JIMA Vol. 74, No. 2 (June 2022) pp. 61-81.

Original

Diffusion kurtosis imaging study of childhood epilepsy with and without motor coordination problems

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(Received on December 29, 2021 & Accepted on February 8, 2022)

Abstract

We evaluated whether magnetic resonance diffusion kurtosis imaging (DKI) could reveal brain microstructural changes in childhood epilepsies with motor coordination problems (MCP) and whether DKI findings are correlated with neuropsychological assessments. Sixteen patients with childhood epilepsies were included; eight of these had lower scores on the Japanese version of the Developmental Coordination Disorder Questionnaire (DCDQ-J) than the cutoff value, and these patients were categorized as the MCP group. Regions of interest analyses of the cortex were performed to compare the mean kurtosis (MK), fractional anisotropy, and mean diffusivity between the MCP and non-MCP groups. The MK value of the right precentral gyrus (PrCG) was significantly lower in the MCP group than in the non-MCP group ($p = .021$). Significant correlations between diffusion kurtosis metrics and the DCDQ-J scores were observed, particularly in the paracentral lobules. The receiver operating characteristic analysis for all patients indicated that the area under the curve for MK values of the right PrCG was 0.844, and the cutoff MK value to distinguish whether MCP was present was 0.587 (sensitivity, 100%; specificity, 75%). Our results indicate that the DKI findings of the right precentral cortex may be substantially useful as a biomarker for MCP associated with childhood epilepsy.

Key words: *diffusion kurtosis imaging, Developmental Coordination Disorder Questionnaire, motor coordination problems, health-related quality of life, precentral gyrus*

I. Introduction

Some childhood-onset epilepsies are classified as self-limited and/or pharmacoresponsive [1], including childhood absence epilepsy (CAE),

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benign epilepsy with centrotemporal spikes (BECTS), and Panayiotopoulos syndrome (PS). CAE shows intermittent generalized electroencephalogram (EEG) abnormalities, whereas BECTS and PS show localized and intermittent EEG abnormalities on one side of the cerebral hemisphere. Although most of these patients have normal intelligence, some have mild neuropsychological impairments, and variable degrees of cognitive, behavioral, and exercise impairments without structural abnormalities are detectable by conventional magnetic resonance imaging (MRI) [2-5]. To resolve the unmet medical needs of children with epilepsy, neurobehavioral comorbidities caused by CAE, BECTS, and PS are an important research area for the development of suitable diagnostic tools and new therapeutics.

Parent-reported symptoms of developmental coordination disorder (DCD) are common in childhood epilepsies [6]. DCD is a neurodevelopmental disorder that occurs in 5–6% of school-aged children [7]. DCD can cause difficulties in acquiring exercise skills and in all other aspects of daily life, such as playing sports, running, getting dressed, and writing. Moreover, it is associated with low self-esteem among patients [8] and increased risks of obesity, coronary artery disease, anxiety, and depression [9]. Childhood epilepsies with some neurobehavioral comorbidities, including DCD [10], are associated with parent-reported health-related quality of life (HRQOL) [11]. The Developmental Coordination Disorder Questionnaire (DCDQ) is an internationally accepted parent-reported questionnaire that assesses the degree of motor skill impairments [12]. The sensitivity and specificity of the DCDQ are highly applicable in the broader setting of the child's usual daily life [13]. Children with scores below the DCDQ cutoff are considered to have motor coordination problems (MCP) [14]. Advances in brain MRI have led to many reports on the physiological and structural features of epilepsy [15]. Diffusion tensor imaging (DTI) in patients with BECTS has noted increased mean diffusivity (MD) and decreased fractional anisotropy (FA), specifically in the white matter (WM) of the paracentral gyri [16]. Microstructural changes in the WM, particularly in the corpus callosum of patients with CAE, have also been noted [17,18]. Although the causes of dyssynergia in patients with epilepsy are not fully understood, most researchers believe the discharge of repeated spikes causes subtle changes in the axons and glial cells and their functional connections [16]. Conversely, some authors note that cognitive impairment or behavior problems occur before seizures; thus, these psychosocial issues may be an accompanying or precursor symptom [19, 20]. Since DTI assumes that the probability density function of a water molecule is Gaussian water diffusion [21], it cannot accurately estimate diffusion heterogeneity. Diffusion kurtosis imaging (DKI), which quantifies non-Gaussian water diffusion, is a comparatively new and more appropriate clinical imaging technique for evaluating localized minor microstructural complexities of brain tissues [22]. Clinical studies conducted at our institute suggest that DKI provides a more comprehensive and sensitive detection of microstructural alterations in brain tissue [23-28]. Given the complicated diffusion anisotropy of nerve fibers in the central nervous system, particularly in the gray matter (GM), DKI

is more appropriate than DTI. Few studies have evaluated childhood epilepsy using DKI [29]. Most previous studies on DTI or DKI have revealed differences in the brain microstructural changes among children with epilepsy or MCP and those showing typical development; however, to the best of our knowledge, no study has investigated the differences in microstructural changes in childhood epilepsy with and without MCP.

Therefore, this study used DKI to investigate the cerebral micropathological changes in children with epilepsy with and without MCP. The DKI parameter differences between groups and their associations with neuropsychological features were also examined.

II. Materials and Methods

1. Participants

We prospectively recruited 23 patients who were diagnosed with CAE, BECTS, or PS (age range 6–14 years; male-to-female ratio, 10:13; 5 patients with CAE, 12 with BECTS, and 6 with PS, all attending regular schools) who were followed-up at Iwate Medical University Hospital and its collaborating hospitals between November 2018 and August 2019. The patients had no history of cerebral palsy, muscular dystrophy, or any developmental disorders. The patients were diagnosed by a pediatric epileptologist/neurologist (A.K.) or a pediatric neurologist (N.A., M.A.) according to the International League Against Epilepsy criteria.

This study was conducted in compliance with the Declaration of Helsinki and according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Ministry of Health, Labour and Welfare in Japan. The Human Ethics Review Committee of Iwate Medical University approved the study protocol (approval number, H2018-530). Written informed consent and assent were obtained from all participants and their parents. Clinical information (clinical symptoms, medical history, family history, medication status, seizure date, and the most recent seizure date) was extracted from the patients' charts.

MRI, EEG, the Japanese version of the DCDQ (DCDQ-J), the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV), and the Japanese version of KIDSCREEN-52 (J-KIDSCREEN-52) were performed.

2. Neuropsychological assessment

All subjects were individually evaluated on the same day by MRI and EEG. The WISC-IV and its four subscales [verbal comprehension index (VCI), perceptual reasoning index (PRI), working memory index (WMI), and processing speed index (PSI)] were used to assess the full-scale intelligence quotient (FSIQ).

3. Identification of MCP

MCP was evaluated using the DCDQ-J [6]. Since the cutoff score for the DCDQ-J had not been previously determined, the cutoff score for the DCDQ 2007 (DCDQ'07) was used [14]. The DCDQ-J is divided into three general motor behavior categories: control during movement (CDM; six items), fine motor and handwriting (FM/H; four items), and general coordination (GC; five items). Total scores range from 15 to 75, with higher scores indicating better motor skills. We categorized the MCP group, which indicates DCD or suspected DCD, based on cutoff scores of ≦ 46 for children aged 5–7 years 11 months; ≦

55 for children aged 8–9 years 11 months; and ≦ 57 for children aged 10–15 years. Children with scores higher than the above cutoff values were considered the non-MCP group.

4. J-KIDSCREEN-52

The children's self-reported questionnaire KIDSCREEN-52 has been developed and used in many countries to measure HRQOL in children aged 8–18 years. This questionnaire includes 52 items categorized into the following 10 dimensions: Physical Well-being, Psychological Well-being, Moods and Emotions, Self-Perception, Autonomy, Parent Relations and Home Life, Financial Resources, Social Support and Peers, School Environment, and Social Acceptance (Bullying). The item scores are summed and converted to T scores for each dimension with an average of 50 and a standard deviation of 10 based on typical European population samples. The higher the T score, the better the HRQOL [30]. The J-KIDSCREEN-52 has been developed and validated elsewhere [31, 32]. We determined the correlations between the DCDQ-J scores and the self- or parent-reported J-KIDSCREEN-52 scores, respectively, and between the DCDQ-J and WISC-IV scores.

5. Electroencephalogram

EEG was performed using the international 10-20 system to confirm EEG abnormalities. Three pediatric neurologists (A.K., N.A., and M.A.) who were unaware of the subject information read the EEGs blindly. Observations were based on consensus between the two groups. If differing views were noted, the majority decision was adopted.

6. MRI data acquisition

MRI scans were performed without any sedative drug. All participants underwent MRI on a 3T MRI scanner (Discovery MR750, GE Health-care, Milwaukee, WI, USA) with an eight-channel head coil. DKI/DTI source images were obtained using a single-shot spin-echo echo-planar imaging technique.

