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Research Article

Altered Cerebellar Volumes and Intrinsic Cerebellar Network in Juvenile Myoclonic Epilepsy

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Objectives. This study is aimed at investigating the alterations in cerebellar volumes and intrinsic cerebellar network in patients with juvenile myoclonic epilepsy (JME) in comparison with healthy controls. *Methods.* Patients newly diagnosed with JME and healthy controls were enrolled. Three-dimensional T1-weighted imaging was conducted, and no structural lesions were found on brain magnetic resonance imaging. Cerebellar volumes were obtained using the ACAPULCO program, while the intrinsic cerebellar network was evaluated by applying graph theory using the BRAPH program. The nodes were defined as individual cerebellar volumes and edges as partial correlations, controlling for the effects of age and sex. Cerebellar volumes and intrinsic cerebellar networks were compared between the two groups. *Results.* Forty-five patients with JME and 45 healthy controls were enrolled. Compared with the healthy controls, the patients with JME had significantly lower volumes of the right and left cerebellar white matter (3.33 vs. 3.48%, $p = 0.009$; 3.35 vs. 3.49%, $p = 0.009$), corpus medullare (0.99 vs. 1.03%, $p = 0.04$), and left lobule V (0.19 vs. 0.22%, $p = 0.002$). The intrinsic cerebellar networks also showed significant differences between the two groups. The small-worldness index in the patients with JME was significantly lower than that in the healthy controls (0.771 vs. 0.919, $p = 0.04$). *Conclusion.* The cerebellar volumes and intrinsic cerebellar network demonstrated alterations in the patients with JME when compared with those of the healthy controls. Our study results provide evidence that the cerebellum may play a role in the pathogenesis of JME.

1. Introduction

Juvenile myoclonic epilepsy (JME) is one of the most common syndromes of idiopathic generalized epilepsy, with a prevalence ranging from one to three per 10,000 persons [1, 2]. JME presents with myoclonic seizures with or without absence and generalized tonic-clonic seizures [1, 3]. Patients with JME exhibit normal background activity with 3–5.5 Hz generalized spike-wave or polyspike-wave discharges, which are activated during hyperventilation or photic stimulation [1, 3].

Classical neuroimaging findings of patients with JME are normal [1, 3]. However, recent quantitative analysis of brain magnetic resonance imaging (MRI) data has demonstrated significant structural changes in patients with JME. Volumetric studies have shown increased gray matter volumes in the bilateral medial frontal cortex and decreased gray matter volumes in the bilateral thalamus in patients with JME when compared with healthy controls [4]. Another study investigating alterations in cortical morphology in patients with JME has revealed thinning of the cortical thickness in multiple regions, including the postcentral, lingual, orbitofrontal, inferior temporal, and occipital cortices [5]. Additionally, a diffusion tensor imaging study identified widespread white matter microstructural abnormalities in patients with JME in numerous regions, including the corpus callosum, cingulate gyrus, frontal white matter, and anterior parts of the thalamus [6].

Recent development in connectivity and network analysis techniques has led to the establishment of the notion of epilepsy as a network disease, with several studies being conducted on brain network changes in patients with JME. A study using structural covariance network and graph theory reported disrupted topological organization of the global brain network and hub reorganization in patients with newly

diagnosed JME and in a drug-naïve state [7]. Furthermore, the intrinsic thalamic [8] and intrinsic amygdala-hippocampal networks [9] have been suggested to show alterations in patients with JME when compared with healthy controls. All this evidence shows that although patients with JME have traditionally shown normal structural neuroimaging findings, they have a different brain structure than normal controls. These differences may be related to several neuropsychological dysfunctions as well as seizures observed in patients with JME [10, 11].

The cerebellum plays a significant role in motor control. Conventionally, epileptic seizures are believed to be cortical phenomena; however, recent reports have shown seizures originating from cerebellar lesions [12, 13]. Activation of the cerebellum in response to epileptic discharges is also observed in electroencephalography (EEG) recordings during functional MRI [14]. Additionally, an experimental seizure model demonstrated the involvement of the cerebellum in spike-and-wave discharges, suggesting that cerebellar neurons may contribute to spike-and-wave rhythmicity [15]. Furthermore, electrical stimulation of the dentate nucleus in the cerebellum was found to be highly effective in stopping generalized spike-and-wave discharges in animal models [16]. All these findings suggest the involvement of the cerebellum in JME. However, no studies have focused on cerebellar changes in patients with JME.

