r = -0.51, 95% CI -0.63--0.37) and was not markedly heterogeneous (I^2 = 1%, P = 0.41). After pooling 6 studies, the FA in CST correlated with GMFCS (r =-0.43, 95% CI -0.54--0.30) and was not markedly heterogeneous (I^2 = 41%, P = 0.13). However, compared with the PTR and CST, the FA in PLIC most strongly correlated with GMFCS (r = -0.71, 95% CI -0.80--0.60; P < 0.01) after pooling 5 studies, and was not markedly heterogeneous (I^2 = 36%, P = 0.18).

The summary r values for the correlation between FA within different sensorimotor pathways and ULMF are shown in Figure 3. After pooling 4 studies, the FA in STR correlated with GMFCS (r = 0.53, 95% CI 0.40-0.64) and was not markedly heterogeneous (I^2 = 10%, P = 0.34). After pooling 6 studies, the FA in CST significantly correlated with ULMF (r = 0.53, 95% CI 0.40-0.65) and was not markedly heterogeneous (I^2 = 0%, P = 0.74). However, compared with the STR and CST, FA in the PLIC most strongly correlated with ULMF (r = 0.73, 95% CI 0.60-0.82; P < 0.05) after pooling 4 studies, and was not markedly heterogeneous (I^2 = 0%, P = 0.72).

In the subgroup analysis by study design, FA in PLIC significantly correlated with the GMFCS and ULMF in all the subgroups (On-line Table 1). In the meta-regression analysis, no significant effect modification was found for age contribution (P > 0.05). The results of Begg's test indicated no significant publication bias (P > 0.05) (On-line Table 2).

Discussion

To our knowledge, this is the first meta-analysis to investigate the correlation between FA of sensorimotor pathways and motor function scores in patients with SCP. After systematic review and evaluation, we include results from 19 studies, of which 9 studies explore the correlation between FA and GMFCS, and 10 studies explore the correlation between FA and ULMF. This meta-analysis shows that FA of sensorimotor pathways significantly correlates with motor function scores in SCP, and specific white matter tract lesions in the PLIC are most closely related to motor dysfunction.

In the clinic, GMFCS and ULMF (AHA, B&B test, and CHEQ) scales are frequently used to evaluate motor function dysfunction. In the DTI analysis, FA has been used as an objective metric to evaluate the degree of white matter damage, and much research has indicated that motor impairment in SCP is associated with decreased FA which indicates brain white matter damage.[18,34-36] Therefore, the correlation between FA and motor function scores has been widely investigated. However, these studies show significant heterogeneity due to the underlying types of cerebral palsy and the different methodologies used. In contrast to the other heterogeneous CP subtype studies; we included only SCP in this study. We also analyzed bilateral and unilateral SCP, and the different sensorimotor pathways as a

means to provide more convincing evidence. Thus, our results show no significant heterogeneity in the correlation between FA and motor function scores.

In this meta-analysis, FA in both sensory and motor pathways significantly correlated with GMFCS and ULMF. The CST, is the major projectional motor tract in close proximity to the periventricular white matter and is vulnerable in most of the patients with SCP[37]; notably; CST lesions may interrupt the corticomotor circuit governing movement execution. Therefore, CST was the first tract to be investigated for an association with motor function in SCP.[10] Based on DTI, a series of studies have indicated that the degree and extent of CST injury correlates with motor impairment and functional reorganization of motor pathways.[11,12,15,18-21] On the other hand, Hoon et al.[25] reported that damage to the PTR, which connects the thalamus to the posterior parietal and occipital cortices, was related to motor dysfunction in children with SCP; also, a PTR injury decreased sensorimotor cortical connections and attenuated the descending CST. Furthermore, the STR, which connects the thalamus to the somatosensory cortex, was considered to be involved with upper limb function as well.[26] Thus, we performed a comprehensive meta-analysis to enhance the interpretation of multiple studies. Several studies also revealed there was significant correlation between FA of sensorimotor pathways with normal appearance on conventional MRI and motor function scores in SCP.[8,14,38] It suggests that FA is a better measure than conventional MRI for assessing the degree of motor impairment.