The DKI scanning parameters were optimized according to a previous report [33] and used in previous studies [23-28]: b values of 0, 1000, and 2500 s/mm^2; repetition time/echo time, 4300/110.6 ms; motion-probing gradients, 20 directions with a duration of 31.0 ms and a separation of 39.8 ms; field of view, 24 cm; matrix size, 128 × 128; reconstructed matrix size, 256 × 256 (pixel size, 0.94 mm); slice thickness, 4.0 mm without interslice gaps; number of slices, 30; number of excitations, 4; reduction factor of parallel imaging, 2; and acquisition time, 12 min and 12 s. Conventional MR images, including T1- and T2-weighted images, were also obtained.

7. Analyses of imaging data

The imaging analyses were performed by two authors (F.M. and K.I.) who were unaware of the clinical symptoms. Diffusion metric maps of the mean kurtosis (MK), FA, and MD values were calculated using in-house software [33] as in previous studies [23-28]. To identify changes in the whole-brain WM between the MCP and non-MCP groups, we performed a voxel-wise statistical analysis of the MK, FA, and MD maps using tract-based spatial statistics (TBSS) implemented in Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library FSL 6.0.0 [34, 35]. To perform region of interest (ROI) analyses in the anatomical site of the brain, the Johns Hopkins University (JHU) Eve atlas [36] was warped to the native space of each subject using the inverse transformation

matrices that were obtained by the registration of the FA and b0 maps into the corresponding maps of the JHU-Eve and International Consortium for Brain Mapping atlas via methods similar to those described in previous studies [24, 25]. The MK, FA, and MD values of the corticospinal tract (CST), cingulate gyrus (CG), precentral gyrus (PrCG), postcentral gyrus (PoCG), middle frontal gyrus, supplementary motor area, caudate nucleus, globus pallidus (GP), thalamus, and putamen were then automatically measured using ROIs consisting of the foregoing methods.

8. Statistical analysis

For TBSS, to compare voxel values for the MK, FA, and MD between the MCP and non-MCP groups, a two-sample t-test using the nonparametric statistical inference function included in the FMRIB Software Library was performed with 5000 permutation sets. All voxels in the brain were corrected using the threshold-free cluster enhancement method with the family-wise error correction.

Statistical analyses were performed using SPSS for Windows Version 25 (IBM Japan, Tokyo, Japan). The Mann–Whitney U test was used for continuous variables, and categorical variables were evaluated using Fisher's exact test. Furthermore, we examined correlations of the MK, FA, and MD values and the subitems of the WISC-IV or DCDQ-J using Spearman's rank correlation coefficient. Comparisons or correlations were thresholded at an uncorrected level of significance due to the exploratory nature of the study and the small sample size. The diagnostic performance for detecting MCP using DKI/DTI was assessed using the receiver operating characteristic method. The MK, FA, and MD cutoff values for MCP were estimated using the area under the receiver operating characteristic curve and were calculated using the maximum point of the Youden index (sensitivity + specificity − 1). For all tests, $p < .05$ was considered significant.

III. Results

1. Patient characteristics

All examinations were conducted at Iwate Medical University Hospital. Seven participants were excluded because they did not tolerate MRI (n = 4), because of poor image quality due to heavy motion artifacts (n = 2), or because they refused to complete the questionnaire (n = 1). The remaining 16 patients (median age 11 years; range 8–14 years; male-to-female ratio 7 : 9; 3 patients with CAE, 10 with BECTS, and 3 with PS) were studied.

Tables 1 and 2 show the clinical characteristics of all patients and group comparisons. The median age of the MCP group (n = 8) was 9 years and 10 months. The MCP group included 4 patients with BECTS, 1 with CAE, and 3 with PS. Three children had histories of other health issues, including one with refractive amblyopia that was corrected with eyeglasses. He did not experience difficulties with activities in daily life or exercise. Of the other two children, one had acquired right hearing loss and one was a preterm (35 weeks gestation) and low-birth weight infant (2100 g). The median age of the non-MCP group (n = 8) was 11 years and 5 months. The non-MCP group included 6 patients with BECTS and 2 with CAE, including one who had incomplete right bundle branch block, one who had mild neonatal jaundice, and one who had allergic

Table 1. Patient characteristics

Participants	Age at Scan	Sex	Dominant hand	Diagnosis	Demographics		
					Age at diagnosis	AED at scan	Previous history
MCP							
1	8 y 1 m	M	L	BECTS	6 y 8 m	No	Febrile seizure
2	9 y 2 m	F	R	CAE	9 y 2 m	No	No
3	9 y 4 m	M	R	BECTS	6 y 10 m	CBZ	Amblyopia
4	9 y 4 m	F	R	PS	7 y 1 m	CBZ	No
5	10 y 4 m	M	R	BECTS	6 y 6 m	ST	Right sensorineural hearing loss
6	11 y 6 m	M	R	BECTS	9 y 2 m	CBZ	No
7	12 y 4 m	M	R	PS	7 y 10 m	No	Febrile seizure
8	12 y 5 m	F	R	PS	5 y 8 m	CBZ	Gestational age 35 weeks, brith weight 2100 grams
non-MCP							
9	9 y 8 m	M	R	BECTS	4 y 4 m	CBZ	No
10	9 y 8 m	F	R	BECTS	9 y 8 m	No	Incomplete right bundle branch block
11	10 y 2 m	F	R	CAE	7 y 5 m	No	Neonatal jaundice
12	11 y 1 m	M	R	BECTS	9 y 6 m	CBZ	Allergic purpura
13	11 y 9 m	F	R	BECTS	3 y 5 m	VPA	No
14	12 y 1 m	F	R	BECTS	10 y 2 m	No	No
15	12 y 6 m	F	R	CAE	10 y 1 m	LTG	No
16	14 y 8 m	F	R	BECTS	7 y 9 m	No	Febrile seizure

y, years; m, months; M, male; F, femle; L, left; R, right.
BECTS, benign childhood epilepsy with centrotemporal spike; CAE, childhood absence epilepsy; PS, Panayiotopoulos syndorome; AED, anti-epileptic drug; CBZ, carbamazepine; LTG, lamotrigine; ST, sulthiame; VPA, valproic acid; DCDQ-J, the Japanese version of the Developmental Coordination Disorder Questionnaire; MCP, motor coordination problems; CDM, control during movement; FM/H, fine motor/handwriting; GC, general coordination; WISC-IV, the Wechsler Intelligence Scale for Children-Fourth Edition; FSIQ, full scale intelligence quotient; VCI, verbal comprehension index; PRI, perceptual reasoning index; WMI, working memory index; PSI, processing speed index.

purpura. Seven patients had not received any antiepileptic drugs, and nine patients had received one antiepileptic drug. None of the patients took other medications such as methylphenidate.

There were no significant differences in any of the clinical background characteristics between the two groups.

2. EEG results

At the time of inclusion in this study, various EEG patterns were observed. Epileptic spikes in the left cerebral hemisphere were classified as "left spikes." The left spikes included left focal spikes, bilateral focal spikes, and generalized spikes. The same was true for "right spikes." Left spikes were observed in two patients in the MCP group and five in the non-MCP group; right spikes were observed in four patients in the MCP group and three in the non-MCP group. No epileptiform discharge was observed in four patients in the MCP group and three in the non-MCP group. There were no differences in the left and right spikes between the MCP and non-MCP groups (Table 2).

DCDQ-J				WISC-IV				
Total score	CDM	FM/H	GC	FSIQ	VCI	PRI	WMI	PSI
52	25	12	15	106	125	101	91	88
55	22	16	17	90	111	85	82	86
29	12	10	7	109	119	118	97	86
47	19	17	11	113	113	111	94	115
32	15	10	7	80	84	98	68	84
54	21	13	20	102	97	102	112	96
32	13	8	11	74	93	74	68	76
40	21	9	10	110	113	106	106	102
72	30	20	22	100	103	102	88	104
56	24	17	15	94	103	78	97	104
59	19	18	22	92	105	80	91	96
69	26	19	24	102	119	102	82	96
65	25	19	21	107	129	80	88	121
68	26	20	22	107	103	109	100	110
58	24	16	18	118	109	111	120	113
62	22	20	20	106	97	106	106	110

3. Neuropsychological assessment results

1) DCDQ-J

Table 1 shows the patients' raw scores. Patient 3 had the lowest total score. He had BECTS with a normal FSIQ and a relatively lower PSI. As described above, he attended regular class and did not have any learning difficulties. The other patients in both groups did not experience difficulties in their daily lives. As shown in Table 2, the median DCDQ-J scores differed significantly between the MCP and non-MCP groups (43.5 vs. 63.5, $p < .001$); similarly, the median CDM (20 vs. 24.5, $p = .01$), FM/H (11 vs. 19, $p < .001$), and GC (11 vs. 21.5, $p = .002$) scores differed significantly.