Here, we aimed to investigate whether patients with JME showed alterations in cerebellar volumes when compared with healthy controls. We further analyzed the intrinsic cerebellar network based on cerebellar volumes using graph theory in patients with JME and healthy controls and compared the intrinsic cerebellar network between the two groups. We hypothesized that the patients with JME would show significant changes in cerebellar volumes and intrinsic cerebellar network when compared with the healthy controls.

2. Materials and Methods

2.1. Participants. This retrospective study was conducted in a single tertiary hospital. The study was approved by the institutional regional board of our institute. We enrolled patients with JME who fulfilled the following criteria: (1) newly diagnosed with JME at our hospital, with clinical and EEG findings compatible with JME [1]; (2) underwent three-dimensional (3D) T1-weighted imaging, which was of good quality for quantitative analysis, at the time of epilepsy diagnosis; (3) demonstrated no structural lesions on brain MRI; and (4) had no medical, neurological, or psychiatric diseases except JMEs.

We also included age- and sex-matched healthy controls. They were already enrolled as a normal group for our previous study [17]. Of this normal control group, those who did not consent to the use of their data in this study were excluded, and the remaining healthy participants with matched age and sex as the patients with JME were included in the control group. They had a normal brain MRI, with no medical, neurological, or psychiatric diseases.

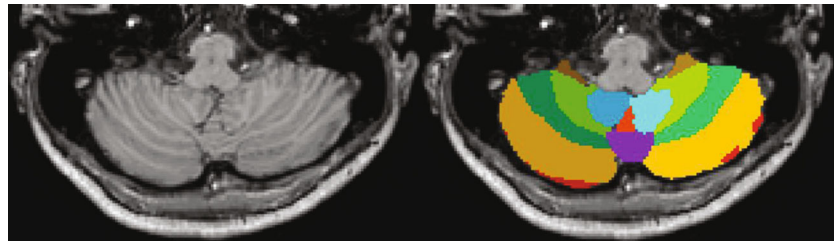
We also obtained the clinical characteristics of the patients with JME, such as age, sex, age at seizure onset, and duration of epilepsy (time from the first seizure onset to MRI).

2.2. MRI Acquisition. Patients with JME and healthy controls were scanned using a 3-Tesla MRI scanner equipped with a 32-channel head coil (Achieva TX, Philips Healthcare). All of the patients with JME underwent MRI scans prior to administration of antiseizure medication (ASM). The MRI routine sequences included 3D fluid-attenuated inversion recovery, oblique coronal T2-weighted fast spin echo, and 3D T1-weighted turbo field echo (T1-TFE) sequences. The 3D T1-TFE sequence was acquired using the following parameters: inversion time = 1300 ms, repetition time/echo time = 8.6/3.96 ms, flip angle = 8°, and isotropic voxel size = 1 mm^3.

2.3. Measurement of Cerebellar Volumes. The cerebellum of each participant was parcellated into subregions using a convolutional neural network-based automatic algorithm (ACAPULCO, version 0.3.0), with 3D T1-TFE as input. This method can produce feature maps that combine local and global information for per-voxel classification during the segmentation task and is known to achieve state-of-the-art accuracy [18]. The 28 cerebellar subregions were as follows: corpus medullare; vermis VI, VII, VIII, IX, and X; and bilateral lobules I-III, IV, V, VI, VIIB, VIIIA, VIIIB, IX, X, crus I, and crus II (Figure 1). The bilateral cerebellar gray and white matter volumes and the intracranial volume (ICV) were acquired using SynthSeg (version 2.0) [19]. Cerebellar volumes were normalized using ICV.

