electrodes. MEG data were recorded for >1 h per patient, collecting data in 4-min blocks at HU, NCNP and TU. At HSC, MEG was recorded in 15 two-minute blocks for a total of 30 min [10]. Patients were lying in the supine position. Sedative agents were used for uncooperative patients. The relative position of the head and the MEG sensors were determined by attaching three small head-position indicator coils to the head. The positions of the coils were digitized and subsequently recorded by the MEG sensors for co-registration with 1.5 T (tesla)/3 T magnetic resonance image (MRI) with high-resolution sequences.

2.4. MEG source analysis

MEG data were digitally filtered using a band filter of 3–30 Hz at HU, NCNP and TU, or at 3–70 Hz at HSC for offline analysis. Segments containing abnormal paroxysms were selected manually. Individual spikes were analyzed to localize the spike source per spike using an equivalent current dipole (ECD) model or dynamic statistical parametric mapping (dSPM) [11,12].

Table 1
Seizure profiles.

Seizure onset	1.3–8.8 years (median, 2.9 years)	
Initial seizures	Focal motor seizures	15 (83%)
	Absences/atypical absences	3 (17%)
Type of seizures in patient history	Drop attacks	16 (89%)
	Focal motor seizures	16 (89%)
	Epileptic negative myoclonus	14 (78%)
	Absences/atypical absences	11 (61%)
	Myoclonic seizures	10 (56%)
	Secondarily generalized tonic-clonic seizures	9 (50%)
	Focal sensory seizures	6 (33%)
	Epileptic spasms	2 (11%)

3. Results

3.1. Seizure profiles (Table 1)

Seizure onsets ranged from 1.3 to 8.8 years with a median age of 2.9 years. The seizures started as focal motor seizures in 15 patients (83%) and absences/atypical absences in three patients (17%).

All patients except one patient had multiple types of seizures in their seizure histories. Drop attacks, in which the precise seizure type remains unknown, were most common (16 patients, 89%). One patient (Patient 17) presented with a history of only drop attack seizures. Focal motor seizures (16 patients, 89%), ENM (14 patients, 78%), absences/atypical absences (11 patients, 61%), myoclonic seizures (10 patients, 56%) and secondarily generalized tonic-clonic seizures (nine patients, 50%) were seen in more than half of the patients (Supplementary videos 1 and 2). Focal sensory seizures (six patients, 33%) and epileptic spasms (two patients, 11%) were also reported.

3.2. Past and family history

There was no past history of epilepsy before the seizure onset in any of the 18 patients, while three patients (17%) had a positive family history of febrile seizures.

3.3. Cognitive functions

Cognitive function was evaluated in 15 patients. All 15 patients had the evaluations while they presented with ENM. A developmental quotient results ranged from 54 to 85 in five patients. The full-scale intelligence quotient test (Wechsler Intelligence Scale for Children) results ranged from 53 to 103 in 10 patients.

3.4. MRI

No patient showed an abnormality on MRI.

3.5. EEG (Fig. 1)

EEG showed interictal centro-temporal spikes in all 18 patients. Continuous generalized and/or centro-temporal spike and waves during sleep were also noticed in all patients. When video EEG captured ENM, generalized high-amplitude spike or polyspikes, and waves were associated with a brief attenuation of EMG activities corresponding to muscle atonia in 12 patients (Supplementary video 1). Absences/atypical absences showed generalized and irregular spike and slow waves around 3 Hz on EEG in 16 patients (Supplementary video 2).

3.6. MEG (Fig. 2 and Table 2)

MEG localized MEGSSs over both Rolandic and sylvian fissures in eight patients, the peri-sylvian region alone in five patients, and the peri-Rolandic region alone in four patients. One patient had MEGSSs in the left parieto-occipital region, even though EEG showed left centro-temporal spikes (Patient 6). Most spike sources were oriented perpendicularly to either the Rolandic or sylvian fissure. The spike sources demonstrated identical orientations in 11 patients (61%). MEGSSs were located in bilateral hemispheres in 10 patients (56%) and in a

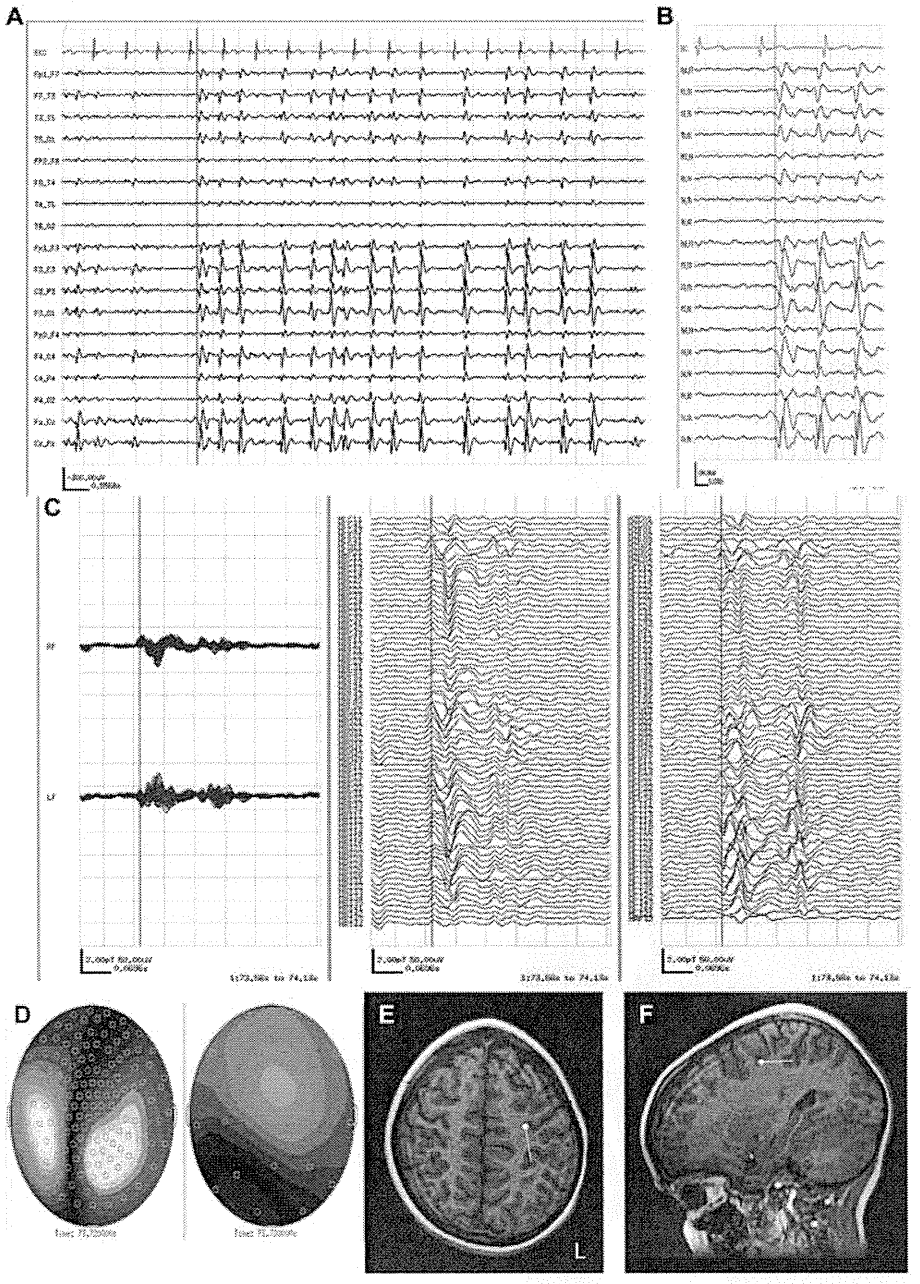

Fig. 1. MEG and EEG in case 18. (A) A–P bipolar EEG shows continuous spike and waves during sleep at the time of MEG study (low frequency filter, 3 Hz; high frequency filter, 70 Hz). (B) The same EEG of A is expanded to demonstrate left centro-temporal spikes preceding to the right central spikes after the red cursor. (C) 151 MEG channels are labeled by two colors (red for right hemisphere and blue for left hemisphere), and show the view of overlay (left), right channels (middle), and left channels (right). MEG shows more complex polyspikes than EEG on the overlay left channels. Note the MEG spikes (red cursor) leading to EEG spikes (behind the red cursor) on B. (D) MEG topography (left) and EEG topography (right). Note that magnetic and electric topographies are perpendicular to each other. (E) Axial MRI shows MEG spike source at the time of red cursor at the left Rolandic region (circle, position; tail, orientation, and moment). (F) Sagittal MRI shows the same MEG spike source of (E) at the left Rolandic region. The equivalent current dipole (spike source) is oriented horizontally, projecting negativity towards the frontal region and positivity towards the parietal region, corresponding to the EEG topography (D, right). (For interpretation of color in Fig. 1, the reader is referred to the web version of this article)

unilateral hemisphere in eight patients (44%). In all 10 patients with bilateral MEGSS, the MEGSS showed identical patterns and locations in the both hemispheres. ECD could not be estimated in one patient due to diffuse right hemispheric discharges without leading spikes. Therefore, we applied dSPM and localized the MEGSSs in the right sylvian fissure (Patient 7). Seven patients underwent multiple MEG studies. Six patients with

