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Relationship between Migration and Outcome in Childhood Epilepsy Using Dipole Analysis

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Abstract ***Background:*** Clinical applications of the dipole localisation method have led to advances in evaluating the location of epileptic discharge. Therefore, we studied the relationship between migration and outcome to clarify the use of dipole analysis in patients with childhood partial epilepsy. ***Methods:*** The patients were 38 children, aged 2-14 years with partial epilepsy. We compared dipole tracing with the traditional scalp electroencephalogram (EEG) for evaluating the changes and migration of epileptic foci with age in childhood partial epilepsy as well as the relationship between migration and outcome. ***Results:*** Scalp EEG did not show a significant relationship between migration and outcome (p=0.65), but there was a significant relationship for dipole analysis (p=0.037). Lack of migration was correlated with a favorable outcome. ***Conclusions:*** Our results suggest that dipole analysis may be useful in assessing outcomes of childhood partial epilepsy.

Key words Childhood; Dipole tracing method; Migration of epileptic focus; Partial epilepsy; Scalp EEG

Introduction

Clinical applications of the dipole localisation method have resulted in advances in evaluating the location of epileptic discharge,[1,2] and dipole analysis is becoming a useful method for presurgical noninvasive evaluation of the epileptogenic region.[3] Homma et al[4] independently developed their own method called dipole tracing (DT). Since potential distributions on the scalp surface can be difficult to measure because of poor conductance of the skull, a realistic multiple-shell head model is necessary to accurately estimate the dipoles. The DT method using a realistic 3-shell (scalp-skull-brain) head model has been called SSB-DT.[5] Previous studies have demonstrated the use of dipole analysis. Ochi et al[6] developed a systematic approach for equivalent current dipole analysis using interictal spikes from a scalp electroencephalogram (EEG) in an effort to localise epileptogenic zones in children with extratemporal lobe epilepsy. Otsubo et al[7] compared EEG with magnetoencephalogram (MEG) dipoles for patients with intractable epilepsy. They showed that the combination of EEG and MEG dipole analysis provides more accurate and comprehensive information on epileptic activities than either method used alone, and it produces comprehensive information of not only epileptic discharges, but also epileptic neural behavior in the brain. Yoshinaga et al[8] performed dipole analysis of interictal spikes in epileptic patients using SSB-DT. Localisation of the epileptic focus estimated by dipole analysis was compared with regional abnormalities revealed by various neuroimaging techniques including single photon emission computed tomography, magnetic resonance imaging (MRI) and MR-spectroscopy, and by clinical manifestations. Furthermore, they investigated the distribution of stable and unstable dipoles

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in various epileptic syndromes, and reported that dipoles in patients with benign childhood epilepsy with centrotemporal spike foci (BCECT) have excellent stability compared with those of other epileptic syndromes.[9] They also examined the stability and locations of dipoles in patients with Panayiotopoulos syndrome.[10] We have previously described a 3-year-old patient with intractable epilepsy.[11] We consider that the DT method is useful for estimating the epileptic focus of childhood epilepsy.

According to Yoshinaga et al,[8-10] the dipoles in patients with benign childhood epilepsy, such as BCECT and Panayiotopoulos syndrome, have excellent stability compared with those of other epileptic syndromes, even if the focus of epileptic discharge on the scalp EEG has migrated to various areas during the course of the investigation. Therefore, we compared DT with traditional scalp EEG for evaluating the migration of epileptic foci as well as the relationship between migration and outcome in patients with childhood partial epilepsy.

