The Relationship between Structure of the Corticoreticular Tract and Walking Capacity in Children with Cerebral Palsy

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ABSTRACT

Background: Disruption in the descending pathways may lead to gait impairments in Cerebral Palsy (CP) children. Though, the mechanisms behind walking problems have not been completely understood.

Objective: We aimed to define the relationship between the structure of the corticoreticular tract (CRT) and walking capacity in children with CP.

Material and Methods: This is a retrospective, observational, and cross-sectional study. Twenty-six children with CP between 4 to 15 years old participated. Also, we used existed data of healthy children aged 4 to 15 years old. CRT structure was characterized using diffusion tensor imaging (DTI). The DTI parameters extracted to quantify CRT structure included: fractional anisotropy (FA), mean (MD), axial (AD), and radial (RD) diffusivity. Balance and walking capacity was evaluated using popular clinical measures, including the Berg balance scale (BBS), Timed-Up-and-Go (TUG; balance and mobility), six-minute walk test (6 MWT; gait endurance), and 10-meter walk Test (10 MWT; gait speed).

Results: There are significant differences between MD, AD, and RD in CP and healthy groups. Brain injury leads to various patterns of the CRT structure in children with CP. In the CP group with abnormal CRT patterns, DTI parameters of the more affected CRT are significantly correlated with walking balance, speed, and endurance measures.

Conclusion: Considering the high inter-subject variability, the variability of CRT patterns is vital for determining the nature of changes in CRT structure, their relationship with gait impairment, and understanding the underlying mechanisms of movement disorders. This information is also important for the development or prescription of an effective rehabilitation target for individualizing treatment.

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Keyword

Diffusion Tensor Imaging; Motor pathway; Muscle Weakness; Muscle Spasticity; Cerebral Palsy

Introduction

Cerebral Palsy (CP) is a common neurologic disease caused by non-progressive injury to the developing brain before, during, and after birth or in early childhood (two first years of life) [1-3]. It includes the permanent motor, posture, cognition, communication, perception, vision and hearing disorders, and seizure [1,2,4] with a prevalence of about 2 to 2.5 per 1000 live births [1,3-5].

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Injury to the brain leads to disruption of the descending tracts. The corticoreticular tract (CRT), one of the major descending pathways, is assumed to be responsible for handling proximal muscles and gross motor functions [6-8]. Characterizing the structure of the CRT in CP children, detecting its abnormalities, and determining the relationship between these abnormalities and gait impairment are necessary for understanding the mechanism behind the motor function impairment in these children, which may lead to prescribing more efficient rehabilitation.

To study the microstructure of the brain and descending pathways, diffusion tensor imaging (DTI) was utilized. The MR signal is sensitive to the water diffusion in the brain. This diffusion is modeled by a tensor [9] with three Eigenvalues, which define DTI parameters.

The existence of the CRT and the activity of reticulospinal neurons were initially investigated in some animals, such as bird embryos, mice, fish, cats, and monkeys [6,10-17]. In monkeys, it was reported that the role of this pathway is motor recovery after corticospinal tract (CST) injury [17] and the coordination of the two sides of the body [16]. In human subjects, the first study was done in 2012 to examine the location and investigate the structure of the CRT using DTI in a healthy population [18]. Although the CST is the major descending pathway that controls the limbs, it was reported that the vulnerability of the CRT is higher than that of the CST in stroke people and those with injured tracts have a weaker motor function than those with injured CST or CRT [19]. Utilizing a comparable methodology, another study in a couple of stroke survivors with one-sided loss of motion and proximal muscle shortcoming indicated that CST structure and function were normal, however, the CRT had a distinct degree of infarction or axonal destruction [8].

Importantly, gait and movement impairment in stroke people were at least partially attributed to the disruption of the CRT [20]. In support of this finding, the discontinuation of the CRT in the basal ganglia observed in a stroke person was found to improve following a 32-month rehabilitation period [21]. In other studies, the proximal weakness of lower extremities in stroke individuals was attributed to CRT injury [22-24]. It is obvious from previous studies that the role of the CRT in motor functions is as important as the role of the CST in stroke people. However, there is still considerable uncertainty about the relationship between the structure of the CRT and walking performance; to the best of our knowledge, no study was conducted on the CRT structure and its relationship with the walking capacity of CP children.

In this study, we aimed to find the relationship between the CRT structure and walking impairments in CP children. We hypothesized that injury to this pathway can cause weakness and spasticity in lower extremities and consequently lead to gait impairments in children with CP. The structure of the CRT in healthy and CP groups was investigated and explored the correlation between the CRT structure and gait clinical parameters in the CP group.