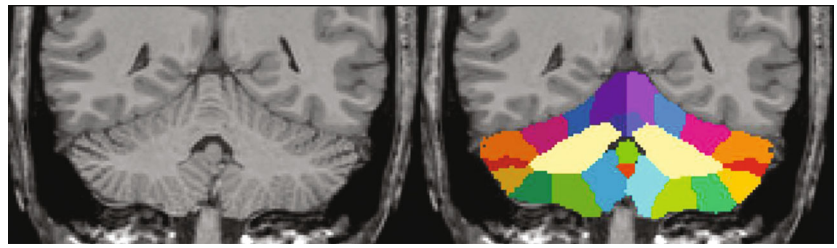
2.4. Evaluation of the Intrinsic Cerebellar Network. Graph theory was used to assess the intrinsic cerebellar network. Graph theory analyzed the network with nodes and edges. In this study, we defined the nodes as individual cerebellar volumes and edges as the partial correlation, controlling for the effects of age and sex. Using the BRAPH program [20], we created a weighted connectivity matrix using nodes and edges in patients with JME and healthy controls. We then extracted the network measures from the connectivity matrix, including the characteristic path length, global efficiency, local efficiency, mean clustering coefficient, and small-worldness index. The measures of the characteristic path length and global efficiency reflected the integration of the brain network, whereas those of the local efficiency and mean clustering coefficient were associated with the segregation of the network [21–23]. The small-worldness index was related to the small-world network. The differences in all these network measures were compared between the two groups [21–23].

2.5. Statistical Analysis. We used Student's *t*-test for comparisons of age and volumes and Fisher's exact test for sex comparison between the two groups. All statistical tests were performed using MedCalc® (MedCalc Software version 20.014; https://www.medcalc.org; 2021). Nonparametric permutation tests with 1000 permutations were used for comparisons of the network measures because the network



Corpus medullare
Left I-III
Right I-III
Left IV
Right IV
Left V
Right V
Vermis VI
Left VI
Right VI
Vermis VII
Left crus I
Left crus II
Left VIIB
Right crus I
Right crus II
Right VIIB
Vermis VIII
Left VIIIA
Left VIIIB
Right VIIIA
Right VIIIB
Vermis IX
Left IX
Right IX
Vermis X
Left X
Right X

(a)



Corpus medullare
Left I-III
Right I-III
Left IV
Right IV
Left V
Right V
Vermis VI
Left VI
Right VI
Vermis VII
Left crus I
Left crus II
Left VIIB
Right crus I
Right crus II
Right VIIB
Vermis VIII
Left VIIIA
Left VIIIB
Right VIIIA
Right VIIIB
Vermis IX
Left IX
Right IX
Vermis X
Left X
Right X

(b)

Figure 1: Example of an overlay of cerebellar parcellation of a healthy control participant in axial (a) and coronal (b) plan.

measures could be obtained at the group level. The permutation test was executed directly within the BRAPH program. Statistical significance was set at $p < 0.05$. However, in the analysis of the differences in cerebellar volumes and intrinsic cerebellar network between the groups, the p value with multiple corrections was set using the Bonferroni method (whole cerebellar volume, $0.05/4 = 0.0125$; cerebellar lobule volumes, $0.05/22 = 0.0022$; cerebellar vermis volumes, $0.05/5 = 0.01$; integration, $0.05/2 = 0.025$; and segregation, $0.05/2 = 0.025$).

Table 1: The differences of the cerebellar volumes between patients with juvenile myoclonic epilepsy and healthy controls.