2) WISC-IV

There were no significant differences in the FSIQ, VCI, PRI, or WMI scores between the two groups, but the PSI was significantly lower in the MCP group ($p = .021$) (Table 2). Significant correlations between the PSI of the WISC-IV and the DCDQ-J total ($r = .564$) and FM/H ($r = .654$) scores were identified. There were no correlations between the other indexes (Table 3).

Table 2. Group comparisons

Measure	MCP (N = 8)	non-MCP (N = 8)	p
Age at scan, median (range)	9 y 10 m (8 y 1 m-12 y 5 m)	11 y 5 m (9 y 8 m-14 y 8 m)	.195
Male	5	2	.315
Dominant hand (right)	8	7	1.000
Family history of convulsions	5	2	.315
Age at diagnosis, median (range)	7 y 0 m (5 y 8 m-9 y 2 m)	8 y 8 m (3 y 5 m-10 y 2 m)	.328
AED at scan	5	4	1.000
Diagnosis to scan (months), median (range)	28.5 (0-81)	31 (0-100)	.645
Last seizure to scan (months), median (range)	27.5 (0-53)	22 (0-100)	1.000
EEG			
Left spikes	2	5	.315
Right spikes	4	2	.608
DCDQ-J, median (range)			
Total score	43.5 (29-55)	63.5 (56-72)	<0.001*
Control during movement	20 (12-25)	24.5 (19-30)	.01*
Fine motor/handwriting	11 (8-17)	19 (16-20)	<0.001*
General coordination	11 (7-20)	21.5 (15-24)	.002*
WISC-IV, median (range)			
Full scale intelligence quotient	104 (74-113)	104 (92-118)	.798
Verbal comprehension index	112 (84-125)	104 (97-129)	1.000
Perceptual reasoning index	101.5 (74-118)	102 (78-111)	.878
Working memory index	92.5 (68-112)	94 (82-120)	.574
Processing speed index	87 (76-115)	107 (96-121)	.021*
J-KIDSCREEN-52 dimensions/self, median (range)			
Physical well-being	47.2 (25.1-73.2)	61.8 (38.5-73.2)	.234
Psychological well-being	53.3 (35.5-68.5)	60.1 (34.1-68.5)	.645
Moods and emotions	44.8 (34.6-70.9)	51.6 (32.5-70.9)	.574
Self-perception	48.8 (33.2-69.8)	46.9 (37.9-69.8)	.798
Autonomy	44.6 (35.6-56.3)	48.4 (42.1-68.8)	.130
Parent relations and home life	42.0 (20.6-65.9)	48.5 (44.1-65.9)	.234
Financial resources	43.1 (23.2-62.9)	45.6 (23.2-62.9)	.959
Social support and peers	41.5 (9.4-71.5)	56.4 (36.8-71.5)	.083
School environment	53.4 (14.0-73.8)	51.3 (36.8-73.8)	.959
Social acceptance (bullying)	47.1 (29.1-58.8)	53.5 (29.1-58.9)	.645
J-KIDSCREEN-52 dimensions/proxy, median (range)			
Physical well-being	39.9 (28.8-52.7)	51.1 (43.7-71.2)	.021*
Psychological well-being	35.8 (30.9-48.9)	50.5 (32.7-69.9)	.015*
Moods and emotions	40.8 (33.0-58.0)	45.2 (29.9-58.0)	.574
Self-perception	41.4 (35.8-61.4)	42.3 (31.1-56.2)	.878
Autonomy	40.5 (33.6-53.9)	40.5 (33.6-67.9)	.798
Parent relations and home life	39.2 (27.2-49.4)	46.9 (34.2-55.1)	.038*
Financial resources	44.7 (29.1-59.3)	50.4 (24.0-65.0)	.382
Social support and peers	42.5 (25.9-57.9)	55.5 (32.7-73.1)	.028*
School environment	41.3 (34.0-52.1)	52.1 (29.4-57.0)	.065
Social acceptance (bullying)	42.1 (30.9-58.8)	54.7 (21.5-58.8)	.234

*$p < .05$.

y, years; m, months; AED, anti-epileptic drug; EEG, electroencephalogram; DCDQ-J, the Japanese version of the Developmental Coordination Disorder Questionnaire; MCP, motor coordination problems; WISC-IV, the Wechsler Intelligence Scale for Children-Fourth Edition; J-KIDSCREEN-52, the Japanese version of the KIDSCREEN-52.

Table 3. Relationship between WISC-IV and DCDQ-J scores in all studied patients

	Total score		CDM		FM/H		GC	
	r	p	r	p	r	p	r	p
Full scale intelligence quotient	.032	.905	.151	.577	.110	.686	−.059	.829
Verbal comprehension index	.081	.765	.262	.327	.041	.880	.059	.827
Perceptual reasoning index	−.038	.888	.006	.983	.102	.707	−.094	.730
Working memory index	.053	.845	.058	.831	.100	.714	.030	.913
Processing speed index	.564	.023 *	.490	.054	.654	.006 *	.401	.124

Spearman's rank correlation coefficient. P values are uncorrected for multiple comparisons. *p < .05.
DCDQ-J, the Japanese version of the Developmental Coordination Disorder Questionnaire; CDM, control during movement; FM/H, fine motor and handwriting; GC, general coordination; WISC-IV; the Wechsler Intelligence Scale for Children-Fourth Edition.

Table 4. Relationship between the DCDQ-J and KIDSCREEN-52 scores in all patients

	Total score		CDM		FM/H		GC	
	r	p	r	p	r	p	r	p
J-KIDSCREEN-52 dimensions/self								
Physical well-being	.300	.259	.274	.305	.138	.610	.233	.385
Psychological well-being	.222	.408	.400	.124	.155	.568	.106	.696
Moods and emotions	.197	.463	.315	.235	.190	.482	.052	.848
Self-perception	.306	.249	.379	.147	.269	.313	.288	.280
Autonomy	.353	.180	.257	.337	.219	.415	.256	.339
Parent relations and home life	.326	.217	.238	.375	.426	.100	.151	.577
Financial resources	.016	.952	.098	.717	.167	.536	−.083	.760
Social support and peers	.455	.077	.281	.292	.451	.079	.330	.212
School environment	.130	.632	.153	.571	.147	.588	.010	.970
Social acceptance (bullying)	.037	.892	.002	.993	.121	.654	−.086	.752
J-KIDSCREEN-52 dimensions/proxy								
Physical well-being	.630	.009 *	.658	.006 *	.583	.018 *	.502	.048 *
Psychological well-being	.752	.001 *	.597	.015 *	.741	.001 *	.728	.001 *
Moods and emotions	.450	.080	.414	.110	.480	.060	.461	.072
Self-perception	.205	.445	.248	.354	.124	.646	.277	.298
Autonomy	.213	.429	.118	.663	.171	.526	.164	.544
Parent relations and home life	.687	.003 *	.559	.024 *	.731	.001 *	.661	.005 *
Financial resources	.329	.213	.398	.127	.391	.134	.264	.323
Social support and peers	.641	.008 *	.386	.140	.598	.014 *	.575	.020 *
School environment	.481	.059	.268	.316	.540	.031 *	.505	.046 *
Social acceptance (bullying)	.397	.128	.352	.182	.444	.085	.384	.142

Spearman's rank correlation coefficient. P values are uncorrected for multiple comparisons. *p < .05.
DCDQ-J, the Japanese version of the Developmental Coordination Disorder Questionnaire; CDM, control during movement; FM/H, fine motor and handwriting; GC, general coordination; J-KIDSCREEN-52, the Japanese version of the KIDSCREEN-52.

