Brain & Development 41 (2019) 507–515

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Disrupted cortico-ponto-cerebellar pathway in patients with hemimegalencephaly

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Received 13 September 2018; received in revised form 7 December 2018; accepted 4 January 2019

Abstract

Objective: Cerebellar dysmaturation and injury is associated with a wide range of neuromotor, neurocognitive and behavioral disorders as well as with preterm birth. We used diffusion tensor MR imaging to investigate a disruption in structural cortico-ponto-cerebellar (CPC) connectivity in children with infantile-onset severe epilepsy.

Methods: We performed CPC tract reconstructions in 24 hemimegalencephaly (HME) patients, 28 West syndrome (WS) of unknown etiology patients, and 25 pediatric disease control subjects without a history of epilepsy nor brain abnormality on MRI. To identify the CPC tract, we placed a seeding ROI separately in each right and left cerebral peduncle. We evaluated the distribution patterns of the CPC tracts to the cerebellum and their correlation with clinical findings.

Results: In control and WS of unknown etiology groups, both sides' CPC tracts descended to bilateral hemispheres in 20 (80.0%) and 21 (75.0%); mixed (bilateral on one side and unilateral on the other side) in five (20.0%) and five (17.9%); and unilateral in zero (0.0%) and two (7.1%), respectively. However, in the HME, both sides' CPC tracts descended to bilateral hemispheres in four (16.7%); mixed in 13 (54.1%); and unilateral in seven (29.2%). These CPC patterns differed significantly between the HME and other groups ($p < 0.001$). Among HME patients, those with a unilateral cerebellar distribution on both sides had significantly earlier seizure onset ($p = 0.049$) and more frequent seizures ($p = 0.052$) at a trend level compared to those with bilateral and mixed distributions.

Conclusion: Disrupted CPC tracts were observed more frequently in HME patients than in WS of unknown etiology patients and controls, and they may be correlated with earlier seizure onset and more frequent seizures in HME patients. DTI is a useful and non-invasive method for speculating the pathology in the developing brain.

Keywords: Hemimegalencephaly; West syndrome; Infantile spasms; MRI; Diffusion tensor; Tractography; Fiber tracking; Cortico-ponto-cerebellar pathway; Epilepsy

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https://doi.org/10.1016/j.braindev.2019.01.002
0387-7604/

1. Introduction

Cerebellar dysmaturation and injury is associated with a wide range of neuromotor, neurocognitive and behavioral disorders, including dystonia, ataxia, hemiplegia, stroke, autism, and preterm brain injury [1–6]. The cerebellum exerts its functions in close communication with the cerebral cortex by exploiting two main pathways: the efferent cerebello-thalamo-cortical (CTC) pathway and the afferent cortico-ponto-cerebellar (CPC) pathway [7]. The association of cerebellar underdevelopment with supratentorial abnormalities may involve remote trophic transneuronal interactions via the CPC pathway [4]. The CPC fibers consist of two neuron chains: the cortico-pontine fibers and the ponto-cerebellar fibers. Successive studies performed with neuronal tracer procedures revealed that the pontine fibers entering the cerebellum innervated both sides of the cerebellum [8,9].

Several authors mentioned disrupted cerebellar development in epilepsy. Michelucci reported CPC axonal loss was demonstrated by specific diffusion tensor imaging in a patient with Rasmussen encephalitis [10]. Messerschmidt reported epilepsy were significantly related to disrupted cerebellar development in preterm infants [5]. However, structural cerebro-cerebellar connectivity in children with infantile-onset severe epilepsy have not been evaluated.

Hemimegalencephaly (HME) is a rare malformation characterized by partial or whole enlargement of one cerebral hemisphere [11], sometimes with many types of abnormal fibers detected by MR diffusion tractography [12–14]. West syndrome (WS) is a one of the epilepsy syndromes composed of the triad of infantile spasms, an interictal electroencephalogram (EEG) pattern termed hypsarrhythmia, and mental retardation. WS includes two etiological groups: symptomatic (including HME) and unknown etiology. Both HME and WS patients often show early-onset severe epilepsy and developmental delays, while cognitive impairment in WS may vary, according to the etiology of the syndrome, ranging from normal to greater cognitive impairment.