Methods

The patients were 38 children (19 males and 19 females), aged 2-14 years (mean±SD, 8.2±3.6 years) with partial epilepsy. All subjects visited the Department of Pediatrics and Child Health, Nihon University Itabashi Hospital, Nihon University School of Medicine, between January 2000 and May 2010. All patients had a history of seizures including complex partial seizures or secondary generalised seizures, and all but one patient had simple partial seizures. They also all had a typical EEG pattern with stereotyped focal spikes in a previous EEG and normal MRI brain scans. In total, 29 patients showed normal development, while 8 patients had mild mental retardation (MR) and only a single patient had moderate MR. Each patient was followed up for at least 1 year, and for up to 7 years (mean±SD, 2.2±1.7 years). All patients in this study were medicated with anticonvulsants including carbamazepine (32 patients), zonisamide (4 patients) and valproic acid (2 patients). Among them, 11 patients had anticonvulsants added or they were exchanged with other anticonvulsants. In all cases, the patient's parents gave informed consent. The study was approved by the ethics committee of Nihon University Itabashi Hospital in accordance with the revised Declaration of Helsinki.

EEGs were recorded on 21-channel machines (EEG -1518 Neurofax; NIHON KOHDEN Co., Tokyo, Japan). We used the standard international 10-20 system with additional electrodes at Fpz and Oz referenced to the ears. The sampling rate of the EEG was 1 kHz. The onset and offset of each spike were determined by visual inspection of the computer display. We analysed the dipole localisations of EEG spikes selected by means of a single moving dipole inverse solution algorithm (SynaPoint; NEC Medical Systems, Tokyo, Japan). In this algorithm, the dipole variables, consisting of the location, orientation and amplitude in a head model, are iteratively adjusted to obtain the best fit between the recorded EEGs and the potentials produced by the assumed dipole, using a non-linear least-squares minimisation technique. The inverse solutions were obtained in a 3-shell spherical head model, with concentric layers representing the brain, skull and scalp. In this model, the ratios of the radius of skull to skin and of brain to skin are 0.92 and 0.87, respectively. The conductivity of the brain and scalp is 0.3 [1/(ohm* m)], and the conductivity ratio of the skull to brain is 0.0125.

Five interictal spikes were analysed in each patient. A window of 25 to 125 ms around the negative peak, through its rise and fall, was examined. The dipole fits occurred every 1 ms. We plotted the dipoles that showed a goodness of fit better than 95%. The dipole localisations were overlaid onto MR images of the patient's brain. MRI (Symphony, Siemens, Germany; 1.5 Tesla) yielded continuous 176 T1-weighted coronal slices with a thickness of 1 mm, a pixel size of 1 mm × 1 mm, and a 250 × 250 image matrix. SynaPoint software was used for super-imposition of the dipoles on the MR images (coronal, axial and sagittal).[6]

EEGs were recorded approximately every 6 months. We investigated the migration of epileptic foci for each patient. We defined the migration of epileptic foci between first and last tracings. We divided the distribution of epileptic foci determined by both EEG and DT to 3 areas (frontal, centroparietal, and occipital) at pre- and post-medication with anticonvulsants. We defined outcomes as follows: if the patient's seizures disappeared within 6 months, it was considered a favourable outcome; if the seizures were still present after 6 months, it was an unfavourable outcome. In this study, patients were regularly seen in our hospital and took medicine in accordance with our directions; therefore, their compliance was relatively favourable.

We tested whether migration of spike foci demonstrated by the DT method correlated better with outcome than migration determined by visual spike localisation based on scalp EEG. Fisher's exact test was used for statistical analysis with a $p<0.05$ level of significance.

Results

Dipole Analysis

Figure 1 shows the results of dipole analysis in a 6-year-old boy with complex partial and secondary generalised seizures. No abnormalities were seen on MRI. His EEG showed focal spikes in the left central to parietal area. Dipoles were localised to the left parietal region, corresponding to the early phase of the EEG spikes.

Distribution of Epileptic Foci

We found a distribution of epileptic foci that was age-dependent. Frontal foci occurred in 11 patients (29%) in all age groups, except for patients under 3 years, and they were especially dominant in patients older than 13 years. Centroparietal foci (including BCECT) were found in 16 patients (42%) in all age groups younger than 13 years, but were most prevalent in patients between 5 and 13 years of age. Occipital foci were observed in 11 patients (29%) in all age groups except for those under 3 years of age, but they were especially dominant in groups under 9 years of age.