Table 5. Diffusion kurtosis and tensor metrics of the participants in the MCP and non-MCP groups

		MK		
		MCP (n = 8)	non-MCP (n = 8)	p
Corticospinal tract	Left	1.015 (0.855-1.133)	1.033 (0.909-1.131)	.959
	Right	1.048 (0.822-1.144)	1.051 (0.974-1.140)	1.000
Cingulate gyrus	Left	0.790 (0.684-0.879)	0.774 (0.657-0.831)	.798
	Right	0.728 (0.652-0.828)	0.765 (0.668-0.787)	.328
Precentral gyrus gray matter	Left	0.565 (0.422-0.589)	0.590 (0.543-0.634)	.161
	Right	0.571 (0.476-0.586)	0.598 (0.550-0.649)	.021*
Precentral gyrus white matter	Left	0.779 (0.615-0.830)	0.836 (0.743-0.854)	.105
	Right	0.781 (0.629-0.807)	0.849 (0.724-0.878)	.105
Postcentral gyrus gray matter	Left	0.568 (0.444-0.619)	0.599 (0.562-0.625)	.195
	Right	0.587 (0.490-0.599)	0.602 (0.559-0.631)	.161
Postcentral gyrus white matter	Left	0.772 (0.590-0.801)	0.787 (0.717-0.838)	.505
	Right	0.763 (0.619-0.796)	0.785 (0.701-0.816)	.505
Middle frontal gyrus	Left	0.533 (0.406-0.579)	0.577 (0.523-0.606)	.065
	Right	0.559 (0.497-0.578)	0.580 (0.498-0.614)	.130
Supplementary motor area	Left	0.544 (0.463-0.564)	0.566 (0.496-0.602)	.083
	Right	0.556 (0.366-0.591)	0.588 (0.530-0.635)	.083
Caudate nucleus	Left	0.562 (0.501-0.652)	0.540 (0.508-0.630)	.645
	Right	0.522 (0.433-0.589)	0.526 (0.503-0.568)	.798
Thalamus	Left	0.808 (0.672-0.911)	0.796 (0.730-0.907)	.959
	Right	0.732 (0.551-0.828)	0.737 (0.708-0.793)	.798
Globus pallidus	Left	0.767 (0.656-0.894)	0.756 (0.703-0.844)	.721
	Right	0.855 (0.762-0.948)	0.799 (0.787-0.966)	.442
Putamen	Left	0.566 (0.430-0.681)	0.566 (0.510-0.652)	.959
	Right	0.643 (0.554-0.756)	0.647 (0.578-0.702)	.959

The Mann-Whitney U test was used to compare the MCP and non-MCP groups. P values are uncorrected for multiple comparisons. *$p < .05$.
Data are presented as the median (range).
MCP, motor coordination problems; MK, mean kurtosis; FA, fractional anisotropy; MD, mean diffusivity.

3) J-KIDSCREEN-52

The self-evaluation results did not differ significantly between groups. Conversely, the children's guardians reported significantly lower scores in the MCP group for Physical Well-being ($p = .021$), Psychological Well-being ($p = .015$), Parent Relations and Home Life ($p = .038$), and Social Support and Peers ($p = .028$) (Table 2).

Similarly, although there were no significant correlations between the DCDQ-J and self-reported J-KIDSCREEN-52 scores, there were statistically significant correlations between the DCDQ-J and parent-reported J-KIDSCREEN-52 scores (Table 4).

4. MRI analysis

The results of the voxel-wise group analysis using TBSS showed no significant differences in the MK, FA, and MD values in the WM tract, including the pyramidal tract, superior longitudinal fasciculus, inferior longitudinal fasciculus, internal capsule, and the corpus callosum, between the MCP and non-MCP groups.

FA			MD		
MCP (n = 8)	non-MCP (n = 8)	p	MCP (n = 8)	non-MCP (n = 8)	p
0.561 (0.497-0.588)	0.580 (0.551-0.598)	.105	0.819 (0.782-0.848)	0.817 (0.775-0.842)	.645
0.577 (0.532-0.601)	0.593 (0.579-0.612)	.130	0.788 (0.753-0.808)	0.785 (0.760-0.807)	.798
0.335 (0.260-0.438)	0.327 (0.264-0.381)	.505	0.835 (0.802-0.878)	0.832 (0.813-0.882)	1.000
0.306 (0.234-0.400)	0.311 (0.290-0.367)	.574	0.825 (0.811-0.866)	0.829 (0.816-0.874)	.645
0.131 (0.125-0.143)	0.136 (0.123-0.142)	.798	1.189 (1.054-1.303)	1.168 (1.038-1.289)	.574
0.139 (0.128-0.153)	0.142 (0.130-0.152)	.328	1.187 (1.036-1.249)	1.132 (1.026-1.222)	.234
0.328 (0.289-0.345)	0.328 (0.314-0.358)	.505	0.821 (0.799-0.855)	0.822 (0.788-0.839)	.721
0.314 (0.292-0.351)	0.339 (0.299-0.351)	.065	0.828 (0.803-0.864)	0.820 (0.788-0.853)	.382
0.119 (0.114-0.144)	0.127 (0.113-0.132)	.574	1.257 (1.084-1.340)	1.201 (1.071-1.351)	.382
0.121 (0.115-0.141)	0.131 (0.121-0.152)	.279	1.236 (1.103-1.309)	1.194 (1.014-1.284)	.328
0.309 (0.270-0.331)	0.316 (0.271-0.352)	.505	0.840 (0.812-0.880)	0.831 (0.785-0.899)	.721
0.312 (0.294-0.325)	0.307 (0.279-0.330)	.328	0.835 (0.819-0.862)	0.839 (0.795-0.879)	.798
0.141 (0.127-0.158)	0.148 (0.142-0.157)	.328	1.115 (1.077-1.237)	1.091 (0.983-1.239)	.195
0.143 (0.124-0.150)	0.143 (0.136-0.153)	.959	1.110 (1.054-1.208)	1.117 (1.019-1.222)	.959
0.149 (0.135-0.176)	0.157 (0.133-0.163)	.328	1.313 (1.189-1.618)	1.247 (1.125-1.444)	.442
0.162 (0.152-0.182)	0.179 (0.157-0.193)	.065	1.209 (1.109-1.413)	1.167 (1.065-1.324)	.382
0.157 (0.123-0.209)	0.160 (0.145-0.170)	.798	0.836 (0.819-0.930)	0.861 (0.830-0.895)	.328
0.124 (0.103-0.189)	0.126 (0.115-0.169)	.721	0.914 (0.866-0.987)	0.906 (0.884-0.950)	.878
0.367 (0.325-0.389)	0.367 (0.363-0.384)	.721	0.803 (0.790-0.830)	0.813 (0.798-0.827)	.442
0.303 (0.283-0.335)	0.324 (0.295-0.337)	.382	0.838 (0.802-0.881)	0.844 (0.826-0.873)	.574
0.247 (0.230-0.253)	0.243 (0.211-0.270)	.382	0.806 (0.790-0.843)	0.830 (0.814-0.849)	.083
0.349 (0.317-0.366)	0.344 (0.301-0.415)	.645	0.836 (0.812-0.881)	0.847 (0.811-0.880)	.645
0.167 (0.137-0.195)	0.171 (0.152-0.196)	.574	0.768 (0.750-0.785)	0.770 (0.762-0.796)	.161
0.187 (0.159-0.213)	0.183 (0.175-0.213)	.645	0.804 (0.788-0.829)	0.809 (0.786-0.832)	.382

The quantitative ROI analysis results are shown in Table 5 and Figure 1. The MK value of the right PrCG was significantly lower in the MCP group [median (range): 0.571 (0.476–0.586)] than in the non-MCP group [0.598 (0.550–0.649)] (p = .021). The FA and MD values did not differ significantly between groups.

The receiver operating characteristic analysis for all patients indicated that the area under the curve for the MK of the right PrCG was 0.844 (95% confidence interval: 0.624–1.000). The cutoff MK value was 0.587 (sensitivity, 100%; specificity, 75%).

5. Correlations between MRI analysis and neuropsychological assessments

The following correlations between the diffusion kurtosis/tensor metrics and the DCDQ-J scores were identified (Table 6): between the FM/H scores of the DCDQ-J and the MK values of the right PrCG GM (r = .504); between the GC scores of the DCDQ-J and the MK values of the right PrCG GM (r = .510); between the GC scores of the DCDQ-J

