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Original article

The association of epileptic focus estimated by magnetoencephalography with cognitive function in non-lesional epilepsy with continuous spikes and waves during slow wave sleep (ECSWS) children

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Abstract

Objective: Epilepsy with continuous spikes and waves during slow sleep (ECSWS) is associated with cognitive deficits. The underlying mechanism is thought to relate to disturbance of functions of the foci by the persistent epileptic activity. However, the relationship between epileptic foci and cognitive deficits remains largely unknown, except for in Landau–Kleffner syndrome. The aim of this study was to evaluate the relationship of epileptic foci estimated from magnetoencephalography (MEG) with cognitive functions at the period of diagnosis in non-lesional ECSWS children, excluding those with Landau–Kleffner syndrome.

Methods: MEG data and the Wechsler intelligence scale for children-III scores at ECSWS diagnosis, and medical records, were reviewed. Multiple regression analysis was performed to examine the relationship of parameters of MEG spike dipole clusters, including anatomical location or laterality, with the Wechsler intelligence scale for children-III scores at ECSWS diagnosis.

Results: Sixteen patients were included, all of whom were right-handed. Epilepsy onset (first unprovoked seizure) ranged from 31 to 110 months (mean, 68.5). The age at ECSWS diagnosis ranged from 72 to 156 months (mean, 108.9). The dipole clusters were estimated on the right Rolandic area (RA) in 4 patients (25%), right supramarginal gyrus (SMG) in 3 (19%), left RA in 2 (13%), left SMG in 2 (13%), bilateral RA in 3 (19%), multiple anatomical locations in 2 (13%). The age at epilepsy onset had the strongest prognostic effect, and full-scale intelligence quotient was relatively less-affected if the cluster was found on the SMG ($\beta = 14.7$, $p = 0.031$). Cases with only a right side cluster exhibited reduced impairment of perceptual organization compared with those with only a left side cluster or bilateral clusters ($\beta = 17.48$, $p = 0.02$). In 12 patients, long-term intellectual prognosis was evaluated, and was associated with intellectual level at the period of ECSWS diagnosis.

Conclusion: In non-lesional ECSWS, the relationship between epileptic focus and cognitive deficits differs from that observed in adults. Rather, it is similar to epilepsies associated with congenital or early infantile brain insults, in that the left epileptic foci in right-handed patients were associated with lower non-verbal functions. Future studies are required to determine the role of plasticity of the immature brain in driving these differences.

Keywords: ECSWS; MEG; WISC-III; Rolandic area; Supramarginal gyrus; Dipole cluster

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1. Introduction

Epilepsy with continuous spikes and waves during slow sleep (ECSWS) was originally classified as Epilepsies and Syndromes Undetermined (with respect to a focal or generalized pattern) in the 1989 ILAE classification [1], and in 2010 was classified as electro-clinical syndromes [2]. The electroencephalography features in ECSWS include a spike-wave index of >85% of non-REM sleep (electrical status epilepticus during sleep: ESES). However, some specialists argue that a spike-wave index of <85% is sufficient for ECSWS diagnosis, because of its influence on cognitive functions [3]. The etiology of ECSWS can be divided into (i) with brain lesions such as congenital brain anomaly or hydrocephalus, or (ii) without such lesions on magnetic resonance imaging (MRI). In non-lesional ECSWS, some cases likely evolve from benign pediatric focal epilepsies including benign epilepsy with centrotemporal spikes (BECTS), although it was suggested that ECSWS and BECTS are extremes of a spectrum of the same epileptic entity [4]. Indeed, the same genetic background was reported for both disorders [5].

ECSWS is an epileptic encephalopathy, with a decrease in cognitive functions associated with epileptic seizures in affected children. The epileptic seizures consist of focal motor seizures, atonic seizures, and atypical absences, which are often readily controlled by optimal anti-epileptic drugs (AEDs). However, the decrease in cognitive function often shows no improvement, despite effective seizure control and electroencephalogram (EEG) normalization [6–11]. The reported prognostic factors affecting cognitive functions in ECSWS are younger age at diagnosis [6,11], low intellectual function at diagnosis [6], and duration of ESES [7,10,11]. In another report [9], Low intellectual function at ECSWS diagnosis was reported to be the only significant prognostic factor for long-term cognitive outcome, with less influence of duration of EEG abnormalities, duration of active epilepsy, and antiepileptic medication.

One of the hypothesized mechanisms of ECSWS involves a disturbance in the normal functions of epileptic foci with persistent epileptic activity during sleep [12], suggesting that the effect and prognosis may differ depending on the location and laterality of the epileptic foci. In Landau–Kleffner syndrome (LKS), an epilepsy that shares similar EEG features to ESES, and which is broadly consistent with ECSWS, affected children show auditory agnosia and aphasia. The epileptic focus of LKS is located in the posterior superior temporal lobe, including Heschel gyrus [13], and an association between clinical symptoms and the epileptic focus is well established. However, the relationship between epileptic foci and cognitive deficits in other ECSWS are largely unknown.