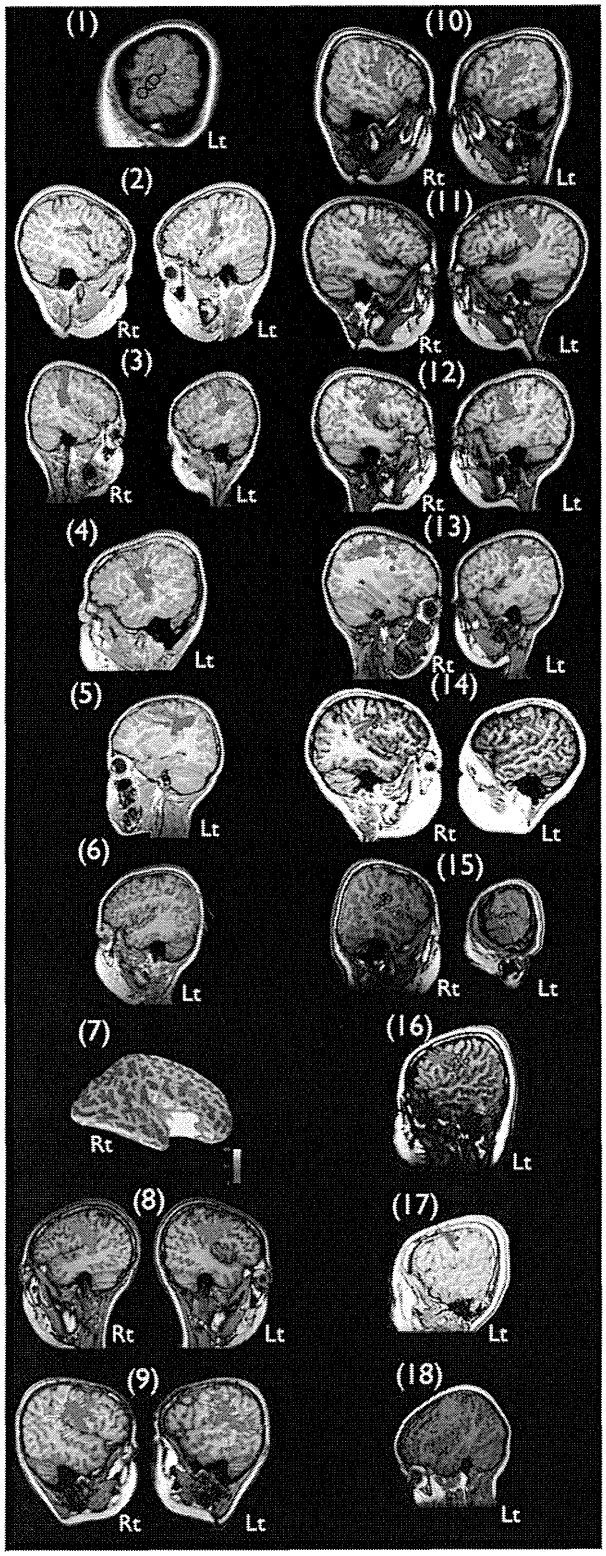

Fig. 2. MRI with MEG spike sources in 18 cases. Red circles demonstrate the source of MEG spikes. Tails indicate orientations and moments of the MEG spike sources. Case 7 shows dynamic statistical parametric mapping. The color bar indicates the P value, ranging from gray, 1×10^{-1} to yellow, $1 \times 10^{-4.3}$. (For interpretation of color in Fig. 1, the reader is referred to the web version of this article)

bilateral MEGSS became unilateral MEGSS. One patient showed consistent unilateral MEGSS. Six patients showed no MEGSS at the last MEG study when they were seizure free.

3.7. Treatments

All 18 patients were administered multiple antiepileptic medications ranging from 2 to 12 medications (mean 5.8) during their courses. Ethosuximide (ESM) succeeded in controlling various seizure types of ABPE, especially ENM and absences/atypical absences in 14 patients (78%); of these, all achieved seizure freedom after ESM was started, and 11 (89%) of the 14 were still on ESM at the last follow-up. Two of three patients in whom ESM was discontinued were no longer on any antiepileptic medication. CBZ was initially started in 16 patients (89%), but 14 (88%) experienced worsening of seizures after CBZ was initiated, and the treatment was discontinued. Two patients were seizure free on a combination of CBZ and ESM (Patient 6) or CBZ, ZNS and CLB (Patient 8). Valproic acid (VPA) was tried in 16 (89%) patients, and six of these (38%) were still on VPA at the last follow-up. Other medications tried included zonisamide (10 patients, 56%), clobazam (10 patients, 56%), clonazepam (eight patients, 44%) acetazolamide (five patients, 28%), phenytoin (five patients, 28%) and diazepam (four patients, 22%). The medications still being used at the last follow-up consisted of zonisamide in 3/10 patients (30%), clobazam in 4/10 patients (40%), clonazepam in 3/8 patients (38%), acetazolamide in 2/5 patients (40%) and diazepam in 2/4 patients (50%).

Two patients underwent epilepsy surgery. Patient 8 underwent cortical excision over the left supra-marginal gyrus at the age of 12 years. Surgical pathology revealed microdysgenesis with increased ganglion cells. She achieved 75–90% seizure reduction after the surgery, and was seizure free on three medications at 17.5 years old. Anterior two-thirds corpus callosotomy was performed at the age of 6 years for drop attacks in Patient 9. The patient was seizure free on two medications at 10 years old.

3.8. Seizure outcome

The age at last follow-up of the 18 patients ranged from 5.4 to 17.5 years (median 11.8 years). All were seizure free, two patients (11%) without any medication. Five patients (28%) were only on one medication, including four patients with ESM. The remaining 11 patients had multiple medications; six were on two medications, four were on three medications, and one patient was on four medications. Among seven patients with multiple MEG studies, medication changes, cognitive results effected less prominent for MEGSS than seizure improvements.

4. Discussion

MEG localized a Rolandic-sylvian epileptic focus of ABPE.

In ABPE, interictal MEG revealed localized clusters of spike sources around the Rolandic-sylvian fissures corresponding to both centro-temporal spikes and CSWS on EEG. The identically clustered Rolandic-sylvian MEGSSs of interictal epileptic discharges in patients with ABPE suggested that the epileptic focus was located around the Rolandic-sylvian regions involving the motor cortex in most cases. In our series, the peri-sylvian region MEGSSs were also recorded in 13 of 18 ABPE patients. In contrast, MEGSSs in BECTS were specifically localized along the Rolandic region with definite identical orientations vertical to the central sulcus [8,9]. In the older children with BECTS, MEGSSs shifted to the lower part of the Rolandic region close to the operculum.

Kubota et al. [10] reported an ictal MEG study localizing the spike source of ENM with generalized EEG spikes at the sylvian fissure in one ABPE patient [7]. ENM was characterized by spike or polyspikes on EEG time-locked to attenuation of EMG activity, which corresponded to muscle atonia [6]. Series of ENM often caused atonic seizures. Both interictal and ictal MEGSSs indicate that a subset of the epileptogenic zones responsible for focal seizures and ENM in ABPE patients is localized around the Rolandic-sylvian regions. In contrast, MEGSSs in three patients with Lennox–Gastaut syndrome with ENM were localized over inconsistent and various brain regions that did not include the Rolandic-sylvian regions [13].

Table 2
MEG spike source localization.

Patients	Regions			Hemispheres	
	Rolandic	Sylvian	Other lobe	Bilateral	Unilateral
1		1			1
2	1	1		1	
3		1		1	
4		1			1
5	1				1
6			Occipital		1
7		1			1
8	1	1		1	
9	1	1		1	
10		1		1	
11	1	1		1	
12	1	1		1	
13	1	1		1	
14	1			1	
15	1	1		1	
16	1				1
17	1				1
18	1	1			1
Total	12	13		10	8

Fifteen of eighteen patients in this series presented with focal motor seizures at the onset, and these persisted in addition to multiple other seizure types developing in 16 patients. ABPE might also be confused diagnostically with BECTS as ABPE appears superficially similar on scalp EEG and also presents with focal motor seizures. In ABPE patients, MEGSS extended to peri-sylvian region in addition to Rolandic region or localized even peri-sylvian region alone.

4.1. MEG localized spike dipoles in CSWS of ABPE

Sleep EEG often shows almost-continuous generalized or centro-temporal spike and waves during sleep in ABPE patients, resembling CSWS. Another differential diagnosis of ABPE is epileptic encephalopathy with CSWS (ECSWS), and there are no reports of source localizations using MEG in patients with ECSWS. The role of MEG remains to be explored in this entity. Kelemen et al. [17] reported three patients with CSWS secondary to destructive lesions in the thalamus [14], and CSWS development was often observed in patients with a thalamic lesion, indicative of thalamo-cortical dysfunction with an epileptic network [15,16]. ESM can be efficacious for seizures in ABPE patients, especially for ENM [6]. In 13 (72%) of the 18 ABPE patients studied herein, ESM completely suppressed their ENM. In other studies, systemic administration of ESM significantly reduced spike and wave discharges in genetic absence epilepsy models [17–19]. Continuous and generalized slow spike and waves during sleep in patients with ECSWS have been associated with secondary bilateral synchrony with leading foci [20,21]. The CSWS in ABPE could also be due to secondary bilateral synchrony, but originating specifically from the Rolandic-sylvian regions. The effect of ESM on the clinical seizures and CSWS indicates that the epileptic substitute of thalamic and Rolandic-sylvian networks produce ABPE.