We have experienced "ipsilateral (uncrossed) cerebellar diaschisis (ICD)" in some patients with HME. In Hamano et al. study [15], ICD was observed in some patients whose brain injuries occurred before the age of 3 years. They speculated that ICD is related to maturation of the CPC fibers. We hypothesized that the CPC pathway might not cross the midline to enter the cerebellum in some pediatric patients with infantile-onset severe epileptic syndrome (that causes cortical damage in early childhood). We aimed to investigate the CPC pathway in HME comparing with WS of unknown etiology by using diffusion tensor MR imaging and their correlation with clinical findings.

2. Methods

2.1. Subjects

Twenty-four patients with HME (8 males, 16 females, age range, 1.6 months to 50 years; median age, 3.9 months) and 28 patients with MRI-negative WS of unknown etiology (16 males, 12 females, age range, 3.7 months to 23 years; median age, 34.9 months) who underwent MR imaging including diffusion tensor imaging (DTI) were identified at our institution between October 2010 and September 2017. All patients were hospitalized for intractable epilepsy, and detailed examinations were performed to determine whether surgical treatment was indicated. The diagnosis was made on the basis of both clinical and imaging findings. Surgical treatment was performed in 17 patients (70.0%) in HME and 3 patients (10.7%) in WS of unknown etiology. Ten patients underwent hemispherotomy, 4 patients had posterior disconnection, 3 patients had callosotomy, 1 patient had prefrontal disconnection, 1 patient had temporal lobectomy, and 1 patient had anterior callosotomy and focal cortical resection. All MR studies for analysis were done before operations.

In the cases of HME, a diffusely or partially enlarged hemicerebrum was confirmed by MRI. Constant features were gross asymmetry with enlargement of one hemisphere, dysplastic cortex, and asymmetry and deformity of the ventricular system. The diagnosis of WS was based on the clinical appearance of infantile spasm, hypsarrhythmia on EEG, and mental retardation. The WS includes two etiological groups: symptomatic and unknown etiology. If any etiological factors related to WS could not be determined, a diagnosis of WS of unknown etiology was made. The present study involved only WS of unknown etiology patients whose MRI scans revealed no remarkable abnormalities other than atrophy. We obtained the clinical data of all subjects, including age, gender, past history, onset age of seizures, frequency of seizures, and history of present illness. Additionally, 25 disease control subjects (16 males, 9 females, age range, 6.0 months to 15 years; median age, 40 months) without a history of epilepsy nor brain abnormality on MRI were enrolled.

This retrospective study was approved by the institutional review board at Japan's National Center of Neurology and Psychiatry, and the need for patient informed consent was waived.

2.2. MR imaging acquisition

The MR images for all subjects were performed on a 3.0-Tesla (T) MR system (Achieva; Philips Healthcare, Best, the Netherlands, or MAGNETOM Verio; Siemens, Erlangen, Germany) with a standard 32-channel head coil.

Diffusion was measured along 12 or 15 non-collinear directions with the use of a diffusion-weighted factor b in each direction for 1000 s/mm^2, and one image was acquired without using a diffusion gradient. DTI data were acquired using a transverse slice orientation and the following parameters: TR, 6774–10000 msec; TE, 58–73 msec; voxel size, 3.0 × 3.0 × 3.0 mm^3; NEX, 1–2; flip angle, 90°; matrix, 76–80 × 76–80, and acquisition time 2.5–4.3 min.

In addition to DTI, convention axial T2-weighted images (TR, 5000 msec; TE, 80 ms; FOV, 220 × 200 mm; slice thickness, 3 mm; NEX, 2 and acquisition time 3 min) and T1-weighted images (TR, 600 msec; TE, 10 msec; FOV, 220 × 200 mm; slice thickness, 3 mm; NEX, 1 and acquisition time 3 min) were obtained. Fluid attenuation by inversion recovery (FLAIR) images (TR, 10000–120000 msec; TE, 94–120 msec; FOV, 220–230 × 183–198 mm; slice thickness, 3 mm; NEX, 1–2 and acquisition time 3 min) were also obtained. Volumetric T1-weighted images were acquired using magnetization-prepared rapid acquisition of gradient-echo (MPRAGE) sequences: TR, 1800 msec; TE, 2.26 msec; flip angle, 90°; voxel size, 0.9 × 0.8 × 0.8 mm^3; NEX, 1 and acquisition time 5.5 min.