Because of the generally bilateral and diffuse distribution of epileptic discharges in ESES, it can be difficult to correctly determine the epileptic focus by visual inspection of EEG. However, this can be determined by magnetoencephalography (MEG), as it is superior to EEG for estimating epileptic foci with higher spatio-temporal resolution. As the magnetic field is not distorted by the skull or other extracerebral tissues [14], a subset of ESES localize as homogenous dipoles with consistent orientations, even for diffuse EEG discharges. Thus, ESES is a good candidate for equivalent current dipole (ECD) estimation to visualize the single/multifocal epileptic foci. In practice, whole head MEG analysis with ECD estimation was reported to successfully detect the foci of epileptic spikes in LKS [13].

The main aim of this retrospective study was to investigate the relationship of location and the laterality of epileptic foci estimated from MEG with cognitive functions at the period of diagnosis in non-lesional ECSWS children (except for those with LKS). We examined the hypothesis that the left side dipole cluster was associated with lower language skills, and right side cluster with lower visuospatial function, and that the anatomical location of the clusters influence cognitive function. We also investigated the prognostic factors affecting cognitive function at ECSWS diagnosis and long-term intellectual prognosis.

2. Materials and methods

2.1. Patients

ECSWS patients were selected from children receiving at least one 24 h overnight video-EEG examination at Nishi-Niigata Chuo Hospital (for evaluation and treatment of epilepsy) from August 1999 to September 2015. The inclusion criteria were: (1) a spike and wave index ≥85% during the first cycle of non-REM sleep, (2) normal development during the infant and toddler periods (walking alone and speaking a few words were accomplished by 18 months), and (3) normal MRI results. Children suffering from auditory agnosia and aphasia, or who were diagnosed with LKS, were excluded. After diagnosis of ECSWS, the first MEG recording and Wechsler intelligence scale for children-III Japanese edition (WISC-III) was examined as soon as possible. All WISC-III testing was performed by the same clinical psychologist (M.Y.). For each patient, the following data were investigated retrospectively from clinical records: age at onset of epilepsy (first unprovoked seizure), age at ECSWS diagnosis in our institution, seizure type, the type of cognitive dysfunction, age at first MEG, all scores of intellectual testing, treatment, age at last seizure, age at complete EEG normalization, and long-term intellectual prognosis.

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Informed consent was obtained from each patient or parent, and the ethics committee at Nishi-Niigata Chuo National Hospital approved this study.

2.2. MEG recording

MEG recording was performed using a helmet-shaped, whole-scalp neuromagnetometer (Neuromag 204/Neuromag 306; Elekta-Neuromag Oy, Finland), involving 204 or 306 planar-type gradiometers in a magnetically shielded room at Nishi-Niigata Chuo Hospital. Each subject was placed in the supine position and received sedatives (triclofos sodium or pentobarbital calcium) if necessary. Before recording, the positions of 3 anatomical fiduciary points (nasion and bilateral preauricular points) and 4 indicator coils on the scalp were digitized as reference points using a three-dimensional electromagnetic digitizer (Polhems, Colchester, VT, USA). MEG data were continuously recorded for over 20 min with the subjects in a light sleep state. MEG data were sampled at 300 Hz using a 0.03–160 Hz bandpass filter, and then analyzed offline using a 3–45 Hz bandpass filter. For MEG analysis, a single ECD was calculated using Source Modeling Software (Elekta-Neuromag Oy, Finland) for the visually determined initial peak of each interictal spike discharge at stage 1 or 2 of the 1st cycle of sleep in a spherical model. Acceptable equivalent current dipoles of the spike sources had a goodness-of-fit >70% and a moment <500 nAm [15]. The dipole moment, in terms of the strengths and orientations of the MEG spike sources, was then evaluated and overlaid onto the spike sources with respect to the 3 anatomic fiduciary points on the MRI of each patients' head. For each patient, the dipole source was estimated for more than 50 interictal spikes. In previous report from our institution, clusters extending within 2 neighboring gyri were defined as focal [16]. However, in the present study, we defined a cluster more extensively, and as long as the ECDs were collected in a localized area, a distribution over ≥3 neighboring gyri were regarded as a focal cluster.

2.3. Data analysis

A descriptive analysis was performed for clinical data and the WISC-III scores. To investigate the relationship of the categorical parameters of the MEG spike dipole clusters (e.g., anatomical location or laterality) with WISC-III scores at the age of ECSWS diagnosis, we performed a stepwise multiple regression analysis with a linear model by selecting the WISC-III scores (FSIQ and index scores) as dependent variables. By reference to previous reports [6,7,9–11], we chose the 'age at epilepsy onset (first unprovoked seizure)', 'age at diagnosis of ECSWS', 'interval between onset of epilepsy and diagnosis of ECSWS', and the 'number of used AEDs in the period until diagnosis of ECSWS' as candidate independent variables (confounding factors) in our regression model. We first investigated the correlation of FSIQ with each chosen variable. The variables with a Pearson's correlation coefficient with FSIQ >0.4 or <−0.4 and a p-value <0.05 were accepted as candidates for independent variables in the linear regression model. In addition to the chosen variables, we also selected the locus (anatomical location on the hemisphere) and laterality (left, right, or bilateral) of the dipole clusters estimated with MEG as independent variables. All the acceptable models had independent variables with p-values <0.05, an adjusted $r^2 > 0.50$, and a variance inflation factor <10 in all variables.