Patry et al. [22] reported six patients with ECSWS, and heterogeneous seizure types of ECSWS that comprise focal motor seizures, absences, and epileptic falls while awake [21] resemble those of ABPE. Consequently, it can be difficult to distinguish ABPE from ECSWS clinically not analyzing the localization of epileptic foci. Further investigation of MEG in ECSWS may therefore serve to differentiate epileptic sources in these patients and improve our understanding of the epileptic networks and mechanisms leading to the observed cognitive disabilities.

5. Conclusions

MEG localized spike dipoles of centro-temporal spikes and CSWS over the Rolandic-sylvian regions in ABPE, indicating that ABPE is the localization-related

epilepsy with Rolandic-sylvian onset seizures. In addition, the effects of ESM on ENM and atypical absences suggest the involvement of thalamo-cortical circuitry in the epileptic network. ABPE is a unique age-related epilepsy involving the Rolandic-sylvian plus thalamo-cortical networks in the developing brain of children.

Disclosure of conflicts of interest

The authors have no financial or personal relations that could pose a conflict of interest.

Acknowledgment

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.braindev.2012.12.011.

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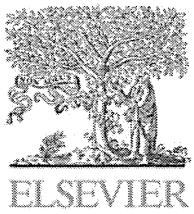

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Magnetoencephalographic analysis of paroxysmal fast activity in patients with epileptic spasms

Keitaro Sueda[a], Fumiya Takeuchi[b], Hideaki Shiraishi[a], Shingo Nakane[c], Kotaro Sakurai[d], Kazuyori Yagyu[a], Naoko Asahina[a], Shinobu Kohsaka[a], Shinji Saitoh[a,*]

[a] *Department of Pediatrics, Hokkaido University Graduate School of Medicine, Japan*
[b] *Department of Health Science, Hokkaido University School of Medicine, Japan*
[c] *Division of Magnetoencephalography, Hokkaido University Hospital, Japan*
[d] *Department of Psychiatry and Neurology, Hokkaido University Graduate School of Medicine, Japan*

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Magnetoencephalography;
Paroxysmal fast activity;
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Lennox–Gastaut syndrome;
Time-frequency analysis;
Short-time Fourier transform

Summary
Purpose: This study sought to demonstrate the origin and propagation of paroxysmal fast activity (PFA) in patients with epileptic spasms (ESs), using time-frequency analyses of magnetoencephalogram (MEG) PFA recordings.
Methods: A 204-channel helmet-shaped MEG, with a 600 Hz sampling rate, was used to examine PFA in 3 children with ESs. We analyzed MEG recordings of PFA by short-time Fourier transform and the aberrant area or high-power spectrum was superimposed onto reconstructed three-dimensional magnetic resonance images as moving images. One ictal discharge was collected. One child and one adult with PFA due to Lennox–Gastaut syndrome were also examined for comparison.
Results: All four PFAs in Patient 1 and five PFAs in Patient 3 were generated from one hemisphere. In Patient 2, four of seven PFAs were generated from one hemisphere and the remaining three were generated from both hemispheres. In Patient 3, one ictal MEG showed ictal discharges that were generated from the same area as the PFA, although the electroencephalogram showed no discharge. In Patients with Lennox–Gastaut syndrome, all 10 PFAs were generated from bilateral hemispheres simultaneously.

* Corresponding author at: Department of Pediatrics, Hokkaido University School of Medicine, North15 West7, Kita-ku, Sapporo 060-8638, Japan. Tel.: +81 11 706 5954; fax: +81 11 706 7898.
E-mail address: ss11@med.nagoya-cu.ac.jp (S. Saitoh).

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Conclusion: Short-time Fourier transform analyses of MEG PFA can show the origin and form of propagation of PFA. These results suggest that ESs are representative of focal seizures and the mechanism of PFA is different between ESs and Lennox–Gastaut syndrome.

Introduction

Epileptic spasms (ESs) are seizures, with axial movements longer than myoclonus and shorter than tonic seizures, which occur either in clusters or periodically. Epileptic spasms have been identified in patients with diverse epilepsies (Ohtsuka et al., 2001; Gobbi et al., 1987). In the International League against Epilepsy (ILAE) Classification (1989), ESs are classified as focal, generalized, or unclear (Berg et al., 2010) and the mechanisms of ESs are unknown (Engel, 2006).

Fast activity is one of the characteristic patterns of an ictal electroencephalogram (EEG) in ESs (Watanabe et al., 2001). Paroxysmal fast activity (PFA) has been described by Brenner and Atkinson (1982), and is characterized by paroxysms of 1–9 s in duration, of high frequency (10–25 Hz) rhythmic activity, preceded or followed by generalized sharp and slow wave complexes. The paroxysms are widespread in distribution and bilaterally synchronous over both hemispheres, but may not always be generalized. Shifting asymmetries are common, but rarely the pattern may show persistent amplitude asymmetry and may be unilateral or even focal. PFA is seen most often in patients with Lennox–Gastaut syndrome (LGS), but is sometimes seen in patients with localized-related epilepsy, such as frontal lobe epilepsy or temporal lobe epilepsy (Markand, 2003).

Markand (2003) considered PFA to be a subclinical discharge. A magnetoencephalogram (MEG), which provides higher spatial and temporal resolution, may provide a method for analyzing PFA, which compensates for the deficiencies associated with EEG. The aim of this study is to describe the localization of MEG discharges corresponding to EEG PFA using short-time Fourier transform (STFT), a method of time-frequency analysis, in order to assess the mechanism of ESs.

Patients and methods

Patients

Three patients at Hokkaido University Hospital were enrolled in this study. The three patients had refractory ESs with multiple PFA on EEG. Two patients who had been diagnosed with LGS with multiple PFA were also enrolled in this study to compare the morphology and mechanism of each PFA. The clinical profiles of the five patients are summarized in Table 1. Tonic seizures, atypical absences and slow spike-waves, with cognitive deterioration were diagnostic of LGS (Arzimanoglou et al., 2009). All patients underwent magnetic resonance imaging (MRI), scalp ictal EEG, scalp interictal EEG and ^{99m}Tc L-ethyl cysteinate dimer single photon emission computerized tomography (^{99m}Tc-ECD-SPECT). The parents of all patients gave written informed consent for the study.

Patient 1
Patient 1 was a 6-year-old boy who had daily seizures. At 5 months of age, he began to have spasms with bilateral upper limbs contraction and head nodding. His EEG showed hypsarrhythmia and he was diagnosed with West syndrome. His MRI was normal. After adrenocorticotrophic hormone (ACTH) therapy, his seizures were resolved with valproate (VPA) and clobazam. At the age of 26 months, he began to have weekly seizures with sudden tonic posture of the extremities, complex partial seizures and spasms. His seizures were symmetric from clinical findings. His EEG showed bilateral central–parietal spikes. His seizures were refractory regardless of various antiepileptic drugs (AEDs): VPA, zonisamide (ZNS), phenytoin (PHT), carbamazepine (CBZ) and phenobarbital (PB). At the age of 36 months, interictal EEG showed Cz–Pz spikes and bilateral frontal spike and wave complexes. At the age of 50 months, interictal EEG showed PFA and bilateral Cz–Pz spikes. Ictal EEG showed fast rhythmic activity at the right central and left posterior temporal–occipital regions, followed by generalized spike and slow wave complexes. He had severe mental retardation. At the age of 6 years, he was referred to our hospital. He was diagnosed with symptomatic generalized epilepsy. Magnetic resonance imaging showed mild brain atrophy, while ^{99m}Tc-ECD-SPECT showed hypoperfusion bilaterally in the frontal lobes.

Patient 2
Patient 2 was a 10-year-old boy who had daily seizures. At the age of 5 months, he began to have spasms with bilateral upper limbs contraction and head nodding. His EEG showed hypsarrhythmia and he was diagnosed with West syndrome. After ACTH therapy, his seizures were initially resolved, but relapsed after 10 months. His spasms were symmetric from clinical findings. At the age of 3 years, asymmetric tonic seizures appeared which were refractory to various AEDs (VPA, PHT, ZNS, and CZP). He had severe mental retardation. At the age of 10 years, he was referred to our hospital. At this time, MRI showed mild brain atrophy. Interictal EEG showed PFA and bilateral diffuse polyspike and diffuse spike and wave complexes. Ictal EEG showed right central–parietal polyspikes and subsequent desynchronization. Bilateral hypoperfusion of the frontal lobes was shown by ^{99m}Tc-ECD-SPECT. He was diagnosed with frontal lobe epilepsy according to the neuroimaging and electro-clinical findings.

Patient 3
Patient 3 was a 19-year-old woman with daily seizures. At the age of 2 months, she began to have spasms with bilateral

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Table 1 Patient profiles, MRI, EEG, interictal ECD SPECT findings.