We evaluated the HME side (right or left) and the presence or absence of ipsilateral cerebellar enlargement by visual assessment.

2.3. Fiber tractography

After the data preparation and quality assessment, two neuroradiologists (Y.S. and E.M. with 11 and 14 years of experience, respectively) independently performed compact fiber tracking using DTI Studio software (Johns Hopkins University, Baltimore, MD; http://cmrm.med.jhmi.edu/). They were blinded to the subjects' age and sex, and clinical data. The fiber tracking was based on the fiber assignment by continuous tracking (FACT) algorithm with a fractional anisotropy (FA) threshold of 0.20 and an angle threshold of 90°.

Anatomically, the CPC fibers arise from a wide area of the cerebral cortex. The CPC fibers descend through the corona radiata, internal capsule, and cerebral peduncle and terminate on the pontine nuclei. Most of the pontine nuclei give rise to the transverse fibers of the pons, which cross the midline and enter the opposite cerebellar hemisphere through the middle cerebellar peduncle, and the rest of the fibers descend to the ipsilateral cerebellum [8,9,16]. The corticospinal tract (CST) originates from the precentral motor cortex and descends through the corona radiata and posterior one-third portion of the limb of internal capsule. The CST continues to descend in the cerebral peduncle surrounded side by side with the CPC tracts down to the level of the pons, and then continues its course caudally to the medulla and spinal cord where the CPC fibers no longer exist [16].

To identify the CPC tract, the neuroradiologists placed a seeding region of interest (ROI) in the cerebral peduncle. However, because the CST was also tracked through it, the fibers which continue caudally to the medulla were removed by using "NOT" operations. ROIs were drawn separately in each right and left cerebral peduncle. We then evaluated the distribution pattern of the CPC tract, and classified the distributions into three patterns (bilateral, mixed, and unilateral) as follows. Bilateral: The CPC tract arises from a unilateral cerebral hemisphere and goes down to bilateral cerebellar hemispheres and is the same on the opposite side. Mixed: The CPC tract arises from a unilateral cerebral hemisphere and goes down to bilateral cerebellar hemispheres, but on the opposite side, it goes down to the ipsilateral or contralateral cerebellar hemisphere. Unilateral: The CPC tract arises from a unilateral cerebral hemisphere and goes down to the ipsilateral or contralateral cerebellar hemisphere and is the same on the opposite side.

We assessed the relationship between the distribution patterns of the CPC tracts and the patients' clinical data including age at seizure onset and the frequency of seizures.

2.4. Statistical analysis

The statistical analysis was performed using R software (version 3.2.2; R Foundation for Statistical Computing, Vienna, Austria) [17]. We used the Fisher's exact test for all categorical data. Between-group comparisons for numerical and ordinal scale data were evaluated using nonparametric tests (Mann-Whitney *U* test and Kruskal–Wallis rank-sum test). All numerical data were nonparametric, and they are expressed as medians and interquartile ranges (IQRs) in brackets. Interobserver reliability for CPC tract pattern was determined with use of the kappa statistic after independent assessment by two neuroradiologists (Y.S. and E.M.). Results were considered significant at $p < 0.05$. The Bonferroni correction was used to adjust for multiple comparisons. The inter-observer agreement for ROI based tractography analyses was calculated as a κ value. The strength of the agreement was considered fair for κ values of 0.21–0.40, moderate for κ values of 0.41–0.60, good for κ values of 0.61–0.80 and excellent for κ values of 0.81 or greater.

3. Results

3.1. Demographics

Table 1 summarizes the clinical demographics of the HME and WS of unknown etiology patients and controls.

Table 1
Demographic profiles of the subjects.