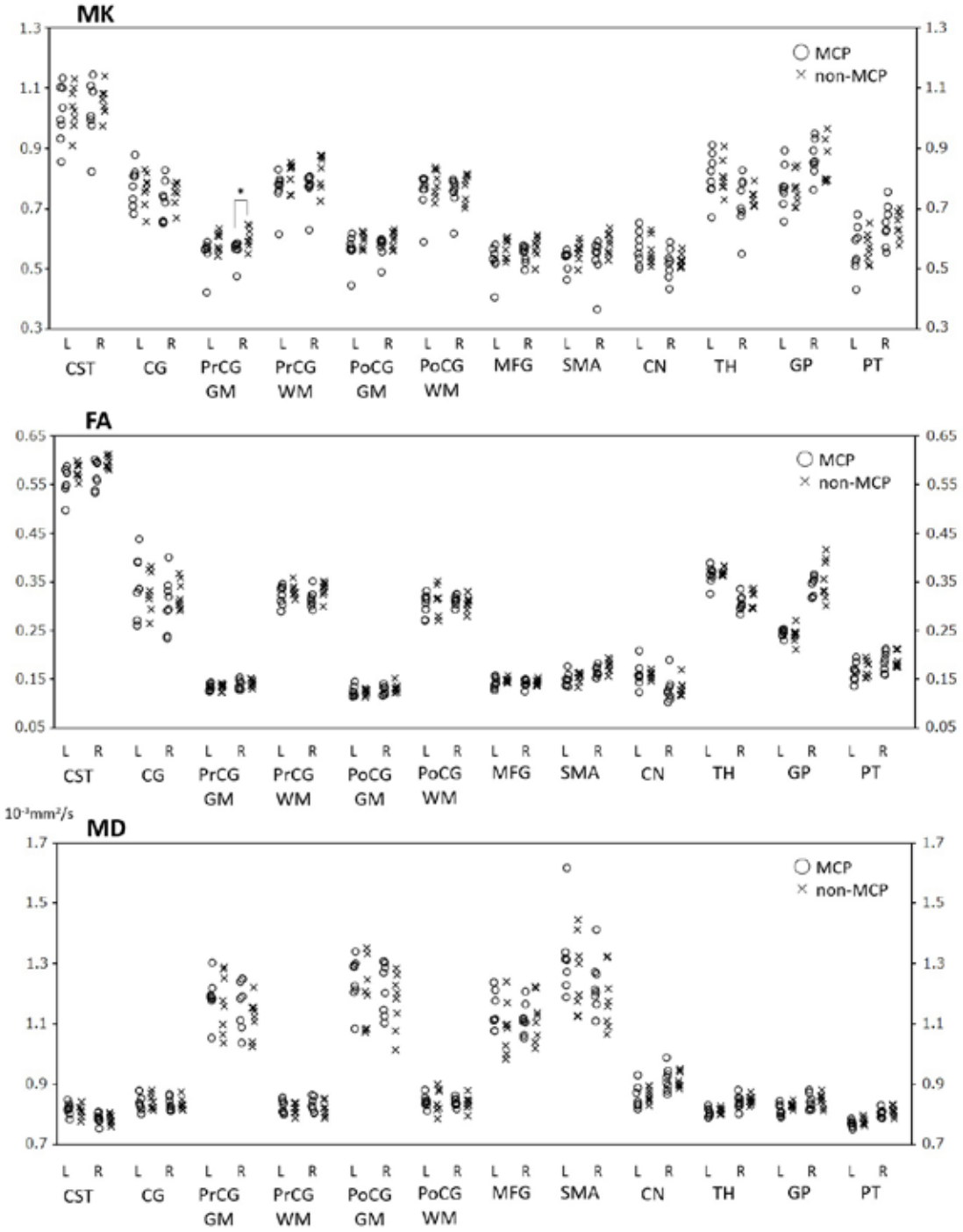

Fig 1. Diffusion kurtosis and tensor metrics of patients in the MCP and non-MCP groups.
The MK values of the right PrCG GM were significantly lower in the MCP group than in the non-MCP group.
MCP, motor coordination problems; MK, mean kurtosis; FA, fractional anisotropy; MD, mean diffusivity; CST, corticospinal tract; CG, cingulate gyrus; PrCG GM, precentral gyrus gray matter; PoCG GM, postcentral gyrus gray matter; PrCG WM, precentral gyrus white matter; PoCG WM, postcentral gyrus white matter; MFG, middle frontal gyrus; SMA, supplementary motor area; CN, caudate nucleus; TH, thalamus; GP, globus pallidus; PT, putamen
* $p < .05$ (Mann–Whitney U test)

and the FA values of the right PrCG WM (r = .641); between the total DCDQ-J scores and the FA values of the right PrCG WM (r = .537); and between the CDM scores of the DCDQ-J and the MD values of the left GP (r = .529).

Table 7 displays the correlations between diffusion kurtosis/tensor metrics and WISC-IV scores. The MK values of the cortical GM displayed significant differences. The greatest correlation was observed between the left PrCG GM and the PSI (r = .701). There were also significant correlations in the GM of the other paracentral lobules: between the left PrCG GM and the FSIQ (r = .622); between the left PrCG GM and the WMI (r = .640); between the right PrCG GM and the WMI (r = .567); between the right PrCG GM and the PSI (r = .624); between the left PoCG GM and the FSIQ (r = .603); between the left PoCG GM and the WMI (r = .613); between the left PoCG GM and the PSI (r = .650); between the right PoCG GM and the FSIQ (r = .538); between the right PoCG GM and the WMI (r = .613); and between the right PoCG GM and the PSI (r = .634).

IV. Discussion

To the best of our knowledge, this is the first study to evaluate diffusional kurtosis abnormalities in the brain microstructure of children with epilepsy with and without MCP. Our major finding was that the MCP group had significantly decreased MK values in the right PrCG. Furthermore, we demonstrated significant correlations across groups between ROI analyses and scores on the DCDQ-J or WISC-IV, particularly for MK values in the cortex of the paracentral lobules. The MK parameter is the average of the diffusion kurtosis along all diffusion directions. The MK tended to decrease with mild histologic changes in demyelination and decreased myelin, axonal, or neuronal density [37, 38], whereas FA and MD are thought to reflect more evident destruction of tissue architecture, such as axonal degeneration, demyelination, neuronal loss, gliosis, and vasogenic edema [39]. In this study, MK performed better than FA and MD in distinguishing among children with epilepsy with MCP and those without MCP. This suggests that mild microstructural changes occur without tissue destruction in children with epilepsy and MCP. These findings suggest that the subtle dysfunction of the sensorimotor system due to micropathological alterations plays an important role in MCP.

The MK values of the right PrCG were positively correlated with the DCDQ-J scores; however, the MK values of the left PrCG did not show significant correlations. Because all participants except one were right-handed, there may be disturbed mechanisms of the transcallosal interhemispheric inhibitory motor control signals from the ipsilateral cortex to the dominant side [40]. Brindley et al. suggested that patients with BECTS have disruption in the cross-hemispheric communication involved in coordination motor control circuits [41]. Although disruption of transcallosal interhemispheric inhibition may be caused by destructive or dysfunctional connectivity [42], our study demonstrated no significant DTI findings on the corpus callosum using TBSS.

We found no significant differences in the DKI/DTI metrics of the WM tracts and the basal ganglia between patients with epilepsy

Table 6. Relationship between diffusion kurtosis/tensor metrics and DCDQ-J scores in all studied patients

	DCDQ-J	MK							
		Total score		CDM		FM/H		GC	
		r	p	r	p	r	p	r	p
Corticospinal tract	Left	−.219	.415	−.400	.124	−.172	.525	−.172	.525
	Right	−.184	.495	−.383	.144	−.198	.462	−.056	.836
Cingulate gyrus	Left	−.188	.485	−.174	.519	−.143	.596	−.180	.504
	Right	.157	.560	−.004	.987	.149	.581	.173	.522
Precentral gyrus gray matter	Left	.227	.399	.133	.624	.231	.390	.226	.399
	Right	.468	.068	.260	.331	.504	.046*	.510	.043*
Precentral gyrus white matter	Left	.196	.468	−.025	.926	.240	.371	.207	.442
	Right	.262	.327	.021	.939	.250	.350	.349	.185
Postcentral gyrus gray matter	Left	.240	.371	.137	.612	.247	.356	.235	.381
	Right	.334	.206	.185	.494	.410	.115	.367	.162
Postcentral gyrus white matter	Left	−.053	.845	−.238	.375	−.009	.974	−.003	.991
	Right	.162	.549	.142	.600	.198	.462	.204	.448
Middle frontal gyrus	Left	.364	.166	.366	.163	.357	.175	.277	.300
	Right	.262	.327	.214	.426	.322	.223	.237	.377
Supplementary motor area	Left	.347	.187	.179	.508	.423	.103	.340	.197
	Right	.293	.271	.179	.508	.274	.305	.302	.256
Caudate nucleus	Left	−.199	.461	−.152	.574	−.244	.362	−.115	.670
	Right	−.049	.858	−.164	.544	−.072	.790	.068	.802
Thalamus	Left	−.113	.676	−.297	.264	−.092	.735	−.004	.987
	Right	−.007	.978	−.192	.476	−.059	.828	.053	.845
Globus pallidus	Left	.043	.875	.006	.983	−.028	.918	.089	.744
	Right	−.308	.247	−.380	.147	−.170	.529	−.322	.223
Putamen	Left	.019	.944	−.115	.671	.022	.935	.074	.785
	Right	.060	.824	−.069	.798	.064	.815	.121	.655

Spearman's rank correlation coefficient. P values are uncorrected for multiple comparisons. *$p < .05$.
MK, mean kurtosis; FA, fractional anisotropy; MD, mean diffusivity; DCDQ-J, the Japanese version of the Developmental Coordination Disorder Questionnaire; CDM, control during movement; FM/H, fine motor and handwriting; GC, general coordination.

with and without MCP. Although previous DTI studies in children with DCD compared with children showing typical development have reported FA reductions in a variety of WM tracts, including the pyramidal tract, superior longitudinal fasciculus, inferior longitudinal fasciculus, and the corpus callosum, there are considerable inconsistencies in those tracts. Furthermore, previous neuroimaging studies have revealed that differences in several brain areas, particularly the basal ganglia and cerebellum, are linked with DCD compared with typically developing children. However, no two studies observed the same differences [43]. Hence, we consider the microstructural lesion of the right PrCG as the principal cause of MCP in children with epilepsy. Brain structure abnormalities may predate the time of diagnosis [44]; therefore, we were unable to clarify whether the microstructural changes in the bilateral paracentral lobules were innate or acquired.