Material and Methods

This is an observational, retrospective, and cross-sectional study. The research had been approved by the Tehran University of Medical Science institutional review boards.

Participants

Twenty-six CP children with spasticity in lower extremities (14 females and 12 males) participated. All subjects met the following inclusion criteria: (1) diagnosed as spastic hemiplegia or diplegia, (2) age 4 to 15 (3) ability to follow the simple instructions, (4) spasticity in the ankle plantar flexors, and (5) could walk at least with a walker. Exclusion criteria included: (1) uncontrolled seizure (2) intensive deformity of the lower extremities, and (3) receiving botulinum toxin less than 4 months before participation in this study.

Also, DTI data of twenty-six normal children (14 males, 12 females; between 4-15 years of age) were used as the control group [25].

Diffusion Tensor Imaging

To characterize CRT structural changes, DTI data was acquired using the 3T Siemens scanner. The CP group was sedated and underwent DTI sequences, FLAIR, and T1. The imaging parameters were direction=64, NEX=2, number of slices=70, and b=1000 mm^2s^{-1}.

Walking Capacity

Gait function was evaluated using clinical measures, including the (1) 10-meter walking test (10 MWT): a measure of gait speed whereby subjects are instructed to walk 10 meters and the time duration is measured [26], (2) 6-minute walking test (6 MWT): an assessment of walking endurance in which the walking distance of the person in 6 min is measured [27], (3) Timed-Up-and-Go (TUG): a measure of mobility and balance in which subjects are instructed to stand up from a chair, walk 3 meters, walk back to the chair, sit down and the performance time is measured [28]. Balance function was evaluated using the Berg balance score (BBS), which consists of 14-item tests with each test rated from 0 (disability) to 4 (ability) [29] and the total scores of these tests are used to evaluate balance.

Data Analysis

Extraction of Corticoreticular tract

Explore DTI software was used to analyze DTI images. Preprocessing analyses were EPI/eddy and motion correction. After calculating DTI parameters, including fractional anisotropy (FA), mean diffusivity (MD), axial (AD), and radial diffusivity (RD), brain tractography was carried out using a 30° angle threshold, 0.15 FA threshold, and fiber length range of 1-50 cm.

As Figure 1 shows, two regions of interest (ROIs) were drawn (Figure 1a and b) to extract the CRT structure (Figure 1c). The seed ROI was placed on the medullary reticular formation (Figure 1a), and the target ROI was placed on the midbrain tegmentum in the axial slices (Figure 1b) [30]. The mean values of FA, MD, RD, and AD of the CRT were computed to quantify its structure.

Statistical analysis

Statistical analysis was performed using SPSS version 24 (SPPS, IBM Corp, USA). Within each group, the paired t-test was utilized to investigate the CRT structural differences between the two sides of the brain for healthy and CP children separately. The independent t-test was used to identify the difference between the CRT structure of the healthy and CP groups. The relationships between the gait performance parameters and CRT structure were assessed by calculating the

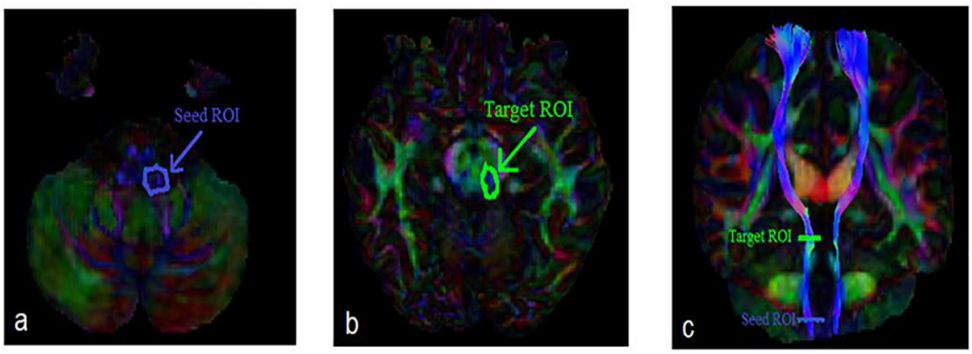

Figure 1: Used regions of interest (ROIs) to extract the corticoreticular tract (CRT) and a typical sample of it. (**a**) a seed ROI around the CRT in the medullary reticular formation, (**b**) a target ROI around the midbrain tegmentum, and (**c**) a sample of the CRT of a normaly child.