	Age and sex	Sz onset	Sz type	Sz frequency	MRI findings	Interictal EEG	Ictal EEG	Interictal ECD SPECT	First diagnosis before MEG
Patient 1	6 y M	5 m	Epileptic spasms CPS Tonic posturing	Weekly	Brain atrophy	PFA Bil F SPW Bil C-P spikes	rt C. Lt pT polyspike →Diffuse spike	Bil F hypoperfusion	SGE
Patient 2	10 y M	5 m	Epileptic spasms Asymmetric tonic seizure Atypical absence	Daily	Brain atrophy	PFA Diffuse SPW	rt C-P polyspike →Desynchronization	Upside F hypoperfusion	FLE
Patient 3	19 y F	2 m	Epileptic spasms Myoclonic seizure Tonic posturing	Daily	NP	PFA Bil F dominant diffuse spikes and SPW	Desynchronization	Bil F-Tp hypoperfusion (L dominant)	SLRE (Undetermined localization)
Patient 4	14 y M	7 m	GT Atypical absence Astatic	Daily	Bil O gliosis	PFA Diffuse slow spike-waves	ND	Bil Tp-O hypoperfusion	Lennox–Gastaut syndrome
Patient 5	27 y F	11 y	Falling Atypical absence GT	Daily	Brain atrophy	PFA Diffuse slow spike-waves	Diffuse polyspike →Diffuse SPW	Bil Tp-O hypoperfusion	Lennox–Gastaut syndrome

Abbreviations: Sz, seizure; M, male; F, female; Lt, left; Rt, right; Bil, bilateral; ND, not done; SPW, spike and wave complex; NP, nothing particular; F, frontal; C, central; P, parietal; O, occipital; pT, posterior temporal; mT, mid temporal; SGE, symptomatic generalized epilepsy; FLE, frontal lobe epilepsy; SLRE, symptomatic localization related epilepsy; CPS, complex partial seizure; GT, generalized tonic seizure.

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upper limbs contraction and head nodding and her EEG showed hypsarrhythmia. She was diagnosed as having West syndrome. After ACTH therapy, her seizures were initially resolved however they relapsed after a while. At the age of 2 years, she had tonic posturing of the upper limb and myoclonic seizures and her seizures were refractory to various AEDs (VPA, CBZ, CZP, PB, acetazolamide and nitrazepam) as well as ketogenic diets. At the age of 17 years, her seizures became ESs and tonic seizures. These seizures were symmetric from clinical findings, but her head deviated to left occasionally. Her interictal EEG showed PFA and bilateral frontal dominant diffuse spikes. Ictal EEG showed diffuse desynchronization in her ESs. At 19 years of age, ^{99m}Tc-ECD-SPECT showed hypoperfusion in the right frontal and temporal lobes dominantly. She was diagnosed with symptomatic localization-related epilepsy

Patient 4

Patient 4 was a 14-year-old boy with daily seizures. At 7 months of age, he had episodes of upper eye deviation with cyanosis and apnea. Phenobarbital and CBZ were administered because his EEG showed focal spikes and his seizures were resolved. At the age of 11 years, he had tonic seizures, drop attacks and atypical absences. Interictal EEG showed slow diffuse spike and waves and PFA, and he was diagnosed as having LGS. Magnetic resonance imaging showed gliosis bilaterally in the occipital and parietal lobes, and ^{99m}Tc-ECD-SPECT showed hypoperfusion in the area where the gliosis existed.

Patient 5

Patient 5 was a 27-year-old woman who had daily seizures. When she was 11 years old, she began to have weekly atypical absence seizures. Her seizures were refractory to various AEDs (VPA, CBZ, PHT, ZNS and clobazam). At the age of 15 years, she began to have tonic seizures with falling. She had mental retardation and was blind because of congenital cataracts. She was diagnosed with LGS. At the age of 27 years, MRI showed mild brain atrophy. Her EEG showed diffuse slow spike and wave complexes and PFA. Ictal EEG corresponding to her tonic seizures showed a diffuse fast rhythm and subsequent diffuse slow spike and wave complexes, while ^{99m}Tc-ECD-SPECT showed bilateral hypoperfusion of the temporal–occipital lobes.

Methods

Magnetoencephalogram recordings

Magnetoencephalograms were recorded by 204-channel helmet-shaped superconducting quantum interference devices (SQUIDs) (Neuromag Vectorview; Elekta-Neuromag, Co. Ltd., Stockholm, Sweden) with pairs of orthogonal planar gradiometers at 102 locations. The recordings were carried out in a magnetically shielded room. The patient lay in a supine position. The MEG data were collected for almost 40 min for each patient with a 600 Hz sampling rate. Scalp EEG was recorded simultaneously using the international 10–20 system with video monitoring. EMG at deltoid and ECG are recorded simultaneously. All patients took intravenous thiopental sodium for sedation to avoid motion artifact. Administration of thiopental sodium is routine and accepted procedure for sedation of child or handicapped patients in Hokkaido University Hospital.

Magnetoencephalogram data analysis

The MEG data were filtered for offline analysis with a band pass of 3–100 Hz. PFA is defined as assumption of rhythmic activity with four times heightened amplitude from background activity for more than 200 ms.The segments of MEG data that contained PFA were manually selected with one second in the vicinity of PFA to obtain whole PFA. The single dipole method (SDM) was used to try to analyze single spikes, to determine the distribution of the genesis of the spikes. PFA of MEG was analyzed by STFT to determine a specific frequency band and its localization.

Single dipole method

Dipole-fit software (Neuromag, Helsinki, Finland) was used to calculate the equivalent current dipoles (ECDs). We accepted significant ECDs with more than 70% of goodness of fit and between 100 and 800 nAm of dipole moment. Goodness of fit is a measure of how well the ECD model explains the measured signals. Acceptable ECDs were superimposed on the MRIs.

Short-time Fourier transform analysis

The STFT method was used to demonstrate the distribution of MEG rhythmic activities (Oppenheim & Schafer, 1999; Sueda et al., 2010). The MATLAB program (MathWorks, Natick, MA) was used to execute the STFT for the MEG signals. Each signal was divided into small sequential frames and fast Fourier transform applied to each frame.

In the present study, the STFT was implemented using a 256-point window. The time of each window was 426.7 ms (i.e., 256 points × 1000 ms/600 Hz). The window was shifted every four points which corresponded to 6.7 ms (i.e., 1000 ms/600 Hz × 4 points). Fast Fourier transform was applied to each window. This process was repeated for all the signals that were selected. The time–frequency distribution can be displayed as a graph as shown in Fig. 1C.

A spectrum was considered to be aberrant when it was observed in the graph to be isolated from the background frequency spectrum. An aberrant frequency spectrum on the graph was superimposed onto a reconstructed three-dimensional (3D)-MRI. The power spectrum of these aberrant frequency spectrums was located at the intersection of the line beneath the planer gradiometer coil and brain surface.

If there was a broadening of the frequency spectrum, the high-power spectrum, which could be seen as the red color on the graph, was selected. The high-power frequency spectrum was superimposed onto a reconstructed 3D-MRI. The location of the PFA origin was decided from the reconstructed 3D-MRI.

The time onset of the PFA in each hemisphere was decided when the oscillation emerged in the reconstructed 3D-MRI which could be seen in yellow or red area. The time

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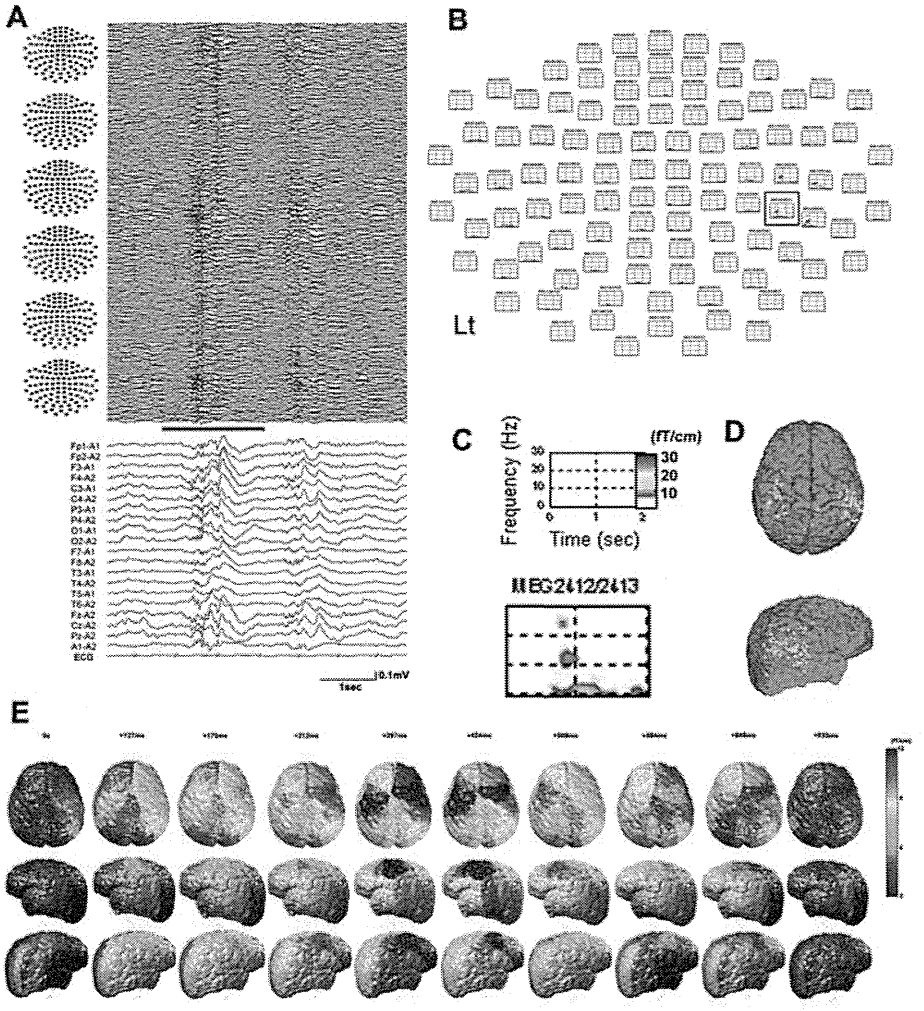

Fig. 1 (A) (Patient 1) Bottom panel demonstrates diffuse paroxysmal fast activity (PFA) of the electroencephalogram (EEG) and top panel shows the corresponding 204-channel magnetoencephalogram (MEG). (B) Short-time Fourier transform (STFT) graph of MEG PFA corresponding to the blue bar of (A). (C) Power spectrogram of MEG electrode 2412/2413 (black square in STFT graph B) using STFT to show the wide range of oscillations from 10 to 25 Hz. (D) Equivalent current dipoles are scattered bilaterally in the parietal region. (E) Specific oscillations at 10–25 Hz are generated in the right front–parietal area and propagated to the left front-parietal area in the superimposed three-dimensional magnetic resonance moving image of (B).

difference between PFA generation in each hemisphere was calculated using that time onset.