Characteristic	HME (n = 24)	WS of unknown etiology (n = 28)	Controls (n = 25)	p-value
Age at MR exam				
Months, median (IQR)	3.9 (2.8, 44.8) (1.6–605.6)	34.9 (14.4,72.4) (3.7–277.5)	40.0 (14.0, 108.0) (6.0–180.0)	0.004[a]
Gender (male/female)	8/16	16/12	16/9	0.079[b]
Age at seizure onset				
Months, median (IQR)	0.8 (0.2, 2) (0.0–144.0)	4 (2.8, 7) (0.1–17.0)	NA	<0.001[a]
Frequency of seizures:				0.592[a]
Daily > 10 times	7	1	NA	
Daily 1–10 times	10	23		
Non-daily (weekly or less)	7	4		

[a] Mann-Whitney U-tests.
[b] Fisher's exact test. HME, hemimegalencephaly; WS, West syndrome; NA, not applicable.

3.2. MR imaging findings and fiber tractography

The MR imaging findings and distribution patterns of the CPC tracts in the two disease groups and controls are illustrated in Figs. 1–3 and summarized in Tables 2–4. The number of subjects whose DTI using 12 directions was 26 and 15 directions was 51. For the ROI based tractography analyses, the interobserver agreement was excellent; the κ value was 0.88.

Among the 25 disease controls group, the distribution patterns of the CPC tracts were bilateral in 20 (80.0%) subjects (Fig. 1), and mixed in five (20.0%). Among the 28 patients with WS of unknown etiology, the distribution patterns of the CPC tracts were bilateral in 21 (75.0%), mixed in five (17.9%) (Fig. 2), and unilateral in two (7.1%) patients. All of the unilateral CPC tracts in both the mixed and unilateral groups were ipsilateral distributions.

Among the 24 patients with HME, the HME side was right in 11 patients (45.8%) and left in 13 (54.2%). Ipsilateral cerebellar enlargement was identified in five (20.8%). The distribution patterns of the CPC tract were bilateral in four (16.7%), mixed in 13 (54.1%), and unilateral in seven (29.2%) patients (Fig. 3). In the unilateral group, all ipsilateral CPC tracts ran down to the ipsilateral cerebellar hemispheres except for one whose CPC tract crossed to the contralateral cerebellar hemisphere. In the mixed group whose CPC tracts showed

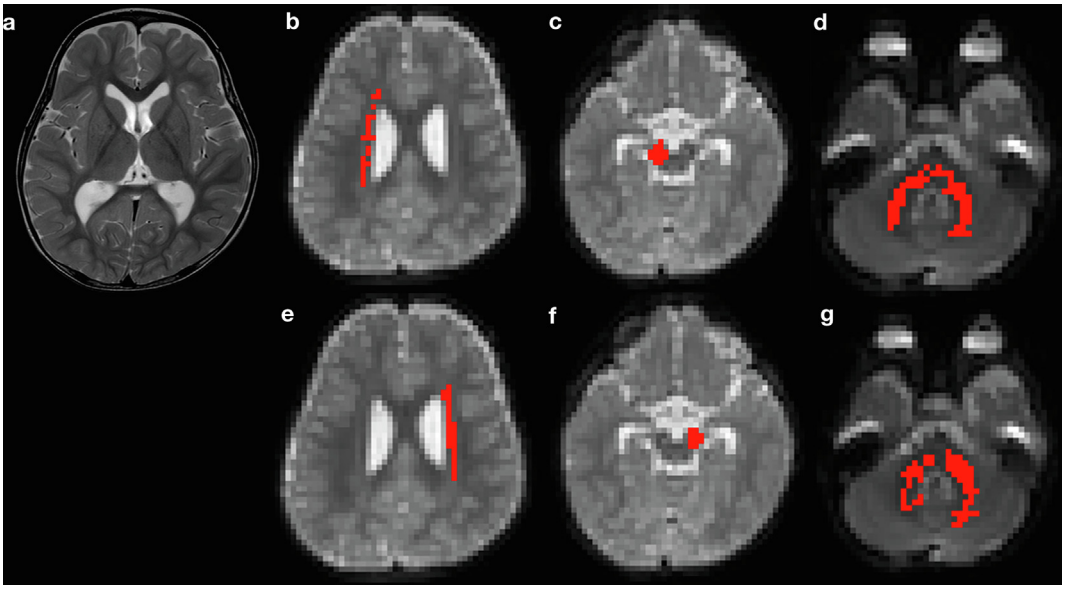

Fig. 1. A 1-year-and-8-month-old disease control; bilateral pattern. a: T2-weighted image shows no apparent abnormal findings other than mild atrophy. b–d: Tractography shows bilateral cerebellar distributions of CPC tracts when the ROI is placed in the right cerebral peduncle. e–g: The same on the left side.