	Patients with JME ($N = 45$)		Healthy controls ($N = 45$)		Difference	p value
	Mean (%)	SD (%)	Mean (%)	SD (%)		
Whole cerebellum						
Rt. cerebellum gray matter	3.3327	0.2701	3.4813	0.2615	0.1486	*0.0095
Rt. cerebellum white matter	1.0777	0.0914	1.0547	0.0842	-0.0230	0.2180
Lt. cerebellum gray matter	3.3516	0.2492	3.4929	0.2590	0.1413	*0.0099
Lt. cerebellum white matter	1.0874	0.0938	1.0574	0.0830	-0.0299	0.1124
Corpus Medullare	0.9939	0.1080	1.0352	0.0813	0.0413	*0.0436
Lobules						
Right I-III	0.0573	0.0174	0.0623	0.0115	0.0050	0.1100
Right IV	0.2067	0.0557	0.2265	0.0282	0.0198	0.0365
Right V	0.2114	0.0681	0.2318	0.0324	0.0204	0.0724
Right VI	0.5547	0.1139	0.6016	0.0776	0.0468	0.0251
Right crus I	0.8949	0.1620	0.9174	0.0951	0.0225	0.4232
Right crus II	0.5500	0.0939	0.5859	0.0816	0.0359	0.0558
Right VIIB	0.4162	0.0784	0.4672	0.0843	0.0510	0.0038
Right VIIIA	0.3040	0.0876	0.3506	0.0631	0.0466	0.0048
Right VIIIB	0.2114	0.0360	0.2282	0.0355	0.0168	0.0282
Right IX	0.2078	0.0460	0.2119	0.0378	0.0042	0.6402
Right X	0.0307	0.0054	0.0312	0.0055	0.0005	0.6679
Left I-III	0.0534	0.0141	0.0600	0.0107	0.0066	0.0139
Left IV	0.2023	0.0571	0.2225	0.0302	0.0202	0.0386
Left V	0.1919	0.0583	0.2225	0.0290	0.0306	*0.0022
Left VI	0.5645	0.1400	0.6212	0.0869	0.0567	0.0234
Left crus I	0.8625	0.1640	0.8884	0.1025	0.0259	0.3721
Left crus II	0.5364	0.0973	0.5263	0.0902	-0.0100	0.6130
Left VIIB	0.4169	0.0657	0.4540	0.0839	0.0371	0.0219
Left VIIIA	0.4081	0.0828	0.4519	0.0680	0.0438	0.0074
Left VIIIB	0.1830	0.0470	0.2055	0.0348	0.0226	0.0112
Left IX	0.2098	0.0392	0.2213	0.0371	0.0115	0.1577
Left X	0.0287	0.0056	0.0297	0.0064	0.0011	0.4043
Vermis						
Vermis VI	0.0934	0.0162	0.0987	0.0137	0.0053	0.0983
Vermis VII	0.0613	0.0130	0.0665	0.0107	0.0052	0.0401
Vermis VIII	0.1363	0.0173	0.1404	0.0209	0.0041	0.3094
Vermis IX	0.0619	0.0080	0.0648	0.0105	0.0028	0.1540
Vermis X	0.0219	0.0042	0.0237	0.0039	0.0017	0.0430

JME: juvenile myoclonic epilepsy; SD: standard deviation. *With statistical significance.

3. Results

3.1. Clinical Characteristics of Patients with JME and Healthy Controls. We enrolled 45 patients with JME and 45 healthy controls. Age and sex were not significantly different between the two groups (mean age, 24.1 vs. 25.0 years, $p = 0.357$; Male, 26/45 (57.8%) vs. 26/45 (57.8%), $p = 1.000$). Median age of seizure onset was 15 years (range 13-17 years), and median duration of epilepsy was 60 months (range 12-120 months). All of the patients with JME had myoclonic seizures. However, only 39 patients with JME (84.7%) had generalized tonic-clonic seizures, and 15 patients (32.6%) had absence seizures. All of the patients showed normal neurological examinations without any tremor.

3.2. Differences between Cerebellar Volumes of Patients with JME and Healthy Controls. Table 1 shows the cerebellar volumes of the patients with JME and healthy controls. The volumes of the right and left cerebellar white matter in the patients with JME were significantly lower than those in the healthy controls (3.33 vs. 3.48%, $p = 0.009$; 3.35 vs. 3.49%, $p = 0.009$). Similarly, the volumes of the corpus medullare and left lobule V in the patients with JME were

Table 2: The differences of the intrinsic cerebellar network between patients with juvenile myoclonic epilepsy and healthy controls.

	Patients with JME ($N = 45$)	Healthy controls ($N = 45$)	Difference	CI lower	CI upper	p value
Integration						
Characteristic path length	4.731	4.594	-0.137	-1.148	1.142	0.459
Global efficiency	0.300	0.260	-0.040	-0.084	0.094	0.201
Segregation						
Local efficiency	0.561	0.357	-0.204	-0.330	0.365	0.203
Mean clustering coefficient	0.248	0.176	-0.072	-0.105	0.114	0.134
Small-world network						
Small-worldness index	0.771	0.919	0.147	-0.144	0.146	*0.047

JME: juvenile myoclonic epilepsy; CI: 95% confidence interval of the difference between the groups. *With statistical significance.

lower than those in the healthy controls (0.99 vs. 1.03%, $p = 0.04$; 0.19 vs. 0.22%, $p = 0.002$, respectively). However, the cerebellar vermis volumes were not different between the two groups.