Pearson's rank correlation coefficients between DTI parameters and walking capacity assessment measures. A significant level of α=0.05 was considered in our study.

Results

Differences in the CRT structure between CP and healthy children

In this study, the average age for CP and healthy groups was 9.03±2.73, and 10.77±3.03 years, respectively. An investigation of the CRT's appearance showed that there is a large inter-subject variability in CRT appearance in CP children. As presented in Figure 2, different CRT appearances, including (1) a very similar to a normal pattern, which we call semi-normal pattern (Figure 2a), (2) a weaker (Figure 2b), or shorter CRT (Figure 2c) because of the presence of a lesion in the brain, and (3) no CRT in the more affected side due to a huge lesion (Figure 2d), were observed in participated children with CP. Two children didn't have CRT the brain's more affected side because of the large brain lesion. Four children had a shorter CRT, eight children had a thinner CRT, and twelve children had a comparative semi-normal appearance of the CRT on different sides of the brain.

A comparison of DTI parameters in healthy and CP groups using an independent t-test shows that there were significant differences between MD (P=0.01 for the first side, and P=0.006 for the second side), AD (P=0.01 for both sides), and RD (P=0.007 for the first side, and P=0.005 for the second side) of the CRT on two sides of the brain in these two groups. When comparing CP with the healthy group, a significant reduction in AD and a significant increase in MD and RD were observed in the CP group.

Interhemispheric differences in healthy and CP groups

Comparison of two hemispheres in CP children using paired t-test, demonstrated that there is no significant difference between CRT structure of two hemispheres (P>0.2). Moreover, when comparing two hemispheres in the healthy group using a paired t-test, no

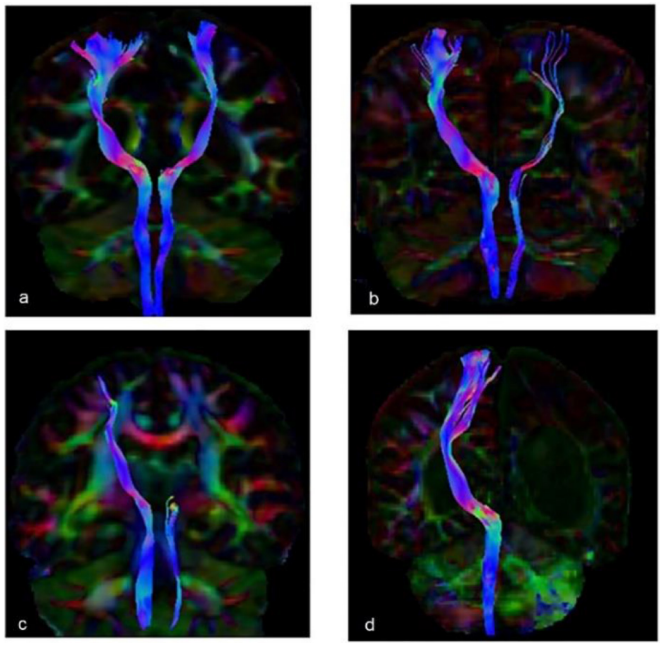

Figure 2: Different patterns of the extracted corticoreticular tract (CRT) in children with cerebral palsy (CP). (**a**) Two similar CRTs, (**b**) one side has a weaker CRT, (**c**) one side has a shorter CRT, (**d**) one side has no CRT.

significant differences were observed between them (P>0.3). Although in the majority of healthy children, the appearance of non-dominant CRT was thinner than the dominant one.

Relationships between the CRT structure and function parameters and walking capacity measures

To understand the relationship between the structure of the CRT and gait impairment, Pearson correlation coefficients of DTI parameters and walking capacity measures were calculated and there were no significant relationships between them (P>0.12). As mentioned before, our subjects had CRTs with high inter-subject variability. To decrease this inter-subject variability, we divided them into two groups. Group-1 contains children who had a shorter or weaker CRT or did not have the CRT in the more affected side of the brain, and group-2 contains children who had semi-normal CRTs in their brain.

Comparing DTI parameters of the CRT in group-1 and the healthy group showed that there are significant differences between MD (P<0.01), AD (P<0.05), and RD (P<0.01) of the CRT on both sides of the brain. Besides, a comparison of DTI parameters of the CRT in group-2 and the healthy group showed that there are not significant differences between measures of CRT structure (P>0.06 for all DTI parameters) on two sides of the brain.

Group-1: CP children who had different appearances of CRT

Table 1 shows the correlation coefficients between gait function parameters and DTI measures of CRT in group-1 and 2.