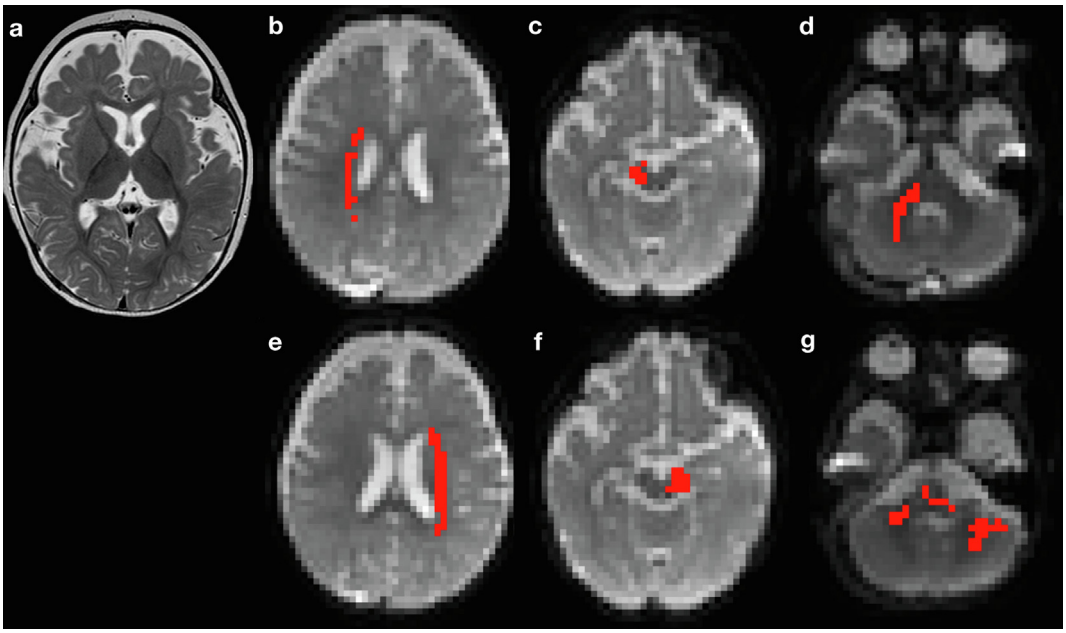

Fig. 2. An 8-month-old patient with MRI-negative West syndrome of unknown etiology; mixed pattern. a: T2-weighted image shows mild brain atrophy after ACTH therapy. b–d: Tractography shows an ipsilateral cerebellar distribution of CPC tracts when the ROI is placed in the right cerebral peduncle. e–g: Tractography shows bilateral cerebellar distributions of CPC tracts when the ROI is placed in the left cerebral peduncle.