Migration of Epileptic Foci During the Clinical Course

Using scalp EEG, migration of epileptic foci was observed in 6 of 38 patients (15.8%) during this study. Direction of foci migration was anterior (2/6, 33.3%) and posterior (4/6, 66.7%). This migration was found in patients

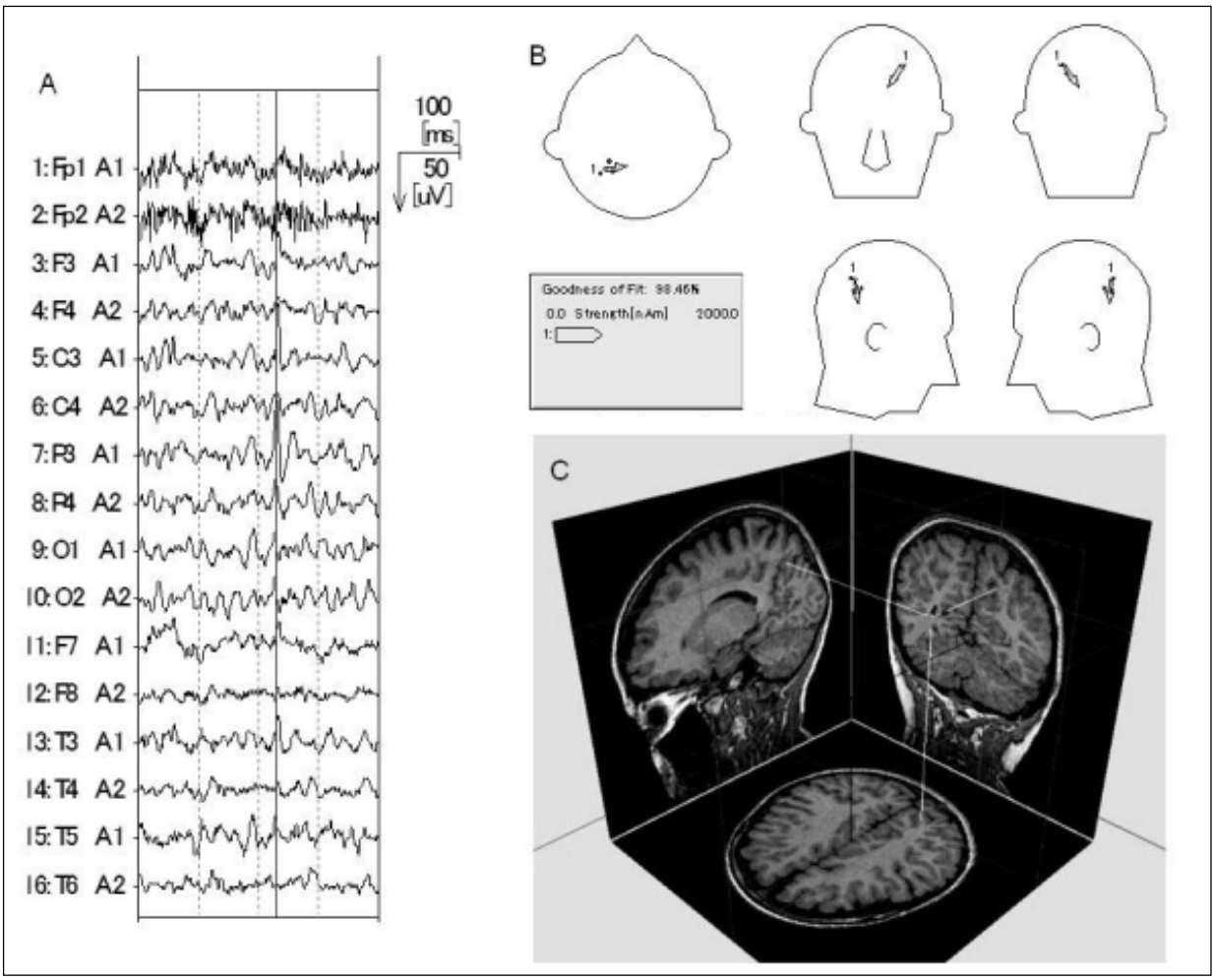

Figure 1 Representative dipole analysis in 1 patient. A: EEG shows a negative peak over the left central to parietal regions. B: Dipoles are concentrated in the parietal region (dipoles with a goodness of fit >95% were plotted). C: Overlay on MRI shows that the dipoles are in the parietal region.