3.3. Differences in the Intrinsic Cerebellar Network between Patients with JME and Healthy Controls. Table 2 shows the intrinsic cerebellar network in the patients with JME and healthy controls. The value of the small-worldness index, which reflects the small-world network, was significantly lower in the patients with JME than in the healthy controls (0.771 vs. 0.919, $p = 0.04$). However, the other network measures of integration (including characteristic path length and global efficiency) and segregation (including local efficiency and mean clustering coefficient) were not different between the two groups.

3.4. Correlation between Clinical Characteristics and Cerebellar Volumes in Patients with JME. Table 3 shows the correlation analysis between clinical characteristics and cerebellar volumes in patients with JME. The volumes of the right lobule VI, right crus I, and left lobules VI and VIIIB were significantly correlated with the age at seizure onset ($r = -0.410$, $p = 0.005$; $r = -0.365$, $p = 0.01$; $r = -0.411$, $p = 0.005$; $r = 0.347$, $p = 0.02$, respectively). Furthermore, the volume of the right lobule VIIIB correlated with the duration of epilepsy ($r = -0.312$, $p = 0.03$). However, no correlation was found between age and cerebellar volumes.

4. Discussion

The main findings of this study were as follows: (1) decreased volumes in the right and left whole cerebellar white matter, corpus medullare, and left lobule V in the patients with JME when compared with the healthy controls; (2) alterations in the intrinsic cerebellar network in the patients with JME, particularly disruption of the small-world network; and (3) significant correlations between clinical characteristics, including age at seizure onset and duration of epilepsy, and volumes of some individual cerebellar lobes in the patients with JME.

Our findings are consistent with those of previous studies. A study that investigated alterations in the spatial distribution of the fraction amplitude of low-frequency fluctuation using functional MRI, which is a measure of intrinsic or spontaneous activity of the brain, demonstrated an increase in the fraction amplitude of low-frequency fluctuation in the cerebellum vermis of patients with JME when compared with healthy controls [24]. The result implicates the involvement of an altered cerebello-thalamocortical network in the genesis and propagation of generalized spike-wave discharges in JME [24]. In a simultaneous EEG and functional MRI study of patients with JME, blood oxygenation level-dependent activations associated with high network variation were mainly located in the cerebellum, which was also involved in dynamic EEG organization [25]. This finding suggests that the cerebellum may be involved in epilepsy generation and propagation in JME [25]. Another study using diffusion tensor imaging showed decreased fractional anisotropy in the cerebellum [26], along with good correlation of the diffusion metrics (including mean diffusivity and axial diffusivity) of the superior, middle, and inferior cerebellar peduncle with the duration of epilepsy. This result indicated that the disease-related white matter changes in the cerebellum might be involved in JME [27]. Kotini et al. analyzed the electromagnetic sources of epileptic activity in patients with JME, and they found that the dipolar source of paroxysmal magnetic encephalography activity was localized in the cerebellar area [28]. All of these previous findings and our results indicate that the cerebellum may play a role in the pathogenesis of JME.

Interestingly, cerebellar changes are not only observed in JME but also in other epilepsies, such as focal epilepsy. A volumetric study of patients with temporal lobe epilepsy (TLE) found significant abnormality in cerebellar volume when compared with healthy controls, with mean reductions of 4 to 6.6%, depending on adjustments [29]. Furthermore, another study investigating the extent and lateralization of atrophy in the cerebellar lobes of patients with unilateral TLE revealed a pattern of bilateral cerebellar pathology characterized by atrophy of the superior and inferior posterior lobes, hypertrophy of the anterior lobe, and no effect on the corpus medullare [30]. In our previous study, we also found that the volume of cerebellar white matter in patients with newly diagnosed focal epilepsy of unknown etiology was significantly smaller than that than that of healthy controls [31]. Furthermore, a network study using functional MRI found that patients with TLE exhibited decreased

Table 3: Correlation analysis between clinical characteristics and cerebellar volumes in patients with juvenile myoclonic epilepsy.