FA								MD							
Total score		CDM		FM/H		GC		Total score		CDM		FM/H		GC	
r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
.234	.383	−.061	.824	.068	.802	.365	.164	.037	.892	.182	.501	.178	.511	.077	.777
.155	.568	−.226	.400	.183	.496	.250	.350	.009	.974	.114	.675	.152	.573	-.003	.991
−.215	.424	−.220	.413	−.160	.554	−.212	.432	.090	.741	.213	.429	.068	.802	.101	.711
.149	.583	.027	.922	.175	.518	.143	.596	.222	.408	.223	.406	.240	.371	.274	.305
−.162	.549	−.201	.456	−.059	.828	−.256	.339	−.068	.803	.025	.926	−.146	.588	−.003	.991
.057	.833	−.208	.439	.178	.511	.072	.790	−.218	.418	−.077	.777	−.417	.108	−.107	.695
.097	.720	−.183	.497	.077	.777	.149	.581	−.004	.987	.264	.322	−.059	.828	−.055	.840
.537	.032*	.238	.375	.496	.051	.641	.008*	−.150	.579	.165	.540	−.180	.504	−.204	.448
−.013	.961	.019	.944	.138	.611	−.135	.619	−.121	.656	−.037	.892	−.185	.493	−.007	.978
.081	.766	−.080	.769	.213	.428	−.044	.870	−.178	.509	−.025	.926	−.274	.305	−.118	.662
.037	.892	−.186	.490	−.096	.723	.200	.458	.107	.692	.269	.314	.183	.496	.053	.845
−.210	.434	−.077	.777	−.256	.339	−.143	.596	−.069	.799	−.072	.790	.104	.703	−.016	.952
.110	.684	.001	.996	.207	.442	.036	.896	−.213	.427	−.037	.892	−.325	.219	−.107	.695
−.155	.568	−.047	.862	.041	.879	−.243	.365	.247	.356	.355	.178	.021	.939	.342	.195
.022	.935	−.071	.794	.192	.476	−.114	.674	.026	.922	.127	.639	−.083	.760	.111	.682
.134	.621	−.043	.875	.228	.396	.007	.978	.019	.944	.137	.612	−.111	.682	.161	.551
.035	.897	.121	.655	.041	.879	.043	.875	.272	.308	.310	.242	.213	.428	.203	.452
.079	.770	.108	.691	.172	.525	.034	.900	.181	.502	.298	.262	.061	.823	.186	.489
−.074	.787	−.034	.901	−.040	.883	−.115	.670	.347	.187	.414	.111	.265	.322	.380	.146
.119	.660	−.032	.905	.266	.319	.038	.888	.272	.308	.269	.314	.166	.540	.352	.181
−.293	.271	−.335	.204	−.093	.731	−.398	.127	.493	.052	.529	.035*	.494	.052	.401	.124
.184	.495	−.092	.736	.275	.302	.318	.230	.293	.271	.459	.073	.107	.695	.197	.465
.312	.239	.278	.298	.284	.286	.324	.221	.313	.237	.371	.157	.280	.294	.241	.368
.252	.347	.236	.378	.189	.482	.272	.308	.386	.140	.375	.152	.324	.221	.374	.153

This study investigated 16 patients with childhood epilepsies, half of whom had MCP, who had normal intelligence and no previous diagnoses of neurodevelopmental disorders. Similarly, a previous report mentioned that no participants had recognized DCD before participating in that study [45]. We used the DCDQ-J, which has been developed and adapted to Japanese culture, to evaluate MCP [12]. In this study, a higher proportion of children with epilepsy had MCP than in the general Japanese population (approximately 20%) [14]. In the United Kingdom, Kirby et al. indicated that 40% of patients with BECTS had suspected DCD according to the DCDQ' 07, and nearly half (47.6%) of patients with BECTS had some motor functioning difficulties based on assessment with the Movement Assessment Battery for children-2 [10].

MCP was not defined as DCD because the DCDQ is only used for screening and not for diagnosing DCD. Nevertheless, the MCP

Table 7. Relationship between diffusion kurtosis/tensor metrics and WISC-IV scores in all patients

		MK									
	WISC-IV	FSIQ		VCI		PRI		WMI		PSI	
		r	p	r	p	r	p	r	p	r	p
Corticospinal tract	Left	.108	.692	−.068	.802	−.074	.786	.318	.231	.041	.879
	Right	.027	.922	−.081	.765	−.071	.794	.295	.267	−.112	.679
Cingulate gyrus	Left	.214	.427	−.353	.179	.102	.707	.570	.021*	.266	.319
	Right	.116	.668	−.337	.202	−.028	.918	.384	.142	.378	.148
Precentral gyrus gray matter	Left	.622	.010*	.328	.215	.207	.442	.640	.008*	.701	.003*
	Right	.357	.175	.112	.679	.092	.736	.567	.022*	.624	.010*
Precentral gyrus white matter	Left	.323	.223	.033	.905	.062	.819	.465	.069	.448	.082
	Right	.264	.323	.001	.996	.108	.691	.561	.024*	.331	.210
Postcentral gyrus gray matter	Left	.603	.013*	.359	.172	.229	.393	.613	.012*	.650	.006*
	Right	.538	.032*	.219	.416	.316	.233	.613	.012*	.634	.008*
Postcentral gyrus white matter	Left	.572	.021*	.390	.135	.219	.416	.434	.093	.420	.105
	Right	.591	.016*	.259	.333	.443	.085	.625	.010*	.389	.137
Middle frontal gyrus	Left	.682	.004*	.470	.066	.303	.254	.480	.060	.689	.003*
	Right	.613	.012*	.340	.198	.371	.157	.601	.014*	.535	.033*
Supplementary motor area	Left	.491	.054	.188	.486	.203	.452	.569	.022*	.698	.003*
	Right	.659	.006*	.350	.183	.334	.206	.697	.003*	.612	.012*
Caudate nucleus	Left	−.268	.315	−.312	.240	−.234	.384	.202	.452	−.347	.187
	Right	.196	.467	−.114	.675	.041	.879	.412	.113	.101	.711
Thalamus	Left	−.221	.411	−.336	.204	−.197	.466	.244	.363	−.173	.522
	Right	−.037	.892	−.245	.360	−.064	.815	.266	.320	−.009	.974
Globus pallidus	Left	−.187	.488	−.313	.237	.006	.983	.087	.748	−.157	.562
	Right	−.150	.578	−.585	.017*	.030	.913	.254	.342	−.135	.619
Putamen	Left	−.140	.605	−.457	.075	.038	.888	.276	.300	−.087	.748
	Right	−.093	.732	−.466	.069	.077	.777	.288	.279	−.015	.957

Spearman's rank correlation coefficient. P values are uncorrected for multiple comparisons. *$p < .05$.
MK, mean kurtosis; FA, fractional anisotropy; MD, mean diffusivity; WISC-IV, the Wechsler Intelligence Scale for Children-Fourth Edition; FSIQ, full scale intelligence quotient; VCI, verbal comprehension index; PRI, perceptual reasoning index; WMI, working memory index; PSI, processing speed index.

group had significantly lower PSI scores than the non-MCP group, and the total and FM/H scores of the DCDQ were highly correlated with the PSI. However, this result may reflect the fine motor problems of the MCP group and should be interpreted with caution.