with centroparietal spike foci (4/16, 25%) and frontal spike foci (2/11, 18%). On the other hand, with dipole analysis, migration of epileptic foci was recognised in 15 of 38 patients (39.5%). Direction of foci migration was anterior (2/15, 13.3%), lateral (8/15, 53.3%) and posterior (5/15, 33.3%). Migration was observed in patients with centroparietal spike foci (5/16, 31.3%), frontal spike foci (6/12, 50%), and occipital spike foci (4/10, 40%).

Migration of Epileptic Foci and Age

The mean age of the 6 patients who had migration observed using scalp EEG was 12.8±2.4 years. The mean age of the 15 patients who had migration recognised by DT was 11.3±3.8 years. With regard to migration and age, there was no significant difference between scalp EEG and DT. In both techniques, there was a higher incidence of migration in pre-adolescent and late school age patients than in younger patients.

Migration of Epileptic Foci and Outcome

Figure 2 shows the migration of epileptic foci and outcome for each patient. Figure 2A shows the localisation by EEG. In 2 patients, frontal spike foci (2/11, 18%) migrated to the occipital area, and their prognosis was not favourable. Centroparietal spike foci (4/16, 25%) migrated to the frontal area in 2 cases and the occipital area in 2 other cases. Of these, 3 patients had favourable prognoses and 1 had an unfavourable prognosis. Occipital spike foci did not migrate to the other areas.

Using dipole analysis (Figure 2B), frontal spike foci (6/12, 50%) migrated to the centroparietal area (4 cases) and occipital area (2 cases). Of these, 2 patients' prognoses were favourable but 4 were unfavourable. Similarly, centroparietal spike foci (5/16, 31.3%) migrated to the frontal area in 2 cases, and to the occipital area in 3 cases. Three patients had favourable prognoses and 2 patients' prognoses were unfavourable. In contrast to scalp EEG,