Magnetic resonance imaging

Magnetic resonance images were acquired with a 1.5 T high-resolution MRI scanner (Magnetom VISION, Siemens AG, Erlangen, Germany) for diagnostic purposes and co-registration with MEG data. Axial T1-weighted imaging (WI), T2–WI, fluid-attenuated inversion recovery (FLAIR), and coronal FLAIR sequences were performed.

Single photon emission computerized tomography

Interictal ^{99m}Tc-ECD-SPECT was performed for all patients. We used a ring-type SPECT scanner (Headtome-SET070; Shimadzu Corp., Kyoto, Japan).

Results

Table 2 summarizes the number of PFAs, pattern of PFA and origin of PFA for each patient with ESs. All four PFAs in Patient 1 and five PFAs in Patient 3 were generated from one hemisphere. For Patient 2, four out of seven PFAs were generated from one hemisphere and the remaining three were generated from both hemispheres simultaneously.

For patients with LGS (Patients 4 and 5), 10 PFAs were recorded, and all were generated from both hemispheres synchronously.

Patient 1

Four PFAs were captured during the recordings in Patient 1. Single dipole analysis was used for the spikes, but ECDs were not clustered. The results showed that his epileptiform

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Table 2 Paroxysmal fast activity and Ictal EEG, MEG findings.

	Number	Pattern of EEG	Number	Origin in MEG	Number
Patient 1	4 PFA	PFA → PFA	2	rt F-P	2
		Single PFA	2	rt F-P	2
Patient 2	7 PFA	PFA → desyn→PFA	3	rt F-P	2
				bil F	1
		rt F-C spike → desyn→PFA	1	bil F	1
		Single PFA	2	rt F-P	2
		PFA → desyn	1	bil F	1
Patient 3	5 PFA	PFA → desyn → PFA	1	rt C-P	1
		PFA → desyn	2	rt F-C-T	1
				rt C-P-T	1
		Single PFA	2	rt F-C	1
				rt C-P-T	1
	1 ictal	No finding	1	rt C-P-T	1

Abbreviations: PFA, paroxysmal fast activity; desyn, desynchronization; rt, right; bil, bilateral; F, frontal lobe; C, central; P, parietal lobe; O, occipital lobe; T, temporal lobe.

discharges were not suitable for single dipole analysis (Fig. 1D). His MEG showed PFA corresponding to the EEG PFA in the bilateral frontal–parietal areas (Fig. 1A, top panel). Analysis using STFT showed a significant power spectrum in the range from 10 to 30 Hz (Fig. 1B and C). The 3D-MRI movie showed that all PFAs were generated in the right frontal–parietal lobe and propagated to the left frontal lobe discontinuously (Fig. 1E). The time differences of the PFA between the right and left hemisphere were 47–161 ms (mean, 129 ms).

Patient 2

Seven PFAs were captured during the recordings in Patient 2. Equivalent current dipoles were scattered throughout both hemispheres in the frontal-parietal lobes. The boy's MEG showed PFA corresponding to the EEG PFA bilaterally in the frontal area. Short-time Fourier transform analysis showed a significant power spectrum in the range from 10 to 30 Hz. The 3D-MRI movie showed that four of the seven PFAs were generated in the right frontal–parietal lobe and propagated to the left frontal lobe discontinuously. The time differences of the PFA between the right and left hemisphere were 73–149 ms (mean, 126 ms). However three PFAs were generated simultaneously from bilateral frontal lobes.

Patient 3

Five PFAs were captured during the recordings in Patient 3. Although ECDs were located in bilateral hemispheres, most ECDs were scattered in the right parietal area (Fig. 2E). The MEG showed PFA corresponding to the EEG PFA in the right central–parietal–temporal area (Fig. 2A, top panel). Analysis of PFA by STFT showed a significant power spectrum in the range from 10 to 25 Hz. The 3D-MRI moving image showed that PFA was generated in the right angular gyrus and propagated contiguously to the postcentral gyrus and superior parietal lobule (Fig. 2B).

Ictal EEG and MEG of ESs were obtained simultaneously (Fig. 2C). Short-time Fourier transform analysis before the onset of a clinical seizure showed a specific aberrant 10–18 Hz oscillation band, although the EEG showed no specific findings (Fig. 2C, shown in the blue line STFT 1). The 3D-MRI moving image showed that the specific oscillation band was generated in the right inferior parietal lobule (Fig. 2D). Analysis by STFT during the onset of a clinical seizure showed no specific aberrant oscillation (Fig. 2C, shown in the blue line STFT 2). The high-power area of the PFA was overlapped with the high-power area of the ictal paroxysmal discharge in the MEG.

Patient 4

Five PFAs were captured during the recordings in Patient 4. The ECDs were not clustered. The 204-channel MEG showed diffuse PFA in bilateral areas corresponding to the EEG PFA (Fig. 3A, top panel). The STFT analysis of the PFA showed that there was a wide range of PFA frequencies from 10 to 30 Hz (Fig. 3B). The power spectrogram of STFT showed constant high-power frequency at 10 Hz (shown in red on the power spectrogram in Fig. 3C). The 3D-MRI movie showed that all PFAs were generated simultaneously from bilateral hemispheres (Fig. 3D).

Patient 5

Five PFAs were captured during the recordings in Patient 5. The ECDs were not clustered. The 204-channel MEG showed diffuse PFA in bilateral areas corresponding to the EEG PFA (Fig. 3E, top panel). Short-time Fourier transform analysis of PFA showed that there was a wide range of PFA frequencies from 10 to 30 Hz, though the high-power frequency was 13–15 Hz (Fig. 3G). The 3D-MRI movie showed that all PFAs were generated simultaneously from both hemispheres (Fig. 3H).

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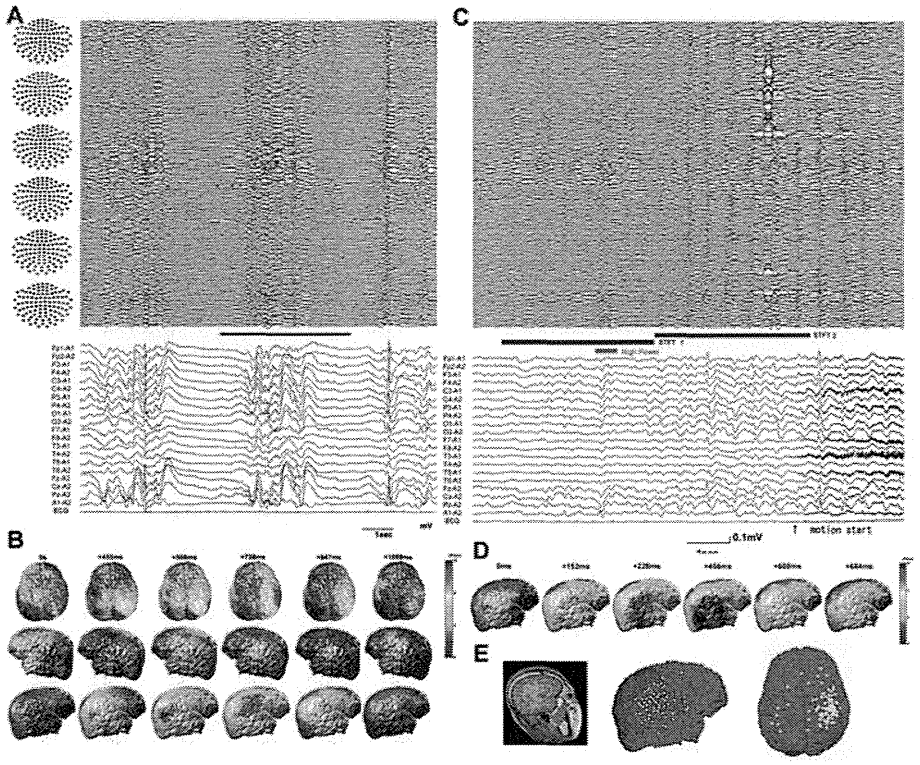

Figure 2 (A) (Patient 3) Bottom panel demonstrates interictal diffuse paroxysmal fast activity (PFA) of the electroencephalogram (EEG) with desynchronization before and after PFA, and top panel shows the corresponding 204-channel magnetoencephalogram (204ch-MEG). (B) Specific oscillations at 10–25 Hz are generated in the right parietal–temporal area in the superimposed three-dimensional magnetic resonance (3D-MRI) moving image. (C) Bottom panel demonstrates ictal EEG. Top panel shows the corresponding 204ch-MEG. Short-time Fourier transform graph shows specific oscillations in the right parietal–temporal area at the timing of the red bar. (D) Specific oscillations at 10–18 Hz are generated in the right parietal–temporal area in the 3D-MRI moving image. (E) Equivalent current dipoles are scattered in the right parietal region.