However, relative to other sensorimotor pathways, this study shows that motor function scores are most strongly correlated with FA in the PLIC. The anterior two-thirds of the main PLIC contain fibers of the CST and are commonly referred to as the CST at the internal

capsule level. Indeed, the descending motor pathways of the PLIC also contain the cortico-rubro-spinal and cortico-reticulo-spinal systems.[39] The densely concentrated descending motor axons and the vulnerability of white matter in the internal capsule level[14,40] indicate that the PLIC plays a very important role in motor dysfunction, than the entire CST and other sensory pathways. Hence, we also investigated the correlation between MD of sensorimotor pathways and motor function scores in SCP (On-line Figures 3 and 4). The correlation for MD in PLIC was weaker than that for FA. In addition, for typical developing children, the FA increases with age, and is most prominent in the early infant phase. Previous studies revealed that FA within sensorimotor pathways in SCP infants were significant related to motor function, but not related to age.[12,41] Similarly, in the current meta-regression analysis, no significant modification was found for age. Thus, our results suggest that specific white matter lesions of the PLIC contribute to motor impairment, and the FA is suitable for evaluation of the degree of motor impairment in SCP.

This meta-analysis has several limitations. First, the number of included studies was small, and future studies might benefit from investigating a larger sample size. Second, the FA asymmetry index was not included in this meta-analysis due to the heterogeneity of previous studies, but it might offer additional insights into the potential unilateral patterns of injury. Third, DTI metrics of thalamocortical projections were also associated with sensory function.[23,24,28] However, heterogeneous analysis methodologies and clinical measures are not directly comparable, and the meta-analysis cannot be performed. Finally, although several studies had longitudinal data, most included studies were retrospective and cross-sectional cohort studies with unclear fidelity in predicting motor outcome at early developmental stage

during infancy. In our future work, we plan to analyze more prospective studies investigating the correlation between FA and follow-up motor function.

In conclusion, despite the limitations of the current meta-analysis, the broader clinical implications are striking. Particularly, in two studies,[12,14] the FA of the PLIC showed strong correlation with the follow-up GMFCS, supporting the feasibility of early prediction of motor outcomes in SCP. FA within the PLIC is more closely related to motor dysfunction, which represents a potential biomarker for evaluating the degree of motor impairment in SCP.

Author Contributions

HJ and HL are joint first authors. The study was designed by HJ and JY. Data was extracted by HJ and HL, and analyzed by XL, ZL, and TH. The first draft of article was prepared by HJ and HL. JY, JL, and HH contributed to the critical revision of the manuscript and approved the final version of the manuscript.

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Figure Legends

Figure 1. Flow chart of search results**.** SCP, spastic cerebral palsy.

Figure 2. Forest plots of the summary correlation coefficient (r) with corresponding 95% CIs for the correlation between FA within the posterior thalamic radiation (PTR). (A) corticospinal tract (CST); (B) posterior limb of the internal capsule (PLIC); (C) gross motor function classification system in patients with SCP.

Figure 3. Forest plots of the summary correlation coefficient (r) with corresponding 95% CIs for the correlation between FA within the superior thalamic radiation (STR) (A) corticospinal tract (CST); (B) posterior limb of the internal capsule (PLIC); (C) upper limb motor function in patients with SCP.

On-line Figure 1. Risk of bias and applicability concerns summary for each included study

On-line Figure 2. Risk of bias and applicability concerns graph

On-line Figure 3. Forest plots of the summary correlation coefficient (r) with corresponding 95% CIs for the correlation between MD within the posterior thalamic radiation (PTR) (A) corticospinal tract (CST); (B) posterior limb of the internal capsule (PLIC); (C) gross motor function classification system in patients with SCP.

On-line Figure 4. Forest plots of the summary correlation coefficient (r) with corresponding 95% CIs for the correlation between MD within the superior thalamic radiation (STR) (A) corticospinal tract (CST); (B) posterior limb of the internal capsule (PLIC); (C) upper limb motor function in patients with SCP.