Children with epilepsy and MCP have a slower processing speed and may have academic problems, such as difficulties with handwriting and achieving study skill tasks; these problems may create difficulties with work in the future. Austin et al. indicated that behavior problems at the seizure onset of children with epilepsy are related to their processing speed [46], and baseline psychomotor slowing was predictive of behavior problems 3 years later. In previous studies, patients with BECTS had lower PSI scores than controls. Vannet et al. reported that psychomotor and fine motor speed are affected in BECTS; they also identified significant negative correlations between the frequencies of left-sided Rolandic spikes and fine motor skills of the right hand [47]. Although our study did not demonstrate any correlations between the interictal epileptiform discharges and cognitive functions, there were significant correlations between the MK values of the bilateral

FA										MD									
FSIQ		VCI		PRI		WMI		PSI		FSIQ		VCI		PRI		WMI		PSI	
r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
.069	.799	.152	.573	-.118	.663	.074	.786	.123	.651	-.044	.871	-.078	.773	.123	.651	.120	.659	-.015	.957
-.100	.712	-.309	.244	.098	.719	.160	.555	-.050	.853	-.066	.807	.109	.687	-.022	.935	-.030	.914	.034	.901
.227	.398	-.415	.110	.302	.256	.258	.334	.232	.387	-.108	.692	.489	.054	-.136	.616	-.225	.403	-.225	.403
.093	.732	-.519	.039*	.157	.562	.250	.351	.386	.140	-.007	.978	.652	.006*	-.129	.635	-.145	.593	-.050	.853
.382	.145	-.127	.639	.132	.627	.487	.055	.482	.059	-.136	.617	-.203	.452	.124	.647	-.024	.931	-.420	.105
-.329	.214	-.612	.012*	-.216	.422	.000	1.000	.075	.781	.077	.778	.183	.497	.101	.711	-.035	.896	-.373	.155
-.385	.141	-.427	.099	-.294	.269	-.315	.235	-.095	.727	.118	.664	.386	.140	.121	.655	.028	.918	-.102	.707
.021	.940	-.239	.372	.044	.870	.188	.487	.328	.215	.140	.605	.464	.070	.145	.592	-.058	.832	-.176	.515
.482	.059	.217	.419	.149	.581	.383	.144	.559	.024*	-.118	.664	-.183	.497	.167	.536	-.078	.773	-.442	.087
.130	.632	-.222	.409	.016	.952	.238	.375	.452	.079	.139	.609	.191	.479	.254	.342	-.034	.901	-.344	.191
-.040	.884	.108	.691	-.251	.348	-.072	.790	.012	.965	.081	.765	.092	.736	.378	.148	-.006	.983	-.130	.631
.184	.495	-.016	.952	.019	.944	.115	.671	-.004	.987	.304	.253	.384	.142	.466	.069	.183	.497	-.052	.849
-.019	.944	-.455	.076	.031	.909	-.093	.732	.302	.256	.069	.799	.069	.798	.319	.228	.016	.952	-.455	.076
.233	.385	-.306	.249	.195	.469	.356	.176	.276	.300	.000	1.000	-.003	.991	.182	.500	-.087	.748	-.173	.522
.610	.012*	.225	.403	.272	.308	.504	.047*	.730	.001*	-.276	.302	-.108	.691	.049	.858	-.310	.242	-.497	.050
.486	.056	.056	.836	.211	.432	.609	.012*	.630	.009*	-.370	.158	-.137	.612	-.081	.765	-.425	.100	-.554	.026*
.296	.265	.028	.918	.188	.486	.207	.442	.288	.279	.155	.567	.149	.581	.101	.711	.341	.196	.126	.643
.249	.352	-.179	.507	.201	.455	.186	.490	.384	.142	-.178	.509	-.010	.970	-.046	.866	-.058	.832	-.273	.305
.333	.207	-.266	.319	.557	.025*	.578	.019*	.035	.896	-.018	.948	.334	.206	-.124	.647	-.077	.777	.078	.773
.339	.199	-.234	.384	.435	.093	.349	.186	.355	.178	-.099	.716	.285	.284	-.188	.486	-.040	.883	-.077	.777
-.052	.850	-.169	.533	.077	.777	-.335	.204	-.115	.671	.162	.549	.511	.043*	.053	.845	.056	.836	.210	.435
-.090	.741	-.375	.152	.160	.555	.162	.548	-.015	.957	-.254	.343	.396	.129	-.529	.035*	-.337	.202	.010	.970
.329	.214	-.043	.875	.458	.074	.353	.180	.279	.295	-.255	.341	.114	.675	-.336	.204	-.180	.504	-.016	.952
.284	.286	.001	.996	.324	.221	.216	.422	.239	.372	-.361	.169	-.024	.931	-.420	.105	-.040	.883	.013	.961

paracentral lobules and the FSIQ, WMI, and PSI scores.

We recommend applying the DCDQ for early and valid consultation for families because it is a simple and suitable tool for children with epilepsy. This report showed that children with epilepsy and MCP had lower parent-reported HRQOL. Children with epilepsy have a lower HRQOL when rated by a parent than when rated by themselves because of parental stress and other factors [48]. Although it remains controversial whether a proxy report is more accurate than a self-report, behavior problems of children as indicated by their parents have neuroanatomical correlations in the brains of those children [49]. To evaluate the HRQOL of children with epilepsy, the DCDQ, an easy screening tool, can be routinely applied.

This study has several limitations. First, a previous study reported that some environmental factors during pregnancy, including maternal alcohol intake and smoking during the first trimester of pregnancy, the mothers' education level, and the annual household income, are related to MCP in the child [30]; however, we did not investigate those factors in this study. Second, although the DCDQ is an internationally accepted parent-

reported questionnaire that can identify children at risk of DCD, such children must be evaluated by an occupational therapist to confirm the diagnosis of DCD; this was not performed in this study. Furthermore, we did not consider the influence of antiepileptic drugs. Third, although the influence of motor coordination on processing speed may be associated with both cortical function and the relationships between the cerebellum and brainstem [42], we did not examine these associations. Fourth, this study was conducted in 1 day. The MRI was performed after the psychological examination. Thus, the DKI results may have been influenced by patient fatigue from the preceding psychological assessment. Finally, although this study included the minimum number of cases necessary for a statistical examination, the sample size was small, and further prospective studies are necessary.

V. Conclusion

Quantitative DKI analyses can detect microstructural changes in the right PrCG in childhood epilepsy with MCP. In particular, MK values can readily differentiate childhood epilepsy with MCP from that without MCP, suggesting this as a promising method for diagnosis of patients with MCP.

Acknowledgements

This study was supported by a Grant-in-Aid for Strategic Medical Science Research (S1491001) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

The authors would like to thank Chihiro Kubo and Shiori Takeishi from the Clinical Psychology Room, School of Medicine, Iwate Medical University, for the neuropsychological assessments.

Conflict of interest: The authors have no conflict of interest to declare.

References

1) **Scheffer IE, Berkovic S, Capovilla G, et al.**: ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia **58**, 512–521, 2017.
2) **Guerrini R** and **Pellacani S**: Benign childhood focal epilepsies. Epilepsia **53** (Suppl. 4), 9–18, 2012.
3) **Caplan R, Siddarth P, Stahl L, et al.**: Childhood absence epilepsy: behavioral, cognitive, and linguistic comorbidities. Epilepsia **49**, 1838–1846, 2008.
4) **Kanemura H, Sano F, Ohyama T, et al.**: Sequential prefrontal lobe volume changes and cognitive dysfunctions in children with Panayiotopoulos syndrome presenting with status epilepticus. Epilepsy Res **112**, 122–129, 2015.
5) **Vannest J, Tenney JR, Gelineau-Morel R, et al.**: Cognitive and behavioral outcomes in benign childhood epilepsy with centrotemporal spikes. Epilepsy Behav **45**, 85–91, 2015.
6) **Reilly C, Atkinson P, Das KB, et al.**: Features of developmental coordination disorder in active childhood epilepsy: a population-based study. Dev Med Child Neurol **57**, 829–834, 2015.
7) American Psychiatric Association: DSM-5 Task Force. Diagnostic and statistical manual of mental disorders, 5th ed. American Psychiatric Publishing, Arlington, VA, 2013.
8) **Zwicker JG, Harris SR** and **Klassen AF**: Quality of life domains affected in children with developmental coordination disorder: a systematic review. Child Care Health Dev **39**, 562–580, 2013.
9) **Caçola P**: Physical and mental health of children with developmental coordination disorder. Front Public Health **4**, 224, 2016.
10) **Kirby A, Williams N, Koelewijn L, et al.**: Benign childhood epilepsy with centrotemporal spikes (BECTS) and developmental coordination disorder. Epilepsy Behav **72**, 122–126, 2017.