We also evaluated the long-term intellectual prognosis in a group of patients aged >15 years old who were followed in our institution until seizure freedom and complete EEG normalization. Patients showing an FIQ ≥70 or who went on to a regular Japanese high school were judged as 'good intellectual prognosis', while patients with an FIQ <70 or who required special education for intellectual disabilities were judged as 'poor intellectual prognosis'. Comparison of variables was performed using Mann–Whitney U test with Bonferroni correction, and a p-value <0.017 was considered statistically significant. All analysis was performed with statistical software (IBM® SPSS ®Statistics Desktop v23.0, for Microsoft Windows).

3. Results

3.1. Profiles of patients

During the study period, 20 cases showed ESES during the first cycle of non-REM sleep, non-lesional MRI, and normal development before the onset of the epilepsy. Within these patients, 3 were diagnosed with LKS and 1 showed an EEG abnormality without seizure. Sixteen patients fulfilled inclusion criteria (10 boys, 6 girls). All of these patients were right-handed. Clinical data are summarized in Table 1. All participants were considered as having benign partial epilepsy of childhood such as BECTS at the age of first unprovoked seizure. The cases with atonic seizures (Cases 2, 5, 7, 8, 10, 11, 13) also fulfilled the diagnostic criteria of atypical benign partial epilepsy [17].

3.2. MEG findings at ECSWS diagnosis

The location and laterality of the dipole clusters were estimated on the right Rolandic area (RA) in 4 patients (25%), right supramarginal gyrus (SMG) in 3 (19%), left RA in 2 (13%), left SMG in 2 (13%), bilateral RA in 3 (19%), and multiple anatomical locations in 2 (13%) (one case on left inferior frontal gyrus and right superior occipital gyrus, and one case on left superior parietal

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Table 1
Clinical profiles and results of Wechsler intelligence scale for children-III (WISC-III) and magnetoencephalography (MEG) examinations of study patients.

Case	Sex	Dominant hand	Epilepsy onset (m)	ECSWS diagnosis (m)	Type of seizure	Cognitive complaints	Comorbidities	AEDs at ECSWS diagnosis	Lt side dipole (%)	Rt side dipole (%)	Location of ECD cluster on MEG	Laterality of ECD cluster on MEG	FIQ, VIQ, PIQ at ECSWS diagnosis	VC, PO, FD, PS at ECSWS diagnosis	Normalization of EEG (m)	Last seizure (m)	Steroid therapy	Final AEDs	Prognosis
1	M	RT	31	72	PMS, aty-ab	academic difficulty, loss of motivation	ADHD, ODD	VPA, CZP, ZNS	43.5%	56.5%	multiple location (preF, O)	LT, RT	46, 55, 47	58, 53, 50, 50	183	97		VPA, CZP, ST	poor
2	M	RT	36	110	PMS, atonic	academic difficulty, dysarthria		VPA, CZP, CBZ	100.0%	0.0%	RA	LT	44, 56, 43	61, 49, 53, 52	134	126		VPA, CLB, ST	discontinued
3	M	RT	39	93	PMS, sGTC	academic difficulty, loss of motivation		CLB, ZNS	100.0%	0.0%	RA	LT	71, 79, 69	79, 74, 79, 75	157	100	pulse	ZNS, CLB, CZP	good
4	M	RT	41	87	PMS. sGTC	academic difficulty, loss of motivation	ASD	VPA, CZP	100.0%	0.0%	SMG	LT	61, 74, 55	79, 63, 71, 50	168	86	pulse + oral	VPA, ST, PSL	poor
5	M	RT	48	127	PMS, aty-ab, sGTC, atonic			VPA, CBZ	0.0%	100.0%	SMG	RT	79, 90, 72	95, 80, 76, 64	132	129		VPA, ZNS	good
6	M	RT	54	88	aty-ab, sGTC	loss of motivation		VPA	0.0%	100.0%	SMG	RT	100, 108, 92	105, 97, 106, 83	164	96		ZNS	good
7	F	RT	58	90	PMS, aty-ab, sGTC, atonic	academic difficulty, dysarthria, dysphagia		VPA, CZP, CBZ	42.2%	57.8%	RA	LT, RT	64, 81, 53	80, 56, 85, 66	150	97	pulse + oral	CZP, CLB, ESM, PSL	poor
8	M	RT	64	122	PMS, sGTC, atonic	dysarthria	ADHD	VPA, CZP	60.4%	39.6%	RA-periSy	LT, RT	62, 79, 51	80, 56, 76, 58	155	148	oral	VPA, CZP, CLB, ST	poor
9	M	RT	72	156	aty-ab, sGTC, atonic	dyslexia	LD	PB, LTG, LEV	65.6%	34.4%	multiple location (SPL, SMG)	LT, RT	61, 65, 65	65, 67, 73, 61	discontinued				
10	F	RT	75	79	aty-ab, sGTC, atonic	dyscalculia, disorientation			96.5%	3.5%	SMG	LT	80, 108, 54	109, 59, 97, 55	107	91	oral	VPA, PSL	good
11	F	RT	77	111	PMS. aty-ab, sGTC	academic difficulty, loss of motivation		VPA, CLB	14.8%	85.2%	RA	RT	73, 84, 66	91, 76, 65, 61	202	137	pulse + oral	VPA, ESM, ST, CZP	good
12	M	RT	93	112	sGTC, atonic	academic difficulty		VPA, ZNS, LEV	0.0%	100.0%	RA	RT	92, 103, 82	103, 89, 106, 75	NA	NA	pulse + oral		NA