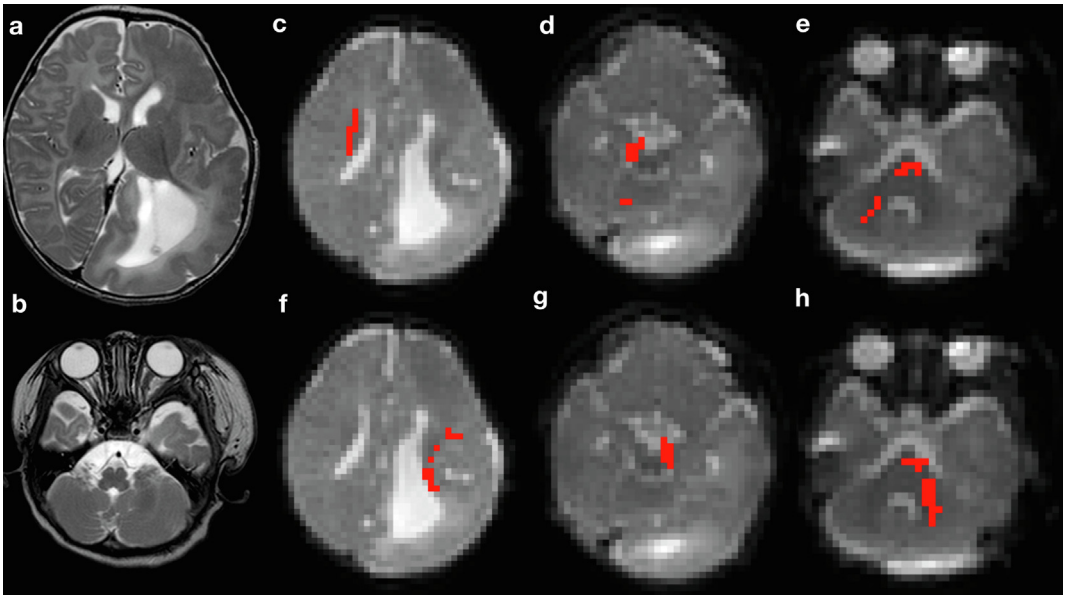

Fig. 3. A 3-month-old patient with hemimegalencephaly; unilateral pattern. a,b: T2-weighted images show left hemimegalencephaly with ipsilateral cerebellar enlargement and ipsilateral facial lipomatous overgrowth. c–e: Tractography shows ipsilateral cerebellar distribution of CPC tracts when the ROI is placed in the right cerebral peduncle. f–h: The same on the left side.

a bilateral cerebellar distribution on one side and unilateral cerebellar distribution on the other side, all unilateral of the CPC tracts were ipsilateral.

There was a significant difference in the distribution patterns of the CPC tracts among the three groups ($p < 0.001$). The HME group showed a significantly higher incidence of unilateral and mixed CPC tracts and a significantly lower incidence of bilateral CPC tracts than WS of unknown etiology patients and controls. However, in the HME patients, there was no significant difference in the CPC distribution pattern regarding whether the CPC tracts originated from the HME side or the contralateral side ($p = 0.08$).

Table 2
MR imaging findings and diffusion tensor tractography analysis.

MRI findings & tract patterns	HME (n = 24)	WS of unknown etiology (n = 28)	Controls (n = 25)	p-value
HME side (right/left)	11/13	NA	NA	
Ipsilateral cerebellar enlargement	5 (20.8%)	NA	NA	
CPC tracts pattern:[†]				<0.001[a]
Bilateral	4 (16.7%)	21 (75.0%)	20 (80.0%)	
Mixed	13 (54.1%)	5 (17.9%)	5 (20.0%)	
Unilateral	7 (29.2%)	2 (7.1%)	0 (0.0%)	

[a] Fisher's exact test.
[†] Bilateral: The CPC tract arises from a unilateral cerebral hemisphere and goes down to bilateral cerebellar hemispheres and is the same on the opposite side. Mixed: The CPC tract arises from a unilateral cerebral hemisphere and goes down to bilateral cerebellar hemispheres, but on the opposite side, it goes down to the ipsilateral or contralateral cerebellar hemisphere. Unilateral: The CPC tract arises from a unilateral cerebral hemisphere and goes down to the ipsilateral or contralateral cerebellar hemisphere and is the same on the opposite side.

Table 3
Comparison of the clinical findings between the groups with bilateral, mixed and unilateral CPC tracts in the patients with HME.