These results showed that speed had an inverse relationship with MD (rho=-0.694, P=0.012), AD (rho=-0.67, P=0.017) and RD (rho=-0.682, P=0.015) of CRT on the more affected side of the brain. In addition, fast velocity had an inverse relationship with MD (rho=-0.68, P=0.015), AD (rho=-0.57, P=0.012) and RD (rho=-0.653, P=0.021) of the CRT on more affected side and a direct relationship with FA (rho=0.544, P=0.044) of the less affected CRT. Moreover, 6 MWT had an inverse relationship with MD (rho=-0.673, P=0.016), AD (rho=-0.756, P=0.004) and RD (rho=-0.594, P=0.042) of the CRT on more

Table 1: Correlation coefficients between diffusion tensor imaging (DTI) parameters of the corticoreticular tract (CRT) and clinical parameters in cerebral palsy (CP) group-1 and 2.

	Gait Parameters	More Affected CRT				Less Affected CRT			
		FA	MD	AD	RD	FA	MD	AD	RD
Group-1	speed	0.455	*-0.694	*-0.67	*-0.682	-0.508	0.182	-0.032	0.323
	Fast speed	0.382	*-0.680	*-0.57	*-0.653	*0.544	0.127	-0.099	0.293
	TUG	0.136	0.383	0.388	0.365	0.481	-0.166	0.083	-0.342
	6 MWT	0.182	*-0.673	**-0.756	*-0.594	**0.652	0.339	0.050	0.507
	Berg	0.478	*-0.599	-0.547	*-0.607	-0.275	0.442	0.309	0.445
Group-2	speed	0.386	0.064	0.218	-0.031	0.367	-0.218	-0.163	-0.247
	Fast speed	0.324	0.041	0.165	-0.036	0.484	-0.210	-0.125	-0.257
	TUG	-0.238	-0.100	-0.210	-0.031	-0.107	0.050	0.029	0.063
	6 MWT	0.392	0.110	0.277	0.004	0.358	-0.170	-0.091	-0.215
	Berg	0.433	0.012	0.168	-0.084	0.355	-0.233	-0.184	-0.259

CRT: Corticoreticular Tract, FA: Fractional Anisotropy, MD: Mean Diffusivity, AD: Axial Diffusivity, RD: Radial Diffusivity, TUG: Timed-Up-and-Go, 6 MWT: Six-Minute Walk Test

* P<0.01, ** P<0.001

affected side of the brain and a direct relationship with FA (rho=0.652, *P*=0.012) of the less affected CRT. Furthermore, berg parameter had an inverse relationship with MD (rho=-0.599, *P*=0.04) and RD (rho=-0.607, *P*=0.036) of more affected CRT. All of these relationships revealed the correlation between AD of the more affected side and walking speed and 6 MWT.

Discussion

We aimed to characterize the abnormalities in the CRT structure in CP children and determine the relationship of these abnormalities with gait and balance impairments. CRT structure has not been studied in children with CP and its role in locomotion is not fully understood yet, therefore we attempted to find the relationship between different structural patterns of CRT and walking capacity parameters in children with CP. Our results show that there is no specific CRT pattern in this population. Indeed, in CP children with a weaker and shorter CRT, there was a significant correlation between CRT structure and walking capacity measures, including walking speed, balance, and endurance. This information may help clinicians focus on developing new therapies for the enhancement of motor impairment.

Relationship between structural changes of the CRT, balance, and walking disorders

Based on the results, MD of the more affected CRT, which has an inverse relationship with the density of pathway, was higher in the patient group and had an inverse relationship with speed, maximum speed, and 6 MWT indicating walking endurance and BBS parameter indicating balance. In CP children, an increase in MD and a decrease in the density of the CRT in the more affected side of the brain lead to a reduction in balance, walking speed, and gait endurance. In fact, gait disorder worsened; our findings revealed that AD indicating the axonal integrity was lesser in the CP group, and AD of the more affected CRT with speed, maximum speed, and 6 MWT. According to studies on other descending pathways, including CST, increasing AD means improving path structure, and our results are inconsistent with previous findings. This inconsistency can be due to the crossing fibers in each voxel reducing the accuracy of the tensor estimation and tractography and leading to DTI parameter estimation error. RD represents the radial integrity of the brain's pathways and has an inverse relationship with the myelin around the axon; it increases with the disappearance of myelin and is affected by changes in the thickness of fibers or their density [31].