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13	M	RT	95	121	sGTC, atonic	academic difficulty	VPA, TPM	3.3%	96.7%	RA	RT	94, 105, 83	106, 84, 91, 78	138	133		VPA, TPM, CZP	NA	
14	F	RT	97	122	PMS, aty-ab, sGTC		ZNS	0.0%	100.0%	SMG	RT	101, 96, 107	99, 107, 88, 108	125	138		VPA, ZNS, ESM	good	
15	F	RT	106	123	PMS	academic difficulty	CZP, ZNS	13.6%	86.4%	RA-periSy	RT	107, 116, 94	117, 100, 109, 78	133	141		ZNS, CLB, CZP, ST	good	
16	F	RT	110	129	PMS. aty-ab, sGTC		CZP, PHT	63.2%	36.8%	RA-periSy	LT, RT	111, 116, 103	118, 103, 106, 106	165	162	pulse + oral	PHT, CLB, ST, PSL	good	
Mean			68.5	108.9								77.9, 88.4, 71.0	90.3, 75.8, 83.2, 70.0						

M: male; F: female; RT: right; LT: left; PMS: partial motor seizure; aty-ab: atypical absence; atonic: atonic seizure or myoclonic negative seizure; sGTC: secondary generalized tonic-clonic seizure; ADHD: attention deficit and hyperactivity disorder; ODD: oppositional defiant disorder; ASD: autistic spectrum disorder; LD: learning disability; preF: pre-frontal; O: occipital; RA: rolandic area; periSy: perisylvian area; SMG: supramarginal gyrus; SPL: supra parietal lobule; discontinued: follow-up was discontinued; NA: not accomplished; VPA: valproate acid; CZP: clonazepam; ZNS: zonisamide; CBZ: carbamazepine; PB: phenobarbital; LTG: lamotrigine; LEV: levetiracetam; TPM: topiramate; PHT: phenytoin; PSL: prednisolone; CLB: clobazam; ST: sultiame.

lobule and right SMG with scattered ECDs) (Table 1; Fig. 1).

3.3. WISC-III scores at ECSWS diagnosis

The mean WISC-III scores performed at the first MEG study were an FIQ of 77.9 (range approximately 44–111), verbal intelligence quotient (VIQ) of 88.4 (range approximately 55–116), and a performance IQ (PIQ) of 71.0 (range approximately 43–107). Twelve out of 16 patients (75%) showed a VIQ-PIQ $\geq$13, which represents a significant threshold score VIQ-PIQ discrepancy in individual cases [18]. By contrast, no cases showed a PIQ-VIQ $\geq$13. The index scores were a verbal comprehension (VC) of 90.3 (range approximately 58–118), perceptual organization (PO) of 75.8 (range approximately 49–107), freedom from distractibility (FD) of 83.2 (range approximately 50–109), and processing speed (PS) of 70.0 (range approximately 50–108), while there was a trend towards a greater decrease in PO and PS scores. In the WISC-III subtests, 'symbol search' and 'coding' showed the largest score decrease (Fig. 2).

3.4. Relationship of location and laterality of the spike dipole cluster estimated with MEG with WISC-III scores at ESCWS

The 'age at onset of epilepsy' (Pearson's correlation coefficient, $r = 0.804$, $p < 0.001$), 'interval between onset of epilepsy and diagnosis of ECSWS' ($r = -0.640$, $p = 0.008$), and the 'number of used AEDs at the diagnosis of ECSWS' ($r = -0.523$, $p = 0.038$) were significantly correlated with FSIQ. By contrast the 'age at the diagnosis of ECSWS' had a poor correlation ($r = 0.281$, $p = 0.292$). Thus, 'age at onset of epilepsy', 'interval between onset of epilepsy and diagnosis of ECSWS', 'number of used AEDs at the period of diagnosis of ECSWS', 'anatomical cortical location of the dipole cluster (RA, SMG, or multiple anatomical locations)', and 'laterality of the dipole cluster (left side only, right side only, or bilateral)' were candidates for independent variables for regression analysis. For example, in case 2, the scores of these variables were the 'age at onset of epilepsy' = 36 months, 'interval between onset of epilepsy and ECSWS diagnosis' = 74 months, 'number of used AEDs before ECSWS diagnosis' = 3, 'SMG focus' = 1, 'RA focus' = 0, and 'multiple anatomical locations' = 0, 'left side only' = 1, 'right side only' = 0, and 'bilateral' = 0. As a result, FIQ, VC, and PO had acceptable models (Fig. 3 and Table 2), while the 'age at onset of epilepsy' had the strongest influence in all models. Additionally, the FIQ score was relatively less-affected if the cluster was estimated on the SMG (partial regression coefficient [β] = 14.72, standardized partial regression coefficient [β^*] = 0.33, $p = 0.031$; Fig. 3A), the number of used