11) **Reilly C, Atkinson P, Das KB, et al.**: Factors associated with quality of life in active childhood epilepsy: a population-based study. Eur J Paediatr Neurol **19**, 308–313, 2015.
12) **Nakai A, Miyachi T, Okada R, et al.**: Evaluation of the Japanese version of the developmental coordination disorder questionnaire as a screening tool for clumsiness of Japanese children. Res Dev Disabil **32**, 1615–1622, 2011.
13) **Wilson BN, Crawford SG, Green D, et al.**: Psychometric properties of the revised developmental coordination disorder questionnaire. Phys Occup Ther Pediatr **29**, 182–202, 2009.
14) **Suyama S, Yagyu K, Araki A, et al.**: Risk factors for motor coordination problems in preschool-age children. Pediatr Int **62**, 1177–1183, 2020.
15) **Ostrowski LM, Song DY, Thorn EL, et al.**: Dysmature superficial white matter microstructure in developmental focal epilepsy. Brain Commun **1**, fcz002, 2019.
16) **Ciumas C, Saignavongs M, Ilski F, et al.**: White matter development in children with benign childhood epilepsy with centro-temporal spikes. Brain **137**, 1095–1106, 2014.
17) **Yang T, Guo Z, Luo C, et al.**: White matter impairment in the basal ganglia-thalamocortical circuit of drug naïve childhood absence epilepsy. Epilepsy Res **99**, 267–273, 2012.
18) **Liang JS, Lee SP, Pulli B, et al.**: Microstructural changes in absence seizure children: a diffusion tensor magnetic resonance imaging study. Pediatr Neonatol **57**, 318–325, 2016.
19) **Austin JK, Harezlak J, Dunn DW, et al.**: Behavior problems in children before first recognized seizures. Pediatrics **107**, 115–122, 2001.
20) **Overvliet GM, Aldenkamp AP, Klinkenberg S, et al.**: Impaired language performance as a precursor or consequence of Rolandic epilepsy? J Neurol Sci **304**, 71–74, 2011.
21) **Basser PJ, Mattiello J** and **LeBihan D**: MR diffusion tensor spectroscopy and imaging. Biophys J **66**, 259–267, 1994.
22) **Jensen JH, Helpern JA, Ramani A, et al.**: Diffusional kurtosis imaging: the quantification of non-Gaussian water diffusion by means of magnetic resonance imaging. Magn Reson Med **53**, 1432–1440, 2005.
23) **Ito K, Kudo M, Sasaki M, et al.**: Detection of changes in the periaqueductal gray matter of patients with episodic migraine using quantitative diffusion kurtosis imaging: preliminary findings. Neuroradiology **58**, 115–120, 2016.
24) **Ito K, Ohtsuka C, Yoshioka K, et al.**: Differential diagnosis of parkinsonism by a combined use of diffusion kurtosis imaging and quantitative susceptibility mapping. Neuroradiology **59**, 759–769, 2017.
25) **Ito K, Ohtsuka C, Yoshioka K, et al.**: Differentiation between multiple system atrophy and other spinocerebellar degenerations using diffusion kurtosis imaging. Acad Radiol **26**, e333–e339, 2019.
26) **Sato T, Endo K, Kakisaka K, et al.**: Decreased mean kurtosis in the putamen is a diagnostic feature of minimal hepatic encephalopathy in patients with cirrhosis. Intern Med **58**, 1217–1224, 2019.
27) **Chiba T, Ito K, Mori F, et al.**: Detection of microstructural white matter alterations in functional gastrointestinal disorders assessed by diffusion kurtosis imaging. JGH Open **4**, 958–963, 2020.
28) **Sasaki Y, Ito K, Fukumoto K, et al.**: Cerebral diffusion kurtosis imaging to assess the pathophysiology of postpartum depression. Sci Rep **10**, 15391, 2020.
29) **Liu G, Lyu G, Yang N, et al.**: Abnormalities of diffusional kurtosis imaging and regional homogeneity in idiopathic generalized epilepsy with generalized tonic-clonic seizures. Exp Ther Med **17**, 603–612, 2019.
30) **Ravens-Sieberer U, Gosch A, Rajamil L, et al.**: KIDSCREEN-52 quality-of-life measure for children and adolescents. Expert Rev Pharmacoecon Outcomes Res **5**, 353–364, 2005.
31) **Nezu S, Iwasaka H, Saeki K, et al.**: Reliability and validity of the Japanese version of the KIDSCREEN-52 health-related quality of life questionnaire for children/adolescents and parents/proxies. Environ Health Prev Med **20**, 44–52, 2015.
32) **Furuichi Y, Sakakibara T, Nezu S, et al.**: Analysis of factors related to low health-related quality of life in children with epilepsy using a self-assessed Japanese version of the KIDSCREEN-52. Brain Dev **43**, 78–88, 2012.
33) **Yokosawa S, Sasaki M, Bito Y, et al.**: Optimization of scan parameters to reduce acquisition time for diffusion kurtosis imaging at 1.5T. Magn Reson Med Sci **15**, 41–48, 2016.

34) **Smith SM, Jenkinson M, Johansen-Berg H, et al.**: Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage **31**, 1487–1505, 2006.
35) FMRIB analysis group: FMRIB Software Library v6.0, Last updated September 2020. Available at: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki. Accessed January 20, 2021.
36) **Lim IAL, Faria AV, Li X, et al.**: Human brain atlas for automated region of interest selection in quantitative susceptibility mapping: application to determine iron content in deep gray matter structures. Neuroimage **82**, 449–469, 2013.
37) **Gugliemetti C, Veraart J, Roelant E, et al.**: Diffusion kurtosis imaging probes cortical alterations and white matter pathology following cuprizone induced demyelination and spontaneous remyelination. Neuroimage **125**, 363–377, 2016.
38) **Steven AJ, Zhuo J** and **Melhem ER**: Diffusion kurtosis imaging: an emerging technique for evaluating the microstructural environment of the brain. AJR Am J Roentgenol **202**, W26–W33, 2014.
39) **Assaf Y** and **Pasternak O**: Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. J Mol Neurosci **34**, 51–61, 2008.
40) **Beaulé V, Tremblay S** and **Théoret H**: Interhemispheric control of unilateral movement. Neural Plast **2012**, 627816, 2012.
41) **Brindley LM, Koelewijn L, Kirby A, et al.**: Ipsilateral cortical motor desynchronisation is reduced in benign epilepsy with centro-temporal spikes. Clin Neurophysiol **127**, 1147–1156, 2016.
42) **Wahl M, Lauterbach-Soon B, Hattingen E, et al.**: Human motor corpus callosum: topography, somatotopy, and link between microstructure and function. J Neurosci **27**, 12132–12138, 2007.
43) **Biotteau M, Chaix Y, Blais M, et al.**: Neural Signature of DCD: a critical review of MRI neuroimaging studies. Front Neurol **7**, 227, 2016.
44) **Hermann BP, Jones JE, Jackson DC, et al.**: Starting at the beginning: the neuropsychological status of children with new onset epilepsies. Epileptic Disord **14**, 12–21, 2012.
45) **Reilly C, Atkinson P, Das KB, et al.**: Neurobehavioral comorbidities in children with active epilepsy: a population-based study. Pediatrics **133**, e1586–e1593, 2014.
46) **Austin JK, Perkins SM, Johnson CS, et al.**: Behavior problems in children at time of first recognized seizure and changes over the following three years. Epilepsy Behav **21**, 373–381, 2011.
47) **Vannest J, Tenney JR, Altaye M, et al.**: Impact of frequency and lateralization of interictal discharges on neuropsychological and fine motor status in children with benign epilepsy with centrotemporal spikes. Epilepsia **57**, e161–e167, 2016.
48) **Berg AT, Altalib HH** and **Devinsky O**: Psychiatric and behavioral comorbidities in epilepsy: a critical reappraisal. Epilepsia **58**, 1123–1130, 2017.
49) **Dabbs K, Jones JE, Jackson DC, et al.**: Patterns of cortical and child behavior checklist in childhood epilepsy. Epilepsy Behav **29**, 198–204, 2013.

岩手医誌 74 巻，2 号（令和 4 年 6 月）61-81 頁.

協調運動問題を伴う小児てんかんの拡散尖度画像研究

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(Received on December 29, 2021 & Accepted on February 8, 2022)

要旨

協調運動問題（motor coordination problems: MCP）を伴う小児てんかんにおいて，拡散尖度画像（diffusion kurtosis imaging: DKI）が脳の微細構造の変化を明らかにできるか，DKI 所見が神経心理学的評価と相関するか検討した．小児てんかん患者 16 名を対象とし，そのうち 8 名が日本語版発達性協調運動障害質問票（Developmental Coordination Disorder Questionnaire: DCDQ-J）の得点がカットオフ値より低く，MCP 群に分類した．DKI による大脳皮質の関心領域分析を行い MCP 群と非 MCP 群を比較し，右中心前回灰白質の mean kurtosis（MK）値は，MCP 群が非 MCP 群より有意に低かった（p = .021）．DKI 指標と DCDQ-J 得点の間に有意な相関があり，特に中心傍小葉で強かった．全患者の受信者動作特性解析で，右中心前回灰白質の MK 値に対する曲線下面積は 0.844 であり，MCP の有無を区別するカットオフ MK 値は 0.587（感度 100%，特異度 75%）であった．右中心前回灰白質の DKI は小児てんかんに関連する MCP のバイオマーカーとして有用である可能性が示唆された．