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Focal EEG features and therapeutic response in patients with juvenile absence and myoclonic epilepsy

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HIGHLIGHTS

- We have prospectively scored focal EEG features in 168 consecutive patients with juvenile myoclonic and juvenile absence epilepsy.
- One-hundred-eighteen patients (70.2%) had focal EEG features: 89 patients (53%) had focal epileptiform discharges, and 80 patients (47.6%) had focal slowing.
- None of the focal features influenced the therapeutic outcome.

ABSTRACT

Objective: To investigate the characteristics of focal EEG features in patients with juvenile absence epilepsy (JAE) and juvenile myoclonic epilepsy (JME), and to assess their possible influence on therapeutic response.
Methods: Focal EEG features were prospectively scored in 168 consecutive patients. Ninety-six patients were drug-naïve and 72 patients were already on antiepileptic drugs (AEDs): 38 on adequate medication and 34 on inadequate medication. Therapeutic response was assessed one year after starting adequate therapy.
Results: One-hundred-eighteen patients (70.2%) had focal EEG features: 89 patients (53%) had focal epileptiform discharges, and 80 patients (47.6%) had focal slowing. Most often, these were multifocal and localized in frontal and temporal regions. Among patients already on AEDs, patients with focal EEG features were more often treated with inadequate medication due to misdiagnosis, than patients without focal features. Data on therapeutic response were available for 118 patients; most of them (90.7%) were seizure free. None of the focal EEG features affected therapeutic response.
Conclusion: Focal EEG features are common in patients with JME and JAE, but they do not influence the therapeutic response.
Significance: It is important that physicians are aware of the focal EEG features in order to avoid misdiagnosis and inadequate therapy.

1. Introduction

Typical EEG findings in patients with idiopathic/genetic generalized epilepsies (IGE) are bilateral, synchronous generalized spike-and-wave or polyspike-and-wave discharges, with normal background activity (Janz, 1985, 1998; Betting et al., 2006).

They may also include focal abnormalities and asymmetries particularly in those with juvenile myoclonic epilepsy (JME), juvenile absence epilepsy (JAE) (Betting et al., 2006; Aliberti et al.,

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1994; Panayiotopoulos et al., 1994; Lancman et al., 1994) and childhood absence epilepsies (AE) (Betting et al., 2006; Lombroso, 1997) which may result in diagnostic errors and inappropriate treatment (Panayiotopoulos et al., 1991; Grünewald et al., 1992; Grünewald and Panayiotopoulos, 1993; Murthy et al., 1998; Seneviratne et al., 2014).

There are only few studies addressing the possible influence of focal EEG features on therapeutic response in patients with IGE, and the results are controversial (Seneviratne et al., 2014). Most of the studies are retrospective and based on datasets that were not standardized (widely varying duration of follow-up, different type and number of EEG recordings for the included patients). In addition, diagnostic criteria, characteristics of focal EEG features and the outcome measures were not or poorly defined.

The goal of this study was (1) to elucidate the EEG characteristics of the focal features in patients with JAE and JME, and (2) to assess whether these features influence therapeutic response.

2. Methods

2.1. Data acquisition and evaluation

One-hundred-sixty-eight consecutive patients (99 female patients), diagnosed with JME or JAE, in the period January 2008 to October 2014, at the Institute for Neurology and Neuropsychology (INN), Tbilisi, Georgia, were recruited. Patients gave their informed consent, and the study was approved by the institutional ethics committee. The age of the patients was between five and 63 years (mean: 22.8 years; median: 19.5 years).

As INN has both regional function, as primary referral centre, and national function for epilepsy program (tertiary referral centre), we had two different patient-populations: untreated, drug-naïve patients ($n = 96$) and patients who had previously been diagnosed and treated for epilepsy ($n = 72$).