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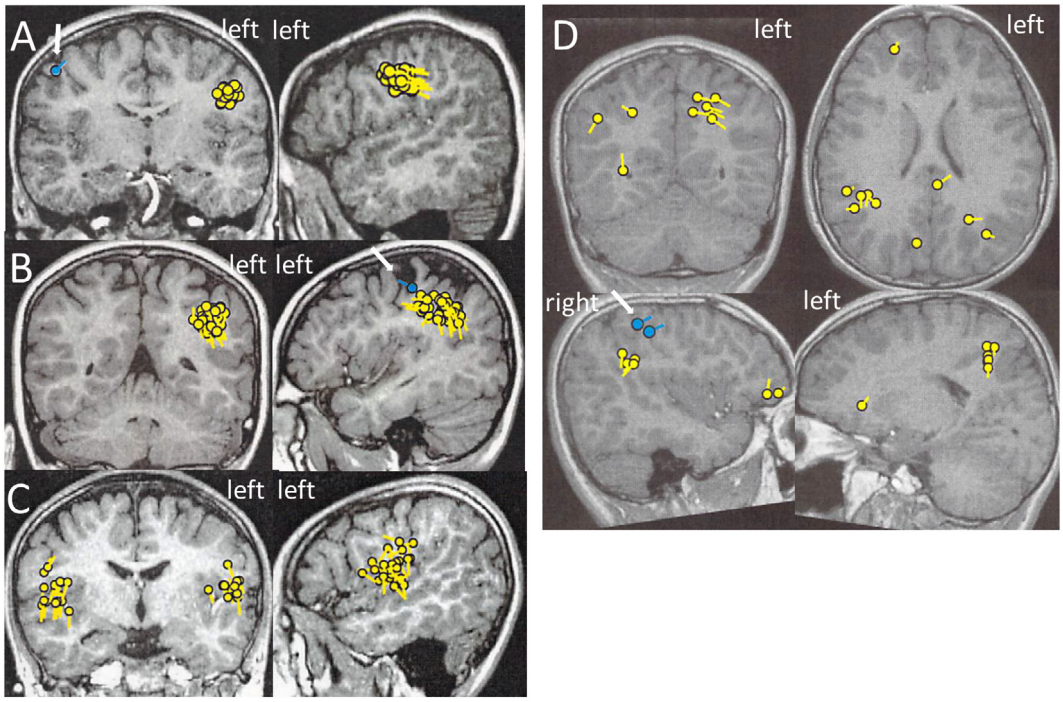

Fig. 1. The dipole clusters estimated with magnetoencephalography (MEG). All images are T1 weighted. The dipoles indicated by white arrows are sensory evoked fields evoked by contralateral median nerve stimulation. (A) In case 3 (7 years, 9 months of age), the dipole cluster was estimated on the middle part of the left Rolandic area. (B) In case 4 (7 years, 3 months of age), the dipole cluster was estimated on the left supramarginal gyrus. (C) In case 16 (10 years, 9 months of age), the dipole clusters were estimated on the lower part of the bilateral Rolandic areas and the peri-sylvian areas. (D) In case 9 (13 years, 0 months of age), the clusters were multifocal and bilaterally located (on the left superior parietal lobule and right supra marginal gyrus) and scattered dipoles also existed.

AEDs was associated with lower VC ($\beta = -9.23$, $\beta^* = -0.43$, $p = 0.010$), and the cases with only a right side cluster showed a relatively higher PO than those with only a left side cluster or bilateral clusters ($\beta = 17.48$, $\beta^* = 0.465$, $p = 0.02$; Fig. 3B).

3.5. Long-term clinical course

During the follow-up period, epileptic seizures were entirely controlled for at least 1 year in 15 patients (88%). The last seizure occurred at a mean time of 122.5 months (range approximately 86–162), and the mean duration between onset of epilepsy and last seizure was 55.6 months (range approximately 16–90). During the same period, in 14 patients (82%) the disappearance of ESES and complete EEG normalization was confirmed at 150.9 months (range approximately 107–202), while the mean duration of abnormal EEG was 45.6 months (range approximately 3–111). Twelve patients were followed over the age of 15 years in our institution, all of whom achieved seizure-free and normal EEG results, while 9 patients (75%) were AED-free. Eight patients (67%) went on to regular Japanese high school, with mean FIQ scores at ECSWS diagnosis of 90.3 (range approximately 71–111); these scores were within the normal or borderline range. By contrast, 4 patients (33%) requiring special educational programs for intellectual disabilities had a lower mean FIQ of 58.3 (range approximately 46–64) at ECSWS diagnosis. Between these groups, there was a significant difference in FIQ at ECSWS diagnosis ($p = 0.007$), while there were no differences in the duration of abnormal EEG ($p = 0.174$) or the interval between onset of epilepsy and the last seizure ($p = 0.396$).