Clinical findings	CPC tracts pattern (n = 24)[†]			p-value
	Bilateral (n = 4)	Mixed (n = 13)	Unilateral (n = 7)	
Age at seizure onset:				0.049[a]
Months, median (IQR)	1.5 (0.9, 37.5) (0.6–144.0)	1.0 (0.2, 2.0) (0.2–8.0)	0.2 (0.0, 0.5) (0.0–1.0)	
Frequency of seizures:				0.052[a]
Daily > 10 times	1	2	4	
Daily 1–10 times	0	7	3	
Non-daily (weekly or less)	3	4	0	

CPC, cortico-ponto-cerebellar.
[a] Kruskal-Wallis tests.
[†] Bilateral: The CPC tract arises from a unilateral cerebral hemisphere and goes down to bilateral cerebellar hemispheres and is the same on the opposite side. Mixed: The CPC tract arises from a unilateral cerebral hemisphere and goes down to bilateral cerebellar hemispheres, but on the opposite side, it goes down to the ipsilateral or contralateral cerebellar hemisphere. Unilateral: The CPC tract arises from a unilateral cerebral hemisphere and goes down to the ipsilateral or contralateral cerebellar hemisphere and is the same on the opposite side.

Table 4
Comparison of the clinical findings between the groups with bilateral, mixed and unilateral CPC tracts in the patients with WS of unknown etiology.

Clinical findings	CPC tracts pattern (n = 28)[†]			p-value
	Bilateral (n = 21)	Mixed (n = 5)	Unilateral (n = 2)	
Age at seizure onset:				0.406[a]
Months, median (IQR)	5.0 (3.0, 7.0) (1.3–17.0)	3.0 (2.0, 8.0) (0.1–10.0)	2.3 (1.45, 3.15) (0.6–4.0)	
Frequency of seizures:				0.7[a]
Daily > 10 times	1	0	0	
Daily 1–10 times	16	5	2	
Non-daily (weekly or less)	4	0	0	

CPC, cortico-ponto-cerebellar.
[a] Kruskal-Wallis tests.
[†] Bilateral: The CPC tract arises from a unilateral cerebral hemisphere and goes down to bilateral cerebellar hemispheres and is the same on the opposite side. Mixed: The CPC tract arises from a unilateral cerebral hemisphere and goes down to bilateral cerebellar hemispheres, but on the opposite side, it goes down to the ipsilateral or contralateral cerebellar hemisphere. Unilateral: The CPC tract arises from a unilateral cerebral hemisphere and goes down to the ipsilateral or contralateral cerebellar hemisphere and is the same on the opposite side.

Compared to the group of HME patients with bilateral CPC tracts, the group of HME patients with unilateral CPC tracts had significantly earlier seizure onset ($p = 0.049$) and more frequent seizures at a trend level ($p = 0.052$) (Table 3). While, among the group of WS of unknown etiology patients, there were no significant differences between the CPC tract patterns and clinical findings including the age at seizure onset ($p = 0.406$) and frequency of seizures ($p = 0.7$) (Table 4).

4. Discussion

We detected a higher incidence of unilateral and mixed CPC fiber distributions in patients with HME than in patients with WS of unknown etiology and disease controls, and they may be correlated with earlier seizure onset and more frequent seizures. These results raise the speculation that the severe damage of epilepsy in the developing brain during childhood may affect the maturation of the CPC tracts. To the best of our knowledge, no previous studies have focused on abnormalities of the CPC pathway in HME and WS of unknown etiology patients.

Cerebellar white matter connections to the other central nervous system areas are functionally classified into three types: the spinocerebellar, vestibulocerebellar, and cerebrocerebellar subdivisions. Cerebrocerebellar connections are composed of feed-forward and feedback connections between the cerebrum and cerebellum, including the CPC pathway (of cortical origin) and the CTC pathway (of cerebellar origin). A major part of the CPC is known to cross at the pons level, whereas a minor part travels uncrossed. Keser et al. [18] observed that the fronto-ponto-cerebellar pathway (which is one of the main components of the CPC pathway) crossed at the pons level, whereas the temporo-ponto-cerebellar pathway and the occipito-ponto-cerebellar and parieto-ponto-cerebellar pathways (which are minor components of the CPC pathway) did not cross at the pons level. This observation is somewhat consistent with previous human neuroanatomy investigations [8,9,19] in which 82% of the cells evidenced in the basilar pontine nuclei were stained by the tracer injected in the contralateral cerebellar cortex and 18% by the tracer injected in the ipsilateral cerebellar cortex [19].