In this study, we showed that there is an inverse relationship between RD of the more affected CRT and speed, maximum speed, 6 MWT, and balance, i.e. reducing RD may result in increasing myelin and improving walking speed, endurance, balance, and finally movement disorder. On the other hand, there was a direct relationship between the FA of the less affected CRT, indicating the microstructural integrity of the pathway and its myelination, maximum speed, and 6 MWT. Increased FA means increased myelination and leads to increased maximum speed and walking endurance.

Among these parameters, TUG is the basic parameter for measuring gait performance, and improvement in gait should be observed in this parameter before any other parameter. Indeed, in order to improve walking speed and endurance, first, there needs to be an improvement in TUG. The relationships between speed, endurance, and balance indicate that the CRT is more involved in skill parameters of gait, for instance, speed. There has been no study to date on the structure of the CRT using DTI and its association with gait function in children with CP, but there have been studies that have explored this pathway without investigation of associations in stroke people. In a study of stroke people, it was found that the tract volume of the intact CRT was

significantly higher in individuals that could walk independently. This was significantly associated with gait function and had a positive correlation with functional ambulation categories (FAC) [32]. We decided to study the structure of the CRT and its relationship with walking disorders in these children to address the lack of adequate information describing the relationship between CRT injury and gait impairment.

Identification of the CRT structural patterns

According to the results of this study, brain lesions altered the structure of the CRT and led to a significant difference between the MD, AD, and RD parameters of the patient and healthy groups. A comparison of these parameters showed that the CP group had higher MD and RD, lower AD, and a weaker structure of the CRT than the healthy group. However, the healthy group had a higher FA than the CP group, which is not significant. These results are consistent with findings from previous studies on the stroke population [19,21]. The comparison of FA and the tract volume in the stroke group, with complete paralysis of the right extremities, and the healthy group showed that there was no significant difference in tract volume between the two groups. However, FA and fiber numbers of the CRT were smaller in the stroke than in the healthy group [19,21].

The identification of the CRT structure in the CP group using DTI showed that this pathway has different structural patterns, making it difficult to understand the relationship between its structure and gait dysfunction. Investigating the relationship between the structure of the CRT and gait function without considering this structural variation does not show any relationship between them because children with CP have a diverse structure of the CRT and the gait function. When we classified them based on the patterns of CRT, there was a significant relationship between the structure of the CRT and gait function in group-1. We tried to reduce inter-subject variability by categorizing these children based on different patterns of the CRT and showed that the CRT, especially the more affected one had a significant relationship with gait and balance disorders.

This study has two major limitations: First, high inter-subject variability of the CRT structure and gait function of CP children were considered, resulting in difficulty in finding the association between them. To address this limitation, the impact of inter-subject variability decreased by identifying two subgroups and determining the relationship between CRT structural measures and walking skill parameters in this two groups. However, due to our sample size limitation, we could only identify two groups of patients. Further studies with larger sample sizes may help identify more subgroups and therefore a better understanding of the underlying mechanisms in gait and balance impairments in children with CP.

Second, a higher error rate is associated with tractography. ROIs are drawn by a skilled neuroanatomist and therefore subjective. One way to reduce this error is registration to a valid atlas, which can be done by the development of registration algorithms.

Conclusion

We were able to identify different CRT patterns in CP children, indicating high inter-subject variability in CRT structure. Due to this issue, we found no significant relationships between CRT structural parameters and walking capacity measures in the entire CP group. However, we were able to find significant relationships by identifying subgroups based on CRT patterns. This may imply that subgroup analysis in CP people may help to determine the associations of altered changes in CRT with impairments in balance and gait, and better understand their underlying mechanisms. This information can also help therapists to develop and individualize treatment for patients.

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Authors' Contribution

Sh. Azizi had contribution to data acquisition, patient recruitment, data Analysis and writing the manuscript. PM. Birgani contributed to data acquisition and data Analysis. M. Ashtiani had contribution to acquiring and analyzing data. A. Irani was responsible for referring patients, clinical evaluation and Analysis. A. Shahrokhi had contribution to referring patients and helping in interpretation of the results. Kh. Meydanloo supervised the statistical analysis of this study. MM. Mirbagheri was responsible for designing and supervising the entire work and writing the manuscript. All authors read and approved the final manuscript.

Ethical Approval

The research had been approved by the Tehran University of Medical Science institutional review boards (approval number: IR.TUMS.REC.1395.2441).

Informed consent

All subjects' guardians signed an informed consent form before the study.

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Conflict of Interest

None

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