4. Discussion

4.1. MEG findings

The foci of ESES estimated by MEG were located on the RA in 56% of patients, the SMG in 31%, and others or multiple locations in 13%. To our knowledge, only one previous MEG study [19] has investigated the epileptic focus of non-lesional ECSWS except for LKS. In contrast to our data, that study reported that in atypical benign partial epilepsy, which is considered a subtype of ECSWS, MEG revealed epileptic foci on the lower RA in 94% of patients, while no cases showed an SMG focus [19]. These differences may be because the diagnosis of atypical benign partial epilepsy requires the existence of epileptic negative myoclonus, the origin of which is considered at the RA. In BECTS, the main

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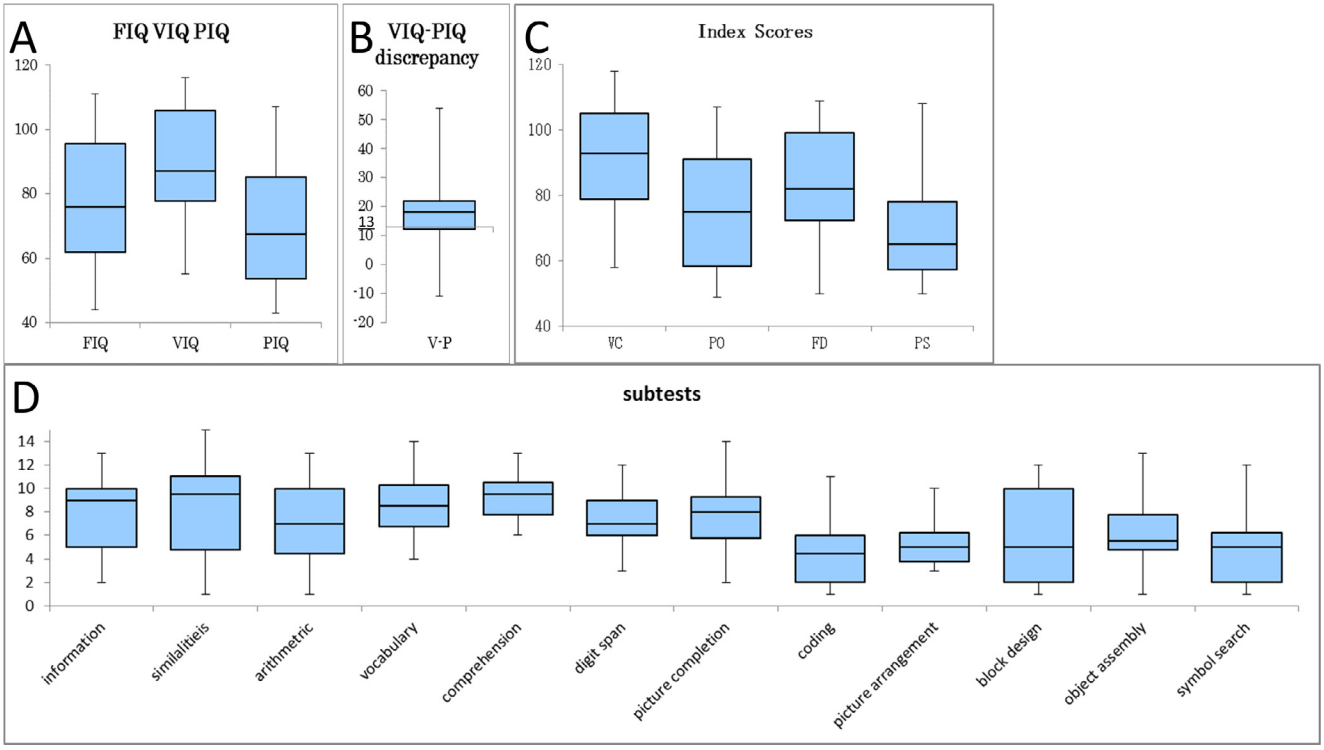

Fig. 2. Wechsler intelligence scale for children-III (WISC-III) scores at the period of diagnosis of epilepsy with continuous spikes and waves during slow sleep (ECSWS). (A, B) There was a global decline in development, although performance intelligence quotient (PIQ) showed a greater decrease than verbal IQ (VIQ), and in 75% of cases, the VIQ-PIQ discrepancy was >13. (C) In index scores, perceptual organization (PO) and processing speed (PS) showed a greater decrease than those for verbal comprehension (VC) and freedom from distraction (FD). (D) In subtests, although tasks involving PO and PS declined globally, 'coding' and 'symbol search' showed the greatest change.

source of epileptic spikes investigated by MEG is the RA [20], suggesting a continuity between non-lesional ECSWS with an RA focus and BECTS. In BECTS, a strong functional connectivity was also reported between the RA and SMG [21]. Thus, ECSWS with SMG foci may also have functional connectivity with the RA, and cases of ECSWS with these 2 foci may share the same network. Although we tried to analyze the initial peak of the epileptic spikes, because of methodological limitations it was not deniable that the location of the ECD did not indicate the actual epileptogenic focus, but rather the gravity center of the discharge at analyzed time point. As such, these 2 clusters may reflect the same epileptogenic discharge.