Diaschisis was described initially by von Monakow as focal cerebral lesions, such as infarction, that cause a temporary impairment of function at a remote site [20]. Crossed cerebellar diaschisis (CCD) is one of the well-investigated diaschises and is defined as the reduction of metabolism and blood flow in the cerebellar hemisphere contralateral to supratentorial pathological lesions. This remote functional depression is believed to occur via the CPC pathway. In pediatric patients with hemiplegia, a second type of cerebellar diaschisis, ipsilateral cerebellar diaschis (ICD): cerebellar hypoperfusion ipsilateral to supratentorial lesions has been observed [15,21,22]. In the Hamano et al. study [15], CCD occurred in the patients who suffered from brain injuries after the age of 7 years, whereas ICD manifested in patients whose brain injuries occurred before the age of 3 years. Hamano et al. speculated that these occurrence differences in cerebellar diaschisis during childhood are related to maturation of the CPC fibers. We hypothesized that the CPC pathway might not cross the midline to enter the cerebellum in some pediatric patients with epileptic syndrome (that causes cortical damage in early childhood) as well as pediatric hemiplegic patients.

The cerebellum has traditionally been considered to be involved in motor coordination. However, the role of this structure in non-motor functions such as cognition, emotion and behavior has recently become evident [1–6]. The precise pathophysiological mechanisms underlying these deficits are unknown and it remains unclear whether functional impairments in non-motor domains are a direct consequence of impaired cerebellar development and function. Significantly less is known about the role of the cerebellum in epilepsy. Some researchers observed significantly smaller cerebellar white matter volumes in patients with newly diagnosed epilepsy compared to healthy controls. The researchers assumed that cerebellar white matter changes meant that the cerebellum is a susceptible structure associated with the development of epilepsy [23]. In epileptic patients, the histologic findings of Purkinje cell loss [24] support the hypothesized disinhibition of their cerebello-thalamo-cerebro-cortical circuits including the CPC pathway. The cognitive and behavioral impairments associated with the severe epileptic encephalopathy may be profound, especially for those with very early onset epilepsy and dysplastic lesions in whom development appears to remain arrested until clinical and subclinical seizure activity is abolished [25]. Such secondary impairment is emerging as the main target for epilepsy surgery in childhood. Cognitive impairment in WS may vary, according to the etiology of the syndrome. Symptomatic forms including HME are generally associated with greater cognitive impairment. On the contrary, WS of unknown etiology are more frequently associated with normal development [26]. The mechanism of the brain injury caused by epilepsy in patients with HME and WS could be cytotoxic edema [27] and accelerated myelination [14]. There is a need for a tool that allows non-invasive assessment of cerebellar maturation in children considered high-risk for neurocognitive disorders.

There are several limitations in this study. First, delineating connections between cerebellar and cerebral cortex using diffusion tractography is challenging in the developing brain in vivo. Few studies have reported diffusion tensor tractography observations of the CPC pathways in infants and children. Pieterman et al. demonstrated crossed CPC tracts in all infants (from 29 to 44 weeks' gestational age) by DTI in vivo, but they did not mention bilateral cerebellar distributions of CPC tracts [28]. Second, we used a deterministic approach that have limited ability to model crossing fibers and limited robustness against measurement noise to reconstruct the CPC tracts. It could be higher the percentage of bilateral CPC tracts in epileptic patients if a probabilistic approach would have been used. Third, DTI

data were acquired using different 12 or 15 directions. It is reported that FA is affected by changes in the number of gradients and an increase in the number of directions results in a decrease in the average FA [29]. Differences in the number of directions may affect the accuracy of the results. Fourth, we discussed the results of MR tractography which were not confirmed by pathological evidence. Finally, long-term observations are needed to clarify the effects of microstructural changes to the CPC pathway on cognitive functions in patients with HME and WS of unknown etiology.

In conclusion, disrupted CPC tracts were more frequently observed in pediatric patients with HME than in patients with WS of unknown etiology and controls, and they may be correlated with earlier seizure onset and more frequent seizures in HME patients. DTI is a useful and non-invasive method for speculating the pathology in the developing brain.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgments

This work was supported by Intramural Grant (30-6) for Neurological and Psychiatric Disorders of NCNP.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2019.01.002.

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