Discussion

In this study, we found that most of the PFA in patients with ESs was generated from a focal area of one hemisphere using STFT analysis of MEG data.

Recently several studies using different neuroimaging techniques, such as positron emission tomography (Chugani et al., 1994), SPECT (Munakata et al., 2004), and near-infrared spectrophotometry (Haginoya et al., 2002), have shown that focal areas play a role in the pathogenesis of ESs. Akiyama et al. (2005) reported that high frequency oscillations, recorded on digital video subdural EEG, were generated from the fronto-temporal region before and during clinical spasm and that focal cortical resection of the prominent area of high frequency oscillation eliminated the spasms. They suggested that ESs have the characteristics of partial seizures with secondary generalization. Panzica et al. (1999) reported that an asymmetric EEG pattern, mainly consisting of a rhythmic burst of fast activity, precedes both symmetric and asymmetric spasms. They suggested that a localized cortical origin of the ictal discharge gives rise to the spasms. In an electrocorticographic (ECoG) study, fast-wave burst activity was correlated with the clinical onset of spasms (Asano et al., 2005). RamachandranNair et al. (2008) reported that the sensory–motor cortex was part of the ictal-onset zone with ictal high-frequency oscillations in patients with ESs, and Asano and colleagues (2005) reported that ESs with fast-wave burst involvement of the sensory–motor cortex appeared to correlate with the severity of contralateral limb movements. Our MEG results support previous reports that a focal area plays a role in the pathogenesis of ESs.

All the patients were injected thiopental sodium intravenously. Thiopental constructs fast activity in the beta range (12–30 Hz). However, these fast activities are bilaterally symmetric and expanded in a frontal–central area, similar to those emerging during drowsiness (Feshchenko et al., 1997, 2004). The fast activity in Patients 1–3 were generated unilaterally. Those in Patients 4 and 5 were generated bilaterally symmetric, though not in a frontal–central area but in diffuse area. Therefore, the fast activity in our study was not attributed to thiopental.

Ictal and interictal PFA

We consider that analysis of interictal fast activity is equivalent to analysis of ictal fast rhythm, since all patients with ESs showed PFA which was followed by

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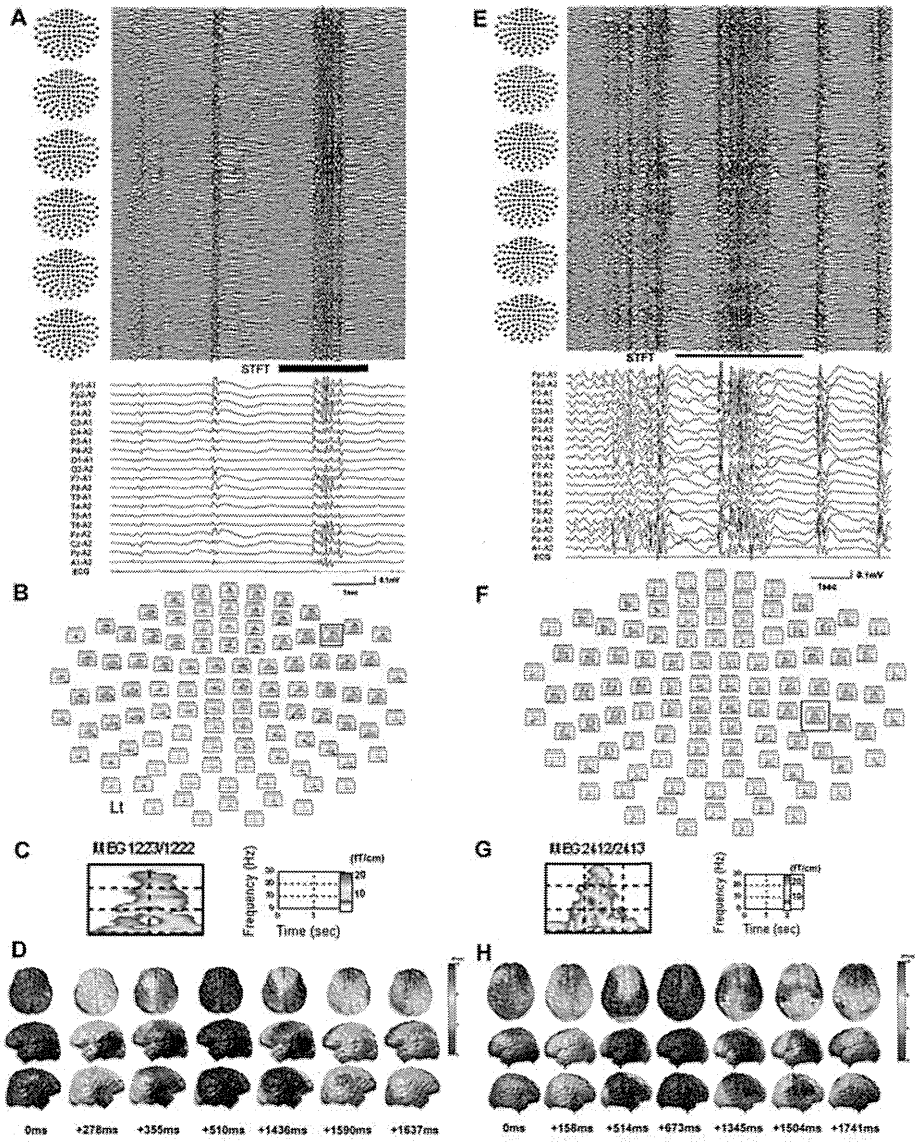

Figure 3 (Patients 4 and 5) Left panel: Patient 4 (A) bottom panel demonstrates diffuse paroxysmal fast activity (PFA) of the electroencephalogram (EEG) and top panel shows the corresponding 204-channel magnetoencephalogram (204ch-MEG). (B) Short-time Fourier transform (STFT) graph of MEG PFA corresponding to the black bar of (A) (C) Power spectrogram of MEG electrode 1223/1222 (black square in STFT graph B) corresponding to the black bar of (A) using STFT to show the wide range of oscillations from 10 to 30 Hz. High-power narrow band oscillations (shown in red) are found at 10 Hz. (D) Superimposed three-dimensional magnetic resonance (3D-MRI) moving image of patient 4 shows oscillations are generated in the bilateral parietal–temporal area and propagated to the whole area. Right panel: Patient 5 (E) Bottom panel demonstrates diffuse PFA of the EEG and top panel shows the corresponding 204ch-MEG. (F) STFT graph of MEG PFA corresponding to the black bar of (E) (G) Power spectrogram of MEG electrode 2412/2413 (black square in STFT graph F) corresponding to the black bar of (E) using STFT to show the wide range of oscillations from 10 to 30 Hz. High-power narrow band oscillations (shown in red) are found at 10–15 Hz. (H) Superimposed 3D-MRI moving image of patient 5 shows oscillations are generated in the bilateral parietal–temporal area and propagated to the whole area.

desynchronization with PFA. This interictal EEG pattern is similar to the ictal EEG pattern of ESs patients (Fusco and Vigevano, 1993; Kellaway et al., 1979). Desynchronization always appears after the clinical spasms and is considered to be a postictal rather than an ictal event (Watanabe et al., 2001).

We successfully recorded an ictal EEG and MEG in Patient 3 and STFT analysis of the ictal MEG showed a focal epileptogenic focus at part of the source of the interictal PFA. Eliashiv et al. (2002) reported that the ictal MEG-defined ictal-onset zone was smaller than the irritative zone defined by interictal MEG and equivalent or superior to invasive

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EEG recordings. In our case, the area of ictal MEG specific oscillation was not smaller but overlapped with the area of interictal PFA generation. This result is a good confirmation that analysis of interictal PFA is equivalent to that of ictal fast activity. The specific oscillation of the ictal MEG recording preceded the onset of the clinical seizure, which was confirmed in video monitoring, by several seconds in Patient 3. A similar pattern has been reported in an ictal ECoG study of ESs with focal spike or fast-wave bursts preceding the spasms in a subset of patients with ESs (Asano et al., 2005). They hypothesized that this focal activity may trigger the ESs, leading them to speculate that the cortex may be a trigger of the ESs, and the spasms associated with fast wave bursts may be derived from a cortico-subcorticocortical pathway rather than a cortico-cortical pathway. Our ictal MEG result supports their speculation and the period of no specific oscillation suggests that oscillations were propagating through a subcortical pathway. Moreover, Asano et al. (2001) reported that surgical resection of the focal area can eliminate the spasms. Electrocorticography is effective for the assessment of epileptic activity and to elucidate the ictal-onset zone. However, ECoG is invasive and, it is also difficult to decide on the placement of electrodes especially in non-lesional cases. We have recently reported that MEG fast activity correlates well with ECoG findings, and is therefore useful for presurgical evaluation (Sueda et al., 2010). Our method may be useful for deciding on candidates for epilepsy surgery by predicting the epileptic zone and placement of invasive electrodes.