4.2. WISC-III scores at ECSWS diagnosis and regression analysis

In our study, although the WISC-III scores at diagnosis showed a global decrease, the PIQ, PO, and PS were more severely decreased. A 75% of cases showed VIQ > PIQ discrepancies over 13-points. These data suggest that non-lesional ECSWS (except LKS) have a greater impact on non-verbal intellectual ability and central processing speed. A potential mechanism for this effect on non-verbal intellectual ability is the 'crowding theory' [22–24] in the developing brain (described below). Alternatively, in children with BECTS, a relationship between impairment in visuospatial functions [25] or visual selective attention [26] and frequent nocturnal epileptic spikes was previously reported, suggesting an important relationship between nocturnal spikes and visuospatial function. Our study excluded patients with LKS and included ECSWS patients without MRI-visible brain lesions and with normal infantile development. Thus, the majority of our cases could be categorized into the most severe extremes of BECTS spectrum, suggesting that previous findings of BECTS patients may be applicable to our cases. However, in the literatures, there are some case reports of a significant VIQ > PIQ discrepancy, although this type of discrepancy was not reported as a common characteristic in ECSWS studies. These differences may also relate to our exclusion and inclusion criteria. For PS scores, Ebus et al. [27] reported a negative relationship between the frequency of inter-ictal epileptic discharge and central processing speed, which may explain our results.

By regression analysis, we found that a younger age at onset of epilepsy (first unprovoked seizure) was the strongest predictive factor for WISC-III at ECSWS diagnosis. In contrast to other studies [6,7,10,11], there was less influence of age at ECSWS diagnosis or the

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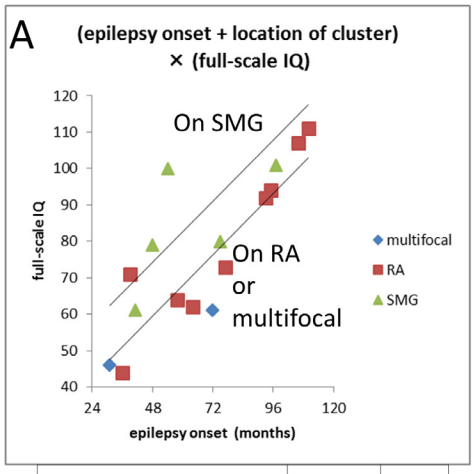
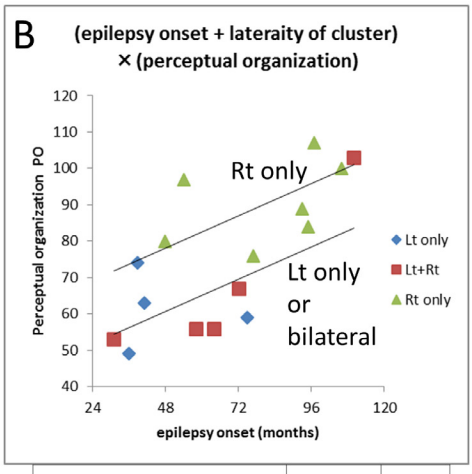


	Partial-regression coefficient	s.e.	Standardized partial-regression coefficient	p-value
intercept	26.000	8.635		0.010
epilepsy onset (months)	0.690	0.130	0.835	0.000
SMG cluster	14.722	6.104	0.334	0.031
adjusted R^2=0.629				



	Partial-regression coefficient	s.e.	Standardized partial-regression coefficient	p-value
intercept	42.826	8.535		0.000
epilepsy onset (months)	0.370	0.130	0.502	0.014
Right-side cluster only	17.482	6.615	0.465	0.020
adjusted R^2=0.719				

Fig. 3. Multiple regression analysis with a linear model. (A) FIQ at the period of ECSWS diagnosis was dependent on the age of epilepsy onset, and a dipole cluster located on only the supramarginal gyrus was associated with a relatively less-affected FIQ. (B) PO at the period of ECSWS diagnosis was also dependent on the age of epilepsy onset, and a dipole cluster located on only the right hemisphere was associated with relatively higher PO. RA: Rolandic area; SMG: supra marginal gyrus.

Table 2
The results of regression analysis of VC, FD and PS. VC had the acceptable model (Adjusted R^2 >0.5).

		Partial regression coefficient		Standardized partial regression coefficient	p-value	Adjusted R^2
		β	s.e.			
VC	intercept	76.486	10.752		0.000	0.7345*
	epilepsy onset (months)	0.494	0.101	0.669	0.008	
	Number of AEDs	−9.697	3.089	−0.430	0.031	
FD	intercept	48.123	9.737		0.000	0.478
	epilepsy onset (months)	0.512	0.133	0.716	0.002	
PS	intercept	38.000	9.774		0.004	0.427
	epilepsy onset (months)	0.467	0.134	0.682	0.000	

VC: verbal comprehension; FD: freedom from distractibility; PS: processing speed; AEDs: antiepileptic drugs.
* Significant.

duration between the onset of epilepsy and the period until intellectual testing on. This is likely because 14 out of 16 patients visited our institution after months or years of unsuccessful treatments at non-epilepsy centers, but then received the first 24 h EEG monitoring and ECSWS diagnosis at our institution. As such, the correct age at the progression to ECSWS was very difficult to estimate. For cases with early onset of epilepsy, the progression towards ECSWS would be also early, and ESES should affect the developing brain. Thus, the brain may be irreversibly damaged during the critical period [28]. It is also possible that the occult epileptogenic pathology that generates ESES may impair intellectual development from the onset of epilepsy, even prior to progression to ECSWS.