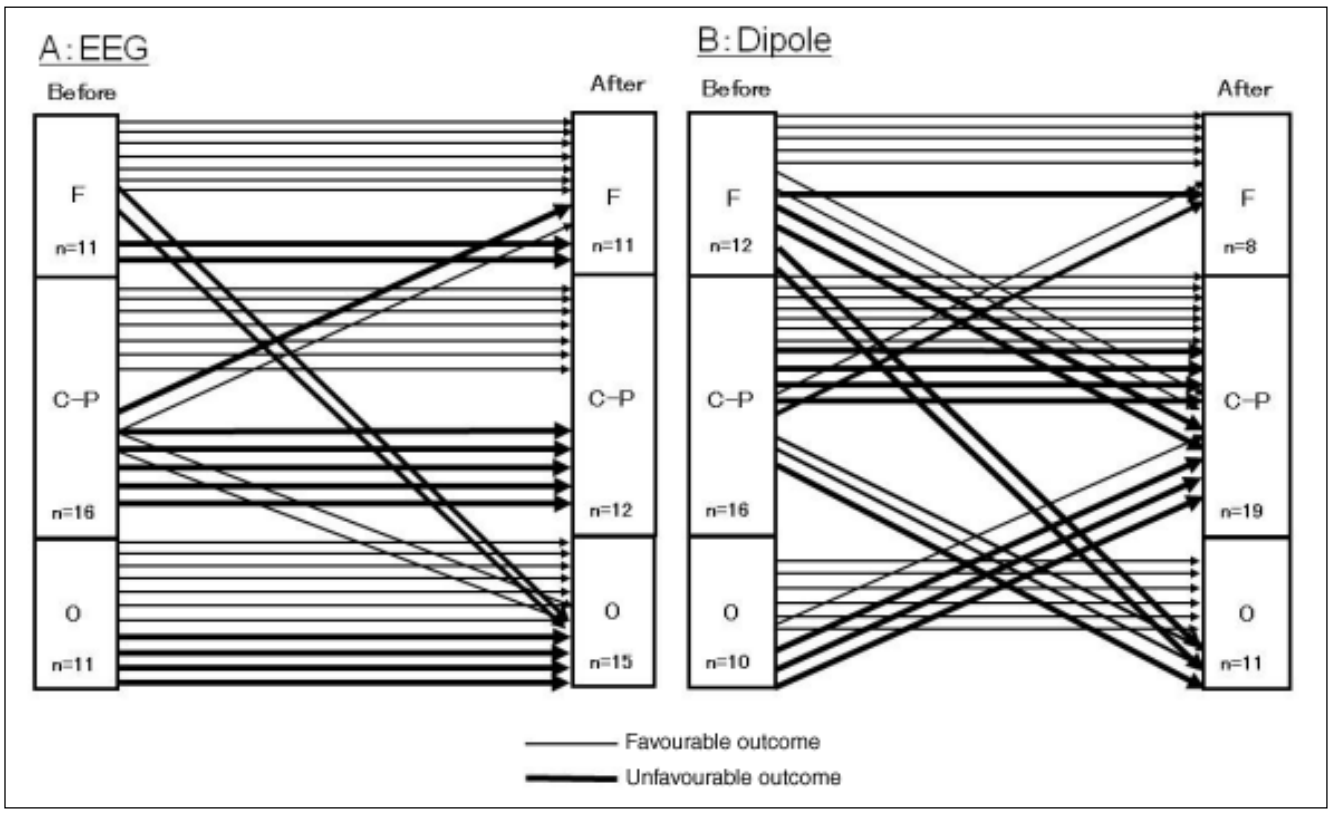

Figure 2 Migration of epileptic foci as determined by scalp EEG (A) and dipole analysis (B). Left: foci location at onset. Right: region of foci on follow-up after potential migration. Thin lines indicate a favourable outcome and thick lines indicate an unfavourable outcome. F, frontal; C-P, central-parietal; O, occipital.

DT identified occipital spike foci migration to the centroparietal area (4/10, 40%). Among patients with occipital to centroparietal migration, only one had a favourable prognosis. With regard to patients who had a favourable prognosis, no migration was observed in 18 patients (frontal, 5/7 [71.4%]; centroparietal, 7/9 [77.8%]; occipital, 6/7 [85.7%]). Furthermore, in 7 patients who had a favourable prognosis with centroparietal spike foci, 4/4 (100%) patients who were evaluated as having BCECT did not have migration to another area. Only 4 of 18 patients were diagnosed with BCECT. Fourteen patients had other epileptic syndromes. Therefore, a lack of migration was not associated with a favourable prognosis because of BCECT.

Relationship Between Migration and Outcome

Figure 3 shows the relationship between migration and outcome. Scalp EEG (Figure 3A) did not show a significant relationship between migration and outcome (p=0.65), but there was a significant relationship for dipole analysis (Figure 3B, p=0.037). Dipole analysis findings indicated that a lack of migration was correlated with a favourable outcome.

Discussion

Many childhood epilepsies show an age-dependent onset and clinical course,[12] which may be related to maturation of the central nervous system. In partial epilepsies, rolandic discharges of BCECT develop at an early school age and disappear before late adolescence.[13] Paroxysmal epileptic discharges in childhood epilepsy are believed to change in distribution and form with age. Gibbs et al[14-18] first reported that migration of EEG foci during the clinical course is common in childhood partial epilepsy. They concluded that the localisation of spike foci was largely determined by age, regardless of etiology, the presence or absence of seizures, and the presence or absence of cerebral lesions. Occipital foci were most common among 3- to 6-year-old, midtemporal foci among 7- to 10-year-old, and anterior temporal spikes in adults. They observed that epileptic foci in children tended to disappear or move to the site characteristic for seizure activity at the age of recording. They termed this shifting of epileptic foci, from posterior to anterior, migration of epileptic foci and believed it to be related to maturation of the brain.