Advantage over ECD model

The ECD model is based on the assumption that the brain activity generating the signals comprises only a small number of focal sources; therefore the ECD model is not suitable for analyzing cases whose activity seems to be generated from a wide area. Although we attempted to investigate the correlation between ECDs and PFA findings, ECDs were not clustered in Patients 1 and 2, and in Patient 3, ECDs were clustered at the right central–parietal region and the area of ECD and high-power area of MEG PFA were almost concordant. RamachandranNair et al. (2008) reported that all older pediatric patients with ESs had unilateral clusters of MEG spike sources like Patient 3, and a cluster of MEG spike sources represented the epileptogenic zone. However ECD analyses are insufficient to decide the epileptogenic zone in cases like Patients 1 and 2, since the ECD analysis is not suitable for propagated discharges. We consider that STFT analyses of MEG PFA are useful for detecting the epileptogenic zones of patients with ESs.

Comparison between the PFA of LGS and the PFA of ESs

PFA is seen most in patients with LGS hence we analyzed the PFA of LGS to compare with ESs. The STFT analyses and 3D-MRI movie of PFA in LGS showed that PFAs were generated from diffuse whole areas and simultaneously from bilateral hemispheres (Fig. 3). These results suggest that the mechanism of PFA is different between ESs and LGS.

For Patients 1 and 3, PFAs were generated from a focal area on one side of the hemisphere. We could predict the region for localization of epilepsy from the MEG findings and provide a diagnosis of symptomatic localization-related epilepsy, although Patient 1 had been diagnosed with symptomatic generalized epilepsy.

For Patient 2, three of the seven PFAs were generated bilaterally from the frontal areas simultaneously and four PFAs were generated from the right frontal–parietal area and propagated to the left frontal hemisphere. His seizure manifestation quite resembled LGS and his EEG was also described as having a diffuse fast rhythm and slow spike and wave complexes. But our current findings using MEG to examine PFA suggest that his right frontal area is affected dominantly and has an epileptogenic lesion. MEG PFA could be helpful for the precise evaluation of cases like Patient 2.

We considered that the findings in Patient 2 demonstrated the mechanism of secondary bilateral synchrony (SBS). Our STFT method would be useful to differentiate primary bilateral synchrony (PBS) from SBS. Distinguishing PBS from SBS is generally difficult using clinical findings or visual assessment of EEG or MEG data. The minimum transcallosal transferring time is reported as approximately 20 ms (Ono et al., 2002). Therefore, when the interval of the cortico-cortical propagation is longer than 20 ms, it could indicate transcallosal propagation, i.e., SBS. For Patients 1 and 2, the time difference between each hemisphere oscillation in PFA could be estimated as more than 20 ms, meaning SBS. On the contrary, for Patients 4 and 5, no time differences were present, so they had PBS. Although a few studies have shown that MEG can be used to analyze SBS with spike and wave complexes (Smith, 2004; Tanaka et al., 2005) these studies used SDM for their evaluation. As we have mentioned previously, the ECD model is difficult to use for PFA. The SDM analysis can be used for focal discharges, since equivalent dipoles can be calculated by solving the inverse problem with the definition of a single generator. Since STFT can be applied to any activity without the above calculations, our method can be useful for evaluating PBS and SBS.

Limitations

Short-time Fourier transform analysis is limited to patients who have aberrant frequency oscillation like PFA detached from background activity, and cannot reveal the depth of the source, because the planar gradiometers evaluate the magnetic field just beneath the sensor. However, unlike ECD and other spatial filtering methods, STFT can analyze the wide area oscillation and temporal changes without solving the inverse problem for source localization. This point is valuable for STFT analyses.

Conclusion

In conclusion, STFT analyses can show the origin and form of propagation of PFA on MEG. Analyses of MEG PFA using STFT suggest that ESs are one of the representative epileptic seizures of localization-related epilepsy. Analysis of PFA by STFT might be one of the most useful tools to define the classification of epilepsies and epileptic syndromes.

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Conflicts of interest

None of the authors has any conflict of interest to disclose.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Original article

Epidemiological study of Landau–Kleffner syndrome (LKS) in Japan

Makiko Kaga*, Masumi Inagaki, Reiko Ohta

National Institute of Mental Health, National Center of Neurology and Psychiatry, Japan

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Abstract

Objective: We aimed to determine the incidence and prevalence of LKS in Japanese children. *Methods:* A questionnaire was sent to all 3004 Japanese hospitals that have a department of pediatrics. The questionnaire asked for the number of first-visit LKS patients and LKS patients who were followed up at or visited their clinic during the past one year Vital statistics of the same year (2008) published by Ministry of Health, Labor and Welfare, Japan were referenced to calculate the estimated incidence and prevalence of LKS among Japanese children. *Results:* Chiefs of 1562 pediatric departments answered our inquiry (51.9% of returns). Six chiefs had one new LKS patient, aged 6–14 years. Thirty two patients with LKS were followed in the same period. The number of children with LKS less than 20 years of age who needed medical care was at least 23 and at most 31. Vital statistics of Japan 2009 revealed that the population of children aged 5–14 years was 11,861,464 and that aged 5–19 years was 18,007,968. *Discussion:* The number of the first-visit LKS patients was 6 in a year. We estimated the incidence of LKS in the 5- to 14-years-old Japanese population as about 1 in 978,000. The number of LKS patients aged 5–19 was estimated to range from 44.2 to 59.6 among a population of 18,007,968. This means the prevalence of LKS under medical care is roughly one in 302,147–407,420 children aged 5–19. This study is the first epidemiological estimation of the incidence and prevalence of children with LKS in Japan or, for that matter, in any other area. *Conclusion:* (1) Incidence of children with LKS aged 5–14 years was about 1 in a million in Japan. (2) Prevalence of children with LKS aged 5–19 and under medical care was one in about 300,000–410,000 in Japan. (3) This study constitutes the first epidemiological estimation of LKS in Japan.

Keywords: Landau–Kleffner syndrome (LKS); Japanese children; Incidence; Prevalence; Epidemiology

1. Introduction

Landau–Kleffner syndrome (LKS) was first reported as acquired aphasia with convulsive disorder in children in 1957 [1]. LKS is a rare neurological disease which emerges in patients around 6 years of age. The main symptom of LKS is auditory agnosia with apparent hearing impairment, regression of speech, and diffuse spike and wave complexes especially in sleep EEG. Those signs and symptoms usually continue for several years [1,2], and a limited number of patients have some auditory verbal sequelae after they reach adulthood [2].

Historically, more than four hundred English studies on LKS have been published as review articles or case reports, although one original paper described the characteristic symptoms of 5 children [1]. However, there has been no systematic epidemiological study in the literature.

The objective of the present research was to elucidate the incidence and prevalence of LKS in Japanese children by sending a questionnaire by mail to the hospitals where certified pediatrician(s and or) child neurologist(s) are employed.

* Corresponding author. Address: Tokyo Metropolitan Tobu Ryoiku Center, 3-3-25 Shinsuna, Koto-ku, Tokyo 136-0075, Japan.
E-mail address: kaga@ncnp.go.jp (M. Kaga).

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2. Methods

A questionnaire package was sent to all Japanese hospitals (3004 hospitals as of March 2009), which have a department of pediatrics. These hospitals are officially registered by Japanese law and are listed for the public at an Internet site managed by the Welfare and Medical Service Agency (http://www.wam.go.jp). The questionnaire asked for the number of first-visit LKS patients the hospital had diagnosed during the past one year (from August 1, 2008 to July 31, 2009). When the hospital had records of the relevant patient visits, we also asked for these patients' age and sex. We also asked for the number of patients who were followed up at their clinic during the same period. In the package, a document explaining our purpose and the definition of LKS (see Table 1) was enclosed to ensure the exact number of patients was obtained.

We analyzed the answers sent back to us during the next 3-month period in 2009. The vital statistics of the same year (2008) published by the Ministry of Health, Labor and Welfare, Japan [3] were referenced in calculating the incidence and prevalence of LKS among all children in Japan.

3. Results

The chiefs of 1562 pediatric departments answered our inquiry (51.9% of returns). Six patients (5 boys and 1 girl) newly diagnosed with LKS aged 6–14 years were reported to have visited the out-patient clinics.

Among 1562 pediatric departments, 26 chief pediatricians replied that they followed-up and saw 32 patients with LKS in the same period. Twenty-two (69%) of these were male. The eldest was 41 years old, and the ages of 8 patients were not described. The ages of the rest of the patients ($n = 23$) were distributed from 6 to 19 years of age. Thus, the number of children with LKS less than 20 years of age who needed medical care in one year was at least 23 (16 males and 7 females) and no more than 31.

Table 1
Explanation and definition of LKS. LKS is a rare neurological disease which begins around age 6 (mainly 2–10).

Signs and symptoms of LKS
(1) Apparent hearing impairment due to abnormal auditory perception (auditory agnosia or word deafness)
(2) Regression of speech, sometimes to sensory aphasia, then to total aphasia
(3) Above symptoms are sometimes associated with behavioral or character change
(4) Diffuse spike and wave complexes especially in sleep EEG
(5) Above signs and symptoms usually continue or show repeated exacerbation/remission in several years with complete recovery
(6) A limited number of patients have some auditory verbal sequelae after they reach adulthood

The vital statistics of Japan 2009 revealed that the population of children aged 5–14 years was 11,861,464 (5–9 years was 5,864,879 and 10–14 years was 5,996,585) [3]. The number of children aged 5–19 years was 18,007,968 (15–19 years was 6,146,504) [3].