Tables

Table 1. Characteristics of the included studies

Study	Year	Country	Sample size	Age at MRI mean (SD)	Design	Field	Sensori motor pathway	Motor scores	*r*	*P*
Arrigoni[11]	2016	Italy	25	11.8 (3.1) y	R	3.0	CST	GMFCS	-0.52	<0.05
							PTR	GMFCS	-0.50	<0.05
Hasegawa[27]	2018	Japan	8	3.5 m	P	1.5	CST	GMFCS	-0.33	>0.05
							PTR	GMFCS	-0.28	>0.05
Jiang[12]	2019	China	20	11.7 (2.1) m	R	3.0	CST	GMFCS	-0.73	<0.01
							PLIC	GMFCS	-0.80	<0.01
							PTR	GMFCS	-0.46	<0.01
Madhavan[13]	2014	USA	8	12 m	P	3.0	PLIC	GMFCS	-0.94	<0.01
							PTR	GMFCS	-0.80	<0.05
Rose[14]	2007	USA	10	2.5 (0.4) m	P	1.5	PLIC	GMFCS	-0.65	<0.05
Trivedi[8]	2010	India	39	8 y	R	1.5	CST	GMFCS	-0.48	<0.01
							STR	GMFCS	-0.66	<0.01
Wang[15]	2014	China	46	22.4 (6.7) m	R	3.0	CST	GMFCS	-0.42	<0.01
Yoshida[16]	2010	Japan	34	2.2 (2) y	R	1.5	CST	GMFCS	-0.10	>0.05
							PLIC	GMFCS	-0.57	<0.01
							PTR	GMFCS	-0.38	<0.05
Ye[17]	2016	China	43	28 (8) m	R	3.0	PLIC	GMFCS	-0.72	<0.05
Holmstrom[18]	2011	Sweden	15	12.4 y	R	1.5	PLIC	B&B test	0.61	<0.05
							CST	B&B test	0.57	<0.05
Hodge[19]	2017	Canada	28	10.3 (4.6) y	R	1.5	CST	AHA	0.61	<0.05
Kuczynski[28]	2017	Canada	14	12 (3.7) y	R	3.0	STR	AHA	0.57	=0.05
Pannek[20]	2014	Australia	50	10.9 (3.2) y	R	3.0	CST	AHA	0.54[a]	<0.01
							STR	AHA	0.53[a]	<0.05
Reid[21]	2016	Australia	24	11.7 (2.7) y	R	3.0	CST	AHA	0.58[a]	<0.05
Schertz[22]	2016	Israel	20	10.9 (1.8) y	P	3.0	CST	AHA	0.19	>0.05
							PLIC	AHA	0.64	<0.05
Tsao[24]	2013	Australia	42	11.3 (3.3) y	R	3.0	STR	AHA	0.35	<0.05
Tsao[23]	2014	Australia	40	11.5 (3.1) y	R	3.0	PLIC	AHA	0.77[a]	<0.01
	2014	Australia	40	11.5 (3.1) y	R	3.0	STR	AHA	0.65[a]	<0.01
Weinstein[7]	2014	Israel	14	10.6 (2.7) y	R	3.0	PLIC	CHEQ	0.76	<0.01
Weinstein[29]	2015	Israel	12	11 (3.6) y	P	3.0	CST	AHA	0.56	>0.05

R, retrospective; P, prospective; CST, corticospinal tract; PLIC, posterior limb of the internal capsule; PTR, posterior thalamic radiation; STR, superior thalamic radiation; GMFCS, Gross Motor Function Classification System; AHA, Assisting Hand Assessment; CHEQ, Children's Hand Experience Questionnaire; B&B, Box and Blocks; r, correlation coefficient between sensorimotor pathways and motor scores; r^a values were calculated based on r^2 values.

On-line Table 1. Subgroup analyses of the study design

	k	r	95% CI	Z	P value
FA and GMFCS					
Retrospective					
PLIC	3	-0.70	(-0.79, -0.57)	8.00	<0.001
Prospective					
PLIC	2	-0.83	(-0.94, -0.54)	4.06	<0.001
FA and ULMF					
Retrospective					
PLIC	3	0.74	(0.61, 0.84)	7.54	<0.001
Prospective					
PLIC	1	0.64	(0.23, 0.86)	2.81	0.005

PLIC, posterior limb of the internal capsule; GMFCS, Gross Motor Function Classification System; ULMF, upper limb motor function.

On-line Table 2. Bias analysis in the meta-analysis

	Publication bias	
	t	P
FA and GMFCS		
PTR	-0.05	0.96
CST	-0.48	0.65
PLIC	-1.03	0.38
FA and ULMF		
STR	0.18	0.88
CST	-0.53	0.62
PLIC	-1.39	0.30

CST, corticospinal tract; PLIC, posterior limb of the internal capsule; PTR, posterior thalamic radiation; STR, superior thalamic radiation; GMFCS, Gross Motor Function Classification System; ULMF, upper limb motor function.