		Age	Age of seizure onset	Duration of epilepsy
Rt. cerebellum gray matter	Correlation coefficient	-0.247	-0.019	-0.179
	p value	0.102	0.902	0.240
Rt. cerebellum white matter	Correlation coefficient	0.018	-0.008	0.040
	p value	0.907	0.959	0.793
Lt. cerebellum gray matter	Correlation coefficient	-0.226	-0.055	-0.114
	p value	0.136	0.719	0.456
Lt. cerebellum white matter	Correlation coefficient	0.036	-0.009	0.064
	p value	0.813	0.955	0.678
Corpus medullare	Correlation coefficient	-0.047	-0.143	0.084
	p value	0.760	0.348	0.582
Right I-III	Correlation coefficient	-0.010	-0.135	0.107
	p value	0.946	0.376	0.484
Right IV	Correlation coefficient	0.014	-0.261	0.229
	p value	0.926	0.083	0.130
Right V	Correlation coefficient	0.019	-0.155	0.143
	p value	0.903	0.310	0.348
Right VI	Correlation coefficient	-0.222	-0.410	0.121
	p value	0.142	*0.005	0.429
Right crus I	Correlation coefficient	-0.203	-0.365	0.125
	p value	0.180	*0.014	0.413
Right crus II	Correlation coefficient	0.057	-0.152	0.199
	p value	0.710	0.320	0.191
Right VIIB	Correlation coefficient	-0.258	0.087	-0.263
	p value	0.087	0.572	0.081
Right VIIIA	Correlation coefficient	-0.235	-0.135	-0.094
	p value	0.121	0.377	0.538
Right VIIIB	Correlation coefficient	-0.121	0.247	-0.312
	p value	0.430	0.101	*0.037
Right IX	Correlation coefficient	0.171	0.133	0.061
	p value	0.261	0.385	0.692
Right X	Correlation coefficient	-0.200	-0.176	-0.050
	p value	0.188	0.248	0.745
Left I-III	Correlation coefficient	-0.057	-0.186	0.119
	p value	0.710	0.220	0.436
Left IV	Correlation coefficient	-0.032	-0.229	0.171
	p value	0.834	0.130	0.262
Left V	Correlation coefficient	0.002	-0.167	0.145
	p value	0.990	0.273	0.343
Left VI	Correlation coefficient	-0.057	-0.411	0.267
	p value	0.711	*0.005	0.076
Left crus I	Correlation coefficient	-0.207	-0.287	0.081
	p value	0.173	0.056	0.595
Left crus II	Correlation coefficient	-0.031	-0.154	0.137
	p value	0.838	0.312	0.370
Left VIIB	Correlation coefficient	-0.086	-0.040	-0.026
	p value	0.574	0.793	0.868
Left VIIIA	Correlation coefficient	-0.107	-0.169	0.032
	p value	0.486	0.268	0.833

Table 3: Continued.

		Age	Age of seizure onset	Duration of epilepsy
Left VIIIB	Correlation coefficient	0.287	0.347	-0.036
	p value	0.056	*0.020	0.814
Left IX	Correlation coefficient	0.190	0.178	0.051
	p value	0.212	0.242	0.737
Left X	Correlation coefficient	-0.267	-0.193	-0.064
	p value	0.076	0.203	0.676
Vermis VI	Correlation coefficient	-0.074	-0.246	0.118
	p value	0.628	0.104	0.441
Vermis VII	Correlation coefficient	-0.045	-0.289	0.199
	p value	0.770	0.054	0.191
Vermis VIII	Correlation coefficient	-0.074	-0.212	0.090
	p value	0.630	0.163	0.557
Vermis IX	Correlation coefficient	-0.262	-0.139	-0.112
	p value	0.082	0.363	0.464
Vermis X	Correlation coefficient	-0.135	-0.131	-0.043
	p value	0.376	0.390	0.779

*With statistical significance.

functional connectivity in the dentate nucleus network and motor network (cerebellar lobule V and putamen), whereas increased functional connectivity was observed in the executive control network (cerebellar crus I and inferior parietal lobule) [32]. This finding highlighted the presence of a disrupted cerebellar-cerebral functional network [32]. Considering these results, cerebellar involvement appears to be related to epilepsy and not a characteristic finding in JME.