4. Discussion

LKS is mainly a childhood disease, with onset in early childhood. Generally, patients' behavior such as their daily conversation grows more and more abnormal, and parents believe that their children have some extraordinary disease for which doctors should be consulted. If these doctors are family physicians, they are sure to recommend further evaluation at the local hospital, which has more facilities for a full work-up.

Thus, we assumed that every LKS patient visited a department of pediatrics at some point in their disease course.

Among the respondents to our questionnaire, the number of the first-visit LKS patients in Japan was 6 in one year. Their age range was 5–14 years. It is reasonable to speculate that if the 1442 (3004 minus 1562) non-answerers experienced LKS, the number would not exceed the ratio of 6 among 1562 departments. Therefore, 11.5 (6 plus 5.5) should be the maximum data of our survey of children from 5 to 14 years of age. Thus, the incidence of LKS in 5- to 14-years-olds was about 1 in 978,000 in Japan.

As above mentioned, the number of children (<20 years) with LKS who needed medical care in the year of study was at least 23 (16 males and 7 females) and no more than 31. Therefore, the number of LKS patients aged 5–19 can be assumed to have ranged from 44.2 (23 plus 21.2) to 59.6 (31 plus 28.6) among the total population of 18,007,968 children age 5–19. This means the prevalence of LKS patients under medical care was one in 302,147–407,420 children of this age group.

There have been no epidemiological reports of LKS in previous studies. The reason may stem from two aspects of LKS: epilepsy and childhood language disorder. From the epileptic point of view, their seizure types and characteristics are not specific to LKS. From the point of view of language disorders, clinical signs and symptoms are not well known even to pediatricians. Thus, our estimated incidence may be low. In this study, we were able to show the clinical features of LKS and obtain data from pediatricians who worked at hospitals and treated this disease.

This study is the first epidemiological estimation of the incidence and prevalence of children with LKS in Japan, or in any other area.

5. Conclusions

(1) The incidence of children with LKS aged 5–14 years was about 1 in a million (978,000) in Japan.

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(2) The prevalence of children with LKS aged 5–19 and under medical care was one in 302,147–407,420 in Japan.
(3) This constitutes the first epidemiological estimation of LKS in Japan.

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特集　小児脳神経外科の課題

脳形成異常と遺伝子

加藤　光広[1)]

1）山形大学医学部小児科学講座

Brain Malformations and Genetic Factors

Mitsuhiro Kato, M.D.[1)]

Department of Pediatrics, Yamagata University Faculty of Medicine

Historically, brain malformations have been classified based on a postmortem examination. The advancement and spread of neuroimaging techniques, particularly magnetic resonance imaging, has made it easier to identify many types of brain malformations, but it has also made classify them more complicated. Moreover, the unveiling of the genes responsible for brain malformations has dramatically changed the classification scheme itself and now most doctors have trouble following it. Although the relationship between genotype and phenotype is complicated, it can be divided into two types, locus heterogeneity and pleiotropy. One of the representative diseases demonstrating locus heterogeneity is holoprosencephaly, which shows an identical disorder of forebrain cleavage caused by 14 genes, such as *SHH* and *ZIC2*, involved in a ventrodorsal patterning of the early prosencephalon. The *ARX* gene shows a typical pleiotropic effect and its mutation causes a wide range of developmental disturbances ranging from severe brain malformations, such as hydranencephaly and lissencephaly, to nonmalformative forms of epileptic encephalopathies, such as Ohtahara syndrome and West syndrome, dyskinetic cerebral palsy, and nonsyndromic mental retardation with a strong genotype-phenotype correlation. Accurate diagnosis based on the most recent knowledge is critical for precise prediction as well as genetic counseling.

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Key words : brain malformations, gene analysis, locus heterogeneity, pleiotropy, interneuronopathies

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はじめに

画像診断技術の進歩と普及により生前から多くの脳形成異常が確認され，一部は外科的な治療対象になっている．その一方，遺伝子解析手法の進歩により脳形成異常の原因遺伝子が加速度的に同定され，脳形成異常の分類根拠は，歴史的に病理から画像，そして原因遺伝子へと軸足を移している．病変が片側性もしくは局在性で遺伝性要素は少ないと考えられていた疾患でも原因遺伝子が明らかにされ始めている．

本稿では，原因遺伝子同定と分子病態の解明が盛んな脳形成異常について最近の知見を紹介したい．

脳形成異常の分類

脳形成異常の分類は，1980年代以降MRIの開発と普及によって多種多数の脳形成異常が生前から診断されるようになり，病理分類のみでは区分されないものが増えてきた．また，1990年代以降には脳形成異常の原因遺伝子が次々に同定され，脳の発生に関する分子生物学的な新しい知見が集積されるようになった[5)]．従来の滑脳症Ⅰ型とⅡ型のような一見類似の形態異常でも，分子病態

連絡先：加藤光広，〒990-9585 山形市飯田西2-2-2　山形大学医学部小児科学講座

Address reprint requests to: Mitsuhiro Kato, M.D., Department of Pediatrics, Yamagata University Faculty of Medicine, 2-2-2 Iida-nishi, Yamagata-shi, Yamagata 990-9585, Japan

Table 1 Classification profile for malformations of cortical development (modified from ref. 1)

I. Malformations secondary to abnormal neuronal and glial proliferation or apoptosis
- A. Severe congenital microcephaly
- B. Megalencephaly
- C. Cortical dysgenesis with abnormal cell proliferation but without neoplasia (hemimegalencephaly, focal cortical dysplasias [FCD] type II, and tuberous sclerosis)
- D. Cortical dysgenesis with abnormal cell proliferation and neoplasia (DNET, ganglioglioma)

II. Malformations due to abnormal neuronal migration
- A. Malformations with neuroependymal abnormalities (periventricular heterotopia)
- B. Malformations due to generalized abnormal transmantle migration (lissencephaly and subcortical band heterotopia)
- C. Malformations presumably due to localized abnormal late radial or tangential transmantle migration
- D. Malformations due to abnormal terminal migration and defects in pial limiting membrane (Walker-Warburg syndrome, muscle-eye-brain disease, Fukuyama congenital muscular dystrophy, and congenital muscular dystrophy with cerebellar hypoplasia)

III. Malformations due to abnormal postmigrational development
- A. Malformations with polymicrogyria (PMG) or cortical malformations resembling PMG (schizencephaly)
- B. Cortical dysgenesis secondary to inborn errors of metabolism (mitochondrial and pyruvate metabolic disorders, peroxisomal disorders)
- C. Focal cortical dysplasias (without dysmorphic neurons, FCD types I, III)
- D. Postmigrational developmental microcephaly

はまったく異なることが明らかになり，現在は，病理所見に加え，主にMRI所見と脳の発生機序に基づき分類されている（Table 1）[1]．原因遺伝子同定と分子病態解明は継続途上であり，数年ごとに分類が更新され複雑性を増しているが，正確な診断は診療においても併発症と予後の予測や遺伝相談に必須であり，最新の分類を知る必要がある．

遺伝型と表現型の相関関係

遺伝子解析技術の進歩に伴い，脳形成異常原因遺伝子が多数同定され，原因遺伝子と脳形成異常の関連性が明らかになってきた．神経細胞移動異常症に限ってみても両者の関連性は交絡し，一見複雑であるが（Fig. 1），遺伝子と遺伝子発現の結果として観察される表現型の関係は，座位異質性（locus heterogeneity）と多面発現（pleiotropy）の2つに区分される．座位異質性とは，染色体上の遺伝子座位が異なる複数の遺伝子によって同一の表現型が認められる現象であり，座位異質性が強い場合は表現型による原因遺伝子の推定が困難になる．多面発現とは，一つの遺伝子によって一見無関係な複数の表現型をきたすことであり，同じ遺伝子の変異でも症状に変動が

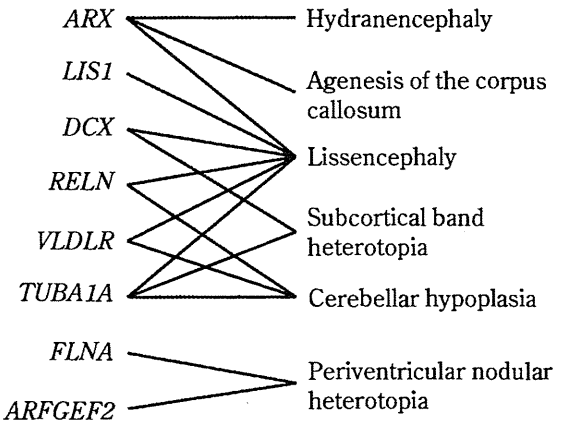

Fig. 1 Causative genes responsible for neuronal migration disorders
The left side shows the gene symbols linked with the associated disorders on the right side. Note that both *ARX* and *TUBA1A* show pleiotropy and that lissencephaly shows locus heterogeneity.

生じる．

座位異質性を示す代表的な脳形成異常として全前脳胞症が挙げられる（Fig. 2）．全前脳胞症は，左右の大脳半球を形成する前脳の腹側誘導が障害されて神経管がそのまま膨らみ，左右の分離が障害された状態である[11]．13