Oguni et al[19] found migration of spike foci in 181 of

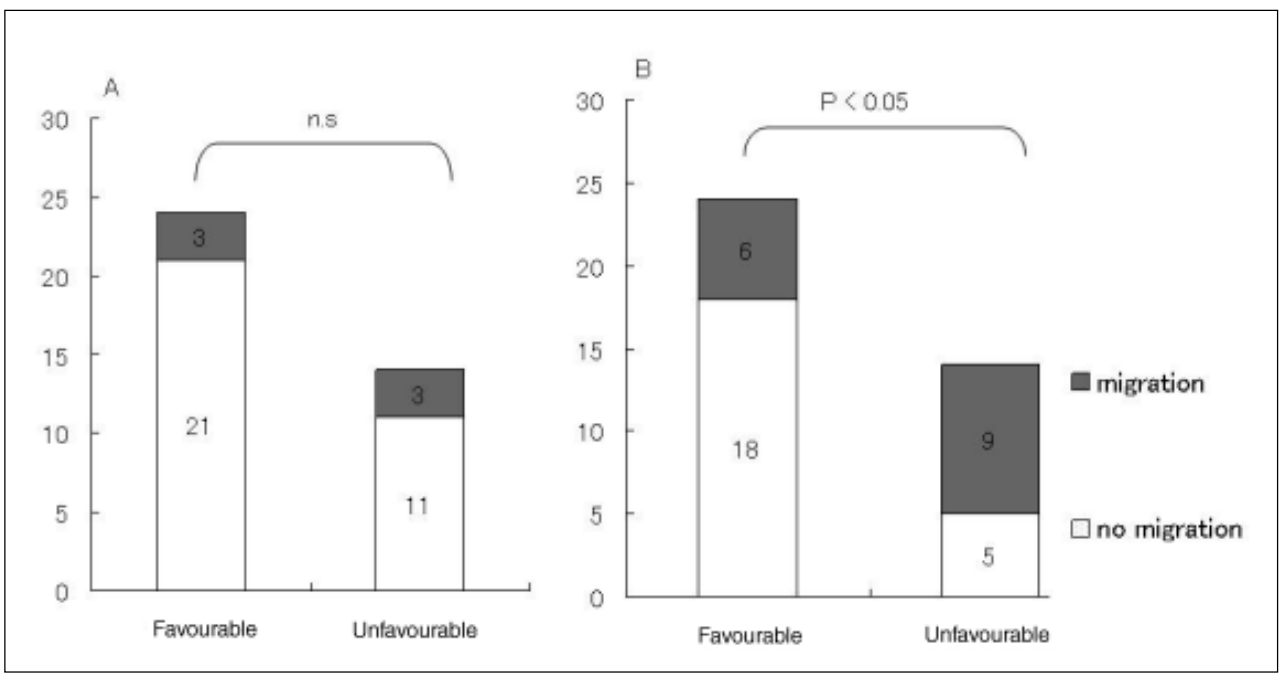

Figure 3 Prevalence of migration as related to prognosis. A: Scalp EEG; Fisher's exact test, p=0.65. B: Dipole; Fisher's exact test, p=0.037.

their 675 patients (27%) during a mean follow-up of 12 years. In other studies,[20-25] the incidence of foci migration ranged from 14% to as high as 75%, although the definition of migration and the subject selection criteria differed (Table 1). Konishi et al[22] reported the migration of EEG foci in 38.9% of 208 patients with childhood partial epilepsy. In the current study, we found that scalp EEG showed migration of epileptic foci in 6 of our 38 patients (15.8%) during a mean follow-up period of 2.2±1.7 years. On the other hand, using the DT method, the migration of epileptic foci increased to 15 of 38 patients (39.5%). Konishi et al[22] reported that migration is more frequently seen in patients with childhood epilepsy with occipital paroxysms, parietal lobe epilepsy and occipital lobe epilepsy, compared with cases of frontal lobe epilepsy and BCECT. Oguni et al[19] demonstrated that the frequency of migration of epileptic foci in all epileptic syndromes except for BCECT (11%) was 22% to 40%, with no significant differences among syndromes. In our study, migration determined by scalp EEG was 25% in patients with centroparietal spike foci. Using our DT method, migration was found in the frontal (50%), centroparietal (31.2%), and occipital (40%) areas. We followed up patients for at least 1 year, and for up to 7 years (mean±SD, 2.2±1.7 years). Longer follow-up periods might have demonstrated more migration of epileptic foci, as Gibbs et al[14-18] showed that migration of EEG foci during the clinical course is common in childhood partial epilepsy.