The pathophysiology of cognitive deficit in ECSWS was suggested to be the same as for LKS, although to our knowledge, there are no reports of the association of the ESES focus estimated by MEG with cognitive functions in non-lesional ECSWS, except for LKS. Interestingly, in benign partial epilepsy in childhood, Wolff et al. reported that a left perisylvian focus estimated by MEG was associated with lower performance in language tests [29]. Our regression analysis revealed that: (1) a dipole cluster located on the SMG was associated with relatively reduced effects on FIQ, and (2) cases with a dipole cluster located only on the right side showed relatively less-affected PO scores.

In our study, 3 of 9 cases with an RA cluster showed dysarthria, in contrast with the 0 of 5 cases with an

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SMG cluster. This difference likely reflects the function of the perisylvian region of the RA. Thus, there may be subclinical fine motor functional impairment in cases with an RA cluster, although we did not examine this. In adults, symptoms associated with injury to the SMG include conduction aphasia [30] and short-term memory impairment [31] on the dominant side, and visuo-spatial cognitive impairment on the non-dominant side. However, in the present study, none of the 5 patients with a dipole cluster located on the SMG exhibited conduction aphasia, and only 1 of 5 patients with a left SMG dipole cluster (case 7) showed geographical disorientation. Further, regression analysis showed that an SMG focus had no significant effect on FD, which includes 'digit span', or on PO. Thus, the symptoms of our patients with an SMG focus were different from that reported in adults. As described above, non-lesional ECSWS with an RA cluster and an SMG cluster may share the same epileptic network, or be derived from the same epileptogenic discharge. Thus, the reason for the association of the SMG cluster with relatively higher FIQ when compared with RA or other clusters is unclear. We suggest that motor dysfunction such as dysarthria in cases with an RA cluster may limit the ability to perform the tasks in the WISC-III. Future studies in cases and with detailed examination on fine motor functions are required to asses this hypothesis.

As all our patients were right-handed, their dominant hemisphere was theoretically left. Thus, we hypothesized that the ESES with a left-sided focus would mainly affect verbal function, and that the VC would decline. However, in our analysis, non-lesional ECSWS cases with only right sided clusters showed relatively less-affected PO scores compared with only left sided cluster or bilateral foci. In particular, ESES with a left-sided cluster was related to PO scores, in contrast to our hypothesis. Left hemispheric injury before 5 years of age was previously reported to cause a greater decrease in PIQ than in VIQ [18]. Gonzalez-Monge et al. [23] also reported that in congenital hemiplegic patients, left hemispheric injury showed a trend towards a lower PIQ than that for right hemispheric injury, especially in epileptic cases. Although these phenomena are difficult to interpret by conventional theory, it was hypothesized that the plasticity in the developing brain may maintain verbal function over non-verbal function (crowding theory [22–24]). This theory may be applicable to our study, although we were unable to identify the actual dominant hemisphere or prove the migration of verbal function. Thus, the mechanism of the relative decline in PO scores in patients with a left-sided cluster is unclear. Nevertheless, the influence of ESES on cognitive function in younger children may be different from that of other focal epilepsies of older children or adolescents, likely because of brain plasticity.

4.3. Long-term prognosis

Valproate acid, benzodiazepines, and steroids are typically used for treatment of ECSWS. Our patients were also treated with other drugs including sultiame, zonisamide, and ethosuximide, while 3 patients in the good prognostic group and 2 patients in the poor prognostic group were treated with methyl-prednisolone pulse and oral prednisolone, although this was not standardized, making it difficult to assess the effects of each drug independently.

Long-term prognosis was verifiable in 12 cases. In 4 cases, the FIQ scores at the period of ECSWS diagnosis were <70, and these cases required special education for intellectual disabilities after standard education. By contrast, all 8 cases with FIQ scores >70 at the period of ECSWS diagnosis entered regular high-school. There were no differences in the duration of active epilepsy or EEG abnormality between these groups. These findings are consistent with those of Japaridze et al. [9], and imply that the long-term prognosis of ECSWS mainly depends on the intellectual level at diagnosis, with less influence of the treatment process. From our regression analysis, cases with clusters only on the right SMG at ECSWS diagnosis may show favorable intellectual prognosis, which was fitted in such cases (case 5, 6, and 14).

5. Conclusion

In this study, we found that an ECD cluster (estimated with MEG) located on the SMG was associated with a relatively less-affected FIQ score, while a cluster located on the left hemisphere was associated with a relatively lower PO score than for the right sided cluster only, at the period of diagnosis in patients with non-lesional ECSWS. These data suggest that in non-lesional ECSWS, the effect of epileptic discharges on cognitive function may be different from that in adults. Rather, it is similar to epilepsies associated with congenital or early infantile brain insults. However, due to the limitation of our study, we could not explain the mechanism of our results sufficiently. Future studies are required to examine the relationship between brain plasticity and cognitive dysfunction in ECSWS. Our results showed that an earlier onset of epilepsy (first unprovoked seizure) severely affected intellectual ability at the period of ECSWS diagnosis. Further, full recovery of intelligence was uncommon, even after EEG normalization. Thus, early identification and treatment of ESES is important for preventing a decline in intellectual abilities, and physicians should consider the possibility of progression to ECSWS in suspected benign partial epilepsies of childhood.

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Conflict of interest

The authors declare no conflict of interest associated with this manuscript.

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