Cerebellar atrophy is well known to be associated with the long-term use of ASM, such as phenytoin [33]. However, in our study, all patients underwent MRI scans prior to ASM administration. Therefore, we could rule out the effect of ASM. Another plausible explanation is that of hypoxic-ischemic nerve cell injury occurring during prolonged seizures. Additionally, we assume that cerebellar abnormalities could be one of the pathogenic mechanisms by which epilepsy occurs. Although the reason for decrease in cerebellar volumes in patients with epilepsy is unclear, these changes could be related to epilepsy. The cerebellum is composed of three histological layers: the excitatory granular layer, inhibitory Purkinje cell layer, and molecular layer. A quantitative neuropathological postmortem analysis revealed that cerebellar atrophy, as demonstrated by significant reductions in hemispheric Purkinje cell linear densities, was confirmed in patients with epilepsy. Furthermore, even in cases of macroscopically normal cerebellum, Purkinje cell loss was evident [34]. Purkinje cells are GABAergic neurons that supply the deep cerebellar nuclei with inhibitory output. A study involving the stimulation of the rat cerebellum showed diminished cerebral cortex response and inhibition of seizure development, indicating that the cerebellum exerts effects on the cerebrum and plays a role in epilepsy development [35]. Therefore, cerebellar disinhibition is reduced by Purkinje cell loss in the cerebellum, which contributes to epileptogenesis by increasing cortex excitation [36].

Another result of our current study was the disruption of the intrinsic cerebellar network in patients with JME. Particularly, the small-worldness index in the patients with JME was found to be lower than that in the healthy controls. The small-worldness index is one of the network measures that simultaneously reflects both integration and segmentation and indicates how well the brain is connected and how efficiently it shares information [37]. Considering that the cerebellar volumes were reduced in the patients with JME in our study, the decrease in small-worldness index value is a sufficiently predictable result that is in line with the aforementioned covariance network analysis based on the cerebellar volumes. This also implies that an altered cerebellar function may contribute to the pathogenesis of JME. The concept of "system disorder" versus "network disorder" is a topic of ongoing debate in the field of JME researches. Genetically determined dysfunctions of crucial cognitive systems, such as visuomotor coordination and linguistic communication, have emerged as key mechanisms of seizure genesis in JME, which suggests a new paradigm to consider JME as a system disorder [38]. However, some researchers have suggested that JME may be a network disorder, as it is associated with abnormalities in multiple brain regions and neural networks [7–9]. Our study also supported the concept of JME as a network disease.

Our study is the first study to evaluate alterations in cerebellar volumes and intrinsic cerebellar network in patients with JME in comparison with healthy controls, wherein we successfully demonstrated differences between the two groups. Additionally, we enrolled only newly diagnosed patients with JME who underwent scanning using the same 3-Tesla MRI scanner to increase the homogeneity of the study. However, this study has some limitations. First, this was a retrospective study conducted at a single tertiary hospital. Thus, the results of this study cannot be generalized.

Second, the cross-sectional design of this study did not allow us to obtain the changes in cerebellar volumes and intrinsic cerebellar network over time. A longitudinal study on the effects of ASM use on cerebellar volumes, the association between ASM response and cerebellar volumes, and the differences in cerebellar volumes according to the duration of epilepsy would be a more meaningful study. Additionally, our patients were initially diagnosed with JME according to the ILAE criteria, but a longitudinal follow-up study is necessary because the diagnosis could change later, such as progressive myoclonic epilepsy or familial adult myoclonic epilepsy. Third, we not only investigated whole cerebellar volume but also volumes of individual cerebellar lobes and subregions, which can be considered another strength of this study. We used the ACAPULCO algorithm for automatic cerebellar subregion parcellation, which is known to have state-of-the-art accuracy and is superior to several previously reported methods. However, the algorithm is not perfect, and considering the small size and complexity of cerebellar structures, the possibility of segmentation errors cannot be completely ruled out [18].

5. Conclusion

Here, we demonstrated alterations in cerebellar volumes and intrinsic cerebellar network in patients with JME when compared with healthy controls. The present results provide evidence that the cerebellum may play a role in the pathogenesis of JME.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

Neither of the authors has any conflict of interest to disclose.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation and data collection and analysis were performed by Ho-Joon Lee, Dong Ah Lee, and Kang Min Park. The first draft of the manuscript was written by Kang Min Park, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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