Oguni et al[19] reported that migration is frequently observed in young school-age children (5 to 7 years old) and preadolescents (9 to 11 years old). Similarly, in the current study, most migration was observed in preadolescents and young patients. The classic scheme of Gibbs et al[16] suggested occipital foci moving to anterior and frontal regions. The results of Oguni et al,[19] as well as those of other investigators,[20-23] do not support this view. They found that not only occipital foci but also frontal, temporal, and centroparietal foci shifted to other regions. Furthermore, they found no statistically significant difference in the incidence between frontal to occipital and occipital to frontal migration, or in patient age at migration among the different cortical regions, suggesting that patient age is more important than the location of the original focus. Our results are consistent with those of Oguni et al[19] in that migration, as observed with dipole analysis, was almost equally prevalent in each area (frontal, centroparietal, and occipital).

In these previous studies regarding the migration of epileptic focus, scalp EEG did not show a significant relationship between migration of epileptic foci and outcome. We compared scalp EEG and dipole analysis as indicators of the relationship between migration and outcome. Although scalp EEG did not show a significant relationship between migration and outcome, the DT method showed that a lack of migration is correlated with a favourable outcome. In our study, using the DT method, no migration was observed in 7 of 9 centroparietal spike foci and 6 of 7 occipital spike foci. In particular, all 4 patients who were evaluated as having BCECT did not have migration to another area. Yoshinaga et al have reported that the spikes in BCECT are characterised by constantly stable dipoles compared with those in other epilepsies, and this is associated with centrotemporal spikes and MR.[9] Wong also reported high dipole stability in typical BCECT, in contrast to atypical BCECT with MR. He hypothesised that even if a common generator was present in the atypical group, as in the typical group, the former would contain

Table 1 Incidence of migration of epileptic foci in the literature

Authors	Years	Subjects	N	Follow-up periods	Incidence of migration (%)
Gibbs et al[16]	1954	Children with occipital spikes	45	Not mentioned	14
Ricci and Scarinci[25]	1963	Children with occipital spikes	70	3-9 yr	17
Trojaborg[20]	1966	Children with focal spikes	233	>3 yr	75
Mikawa[23]	1981	Children epilepsy with focal spikes	203	>2 yr (mean 6 yr 4 mo)	20.7
Scarpa and Carassini[24]	1982	Childhood partial epilepsy	261	4-12 yr	19.06
Hughes[21]	1985	Seizure persisting for >15 yr	224	>15 yr	38.4
Konishi et al[22]	1994	Childhood partial epilepsy	208	>3 yr (mean 5.1 yr)	38.9
Oguni et al[19]	1999	Febrile convulsion, epilepsy	675	>3 yr (mean 12 yr)	27

additional extraneous interactions and would not show a stable dipole.[1] Therefore, Yoshinaga et al suspected that a similarly high dipole stability would also be present in Panayiotopoulos syndrome, which, similar to BCECT, is benign focal epilepsy of childhood with a good prognosis.[10] These findings on the excellent dipole stability in benign idiopathic focal epilepsies of childhood suggest that the good prognosis in these syndromes is related to the good dipole stability, which in turn argues against multiple epileptogenic foci as in symptomatic multifocal epilepsies. In our study, using the DT method, a lack of dipole migration was correlated with a favourable outcome. This result suggested that a lack of dipole migration was correlated with good dipole stability in benign focal epilepsy of childhood with a good prognosis.

In conclusion, we suggest that dipole analysis is more useful than scalp EEG for determining the likely outcome of childhood partial epilepsy.

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