All patients had standard EEG recordings at the time of the initial consultation in our institute. These were standard, awake recordings of 20 min duration and included hyperventilation (3 min for children, 4 for adolescents and 5 for adults) and intermittent photic stimulation. Electrodes were placed according to the 10–20 system (Recommendations for the Practice of Clinical Neurophysiology: Guidelines of the International Federation of Clinical Neurophysiology, 1999). Out of the 168 recordings, drowsiness was present in 39 recordings. None of these standard, awake recordings contained sleep – stage N2, N3 or REM.

JME and JAE were diagnosed according to the ILAE criteria (Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes, 1989). Only unequivocal cases, fulfilling the diagnostic criteria at the initial consultation were included. We diagnosed 110 patients (63 females) with JME (mean age: 25 years) and 58 patients (36 females) with JAE (mean age: 18.5 years). Supplementary material 1 shows the seizure-types in our patients.

The age of onset was between 10 and 23 years in the JME group (mean: 15.7 years) and between 5 and 19 years for the JAE group (mean: 10.7 years).

Seventy-two patients were already on AEDs at the time of the first consultation in our institute. We categorized them into groups with adequate therapy (AT) and inadequate therapy (IAT). AT groups included valproate, levetiracetam, lamotrigine (Machado et al., 2013) and phenobarbital. Phenobarbital was considered AT only for JME, not JAE. Patients on carbamazepine monotherapy or in combination with other AEDs were considered IAT (Seneviratne et al., 2014). We noted the cases in which patients experienced exacerbation while on AEDs, before the first consultation in our institute, and before being changed to adequate therapy.

EEGs were prospectively evaluated by one of the authors (GJ). The characteristics of epileptiform discharges and of focal EEG features in these recordings were then scored and logged in a database together with another author (SB) who was blinded to the clinical data. Both authors are board certified clinical neurophysiologists, with more than 10-year experience in epileptology. Recordings were inspected both in bipolar montages and in common average. In addition, 3D voltage maps were constructed using BESA software (Figs. 1 and 2).

Epileptiform discharges (spike/polyspike and slow wave complexes) and slowing (rhythmic delta or theta activity) were defined according to the IFCN glossary of terms (Recommendations for the Practice of Clinical Neurophysiology: Guidelines of the International Federation of Clinical Neurophysiology, 1999).

All patients had "generalized" (bilateral synchronous) spike/polyspike and slow wave complexes (Fig. 1), since this was part of the inclusion criteria (Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes, 1989; Kasteleijn-Nolst Trenité et al., 2013).

EEG graphoelements were considered focal, when they were only seen over one side, in bipolar montages (allowing though for midline electrodes) and when the distribution of the negative potentials over the head was strictly unilateral and confined to 1–3 regions. Asymmetric bilateral graphoelements were not considered focal.

For the focal EEG features, the following characteristics were scored: morphology, spatial distribution and location. Morphology was scored either as epileptiform discharge (spike, polyspike, sharp-wave) or as slowing (delta or theta activity) (International Federation of Clinical Neurophysiology et al., 1999). Spatial distribution was scored as single focus, bilateral independent foci or multifocal graphoelements (two or more independent foci provided they were not bilateral-independent).

Follow-up: one year after the initial consultation, therapeutic response was classified as seizure-free, >50% seizure-reduction (but not seizure-free), no/minor change.

2.2. Statistical analysis

Descriptive statistics were used. Pearson's chi square test was used to identify associations between the categorical variables. Two-sided probabilities of less than 0.05 were considered statistically significant. The statistical analysis was performed with SPSS, version 21.0 (SPSS, Chicago, Illinois, USA).

3. Results

3.1. Incidence of focal EEG features

One-hundred-eighteen patients (70.2%) had focal EEG features in the initial EEG recording. Focal epileptiform discharges were recorded in 89 patients (53%), while focal slowing was recorded in 80 patients (47.6%) (Fig. 2). There was no significant difference between JME and JAE in the incidence of the focal EEG features (Table 1).

3.2. Characteristics of focal features

Characteristics of focal EEG features (morphology and location) are summarized in Table 2. Examples of focal EEG features are illustrated in Fig. 2. Most often, focal EEG features were multifocal,

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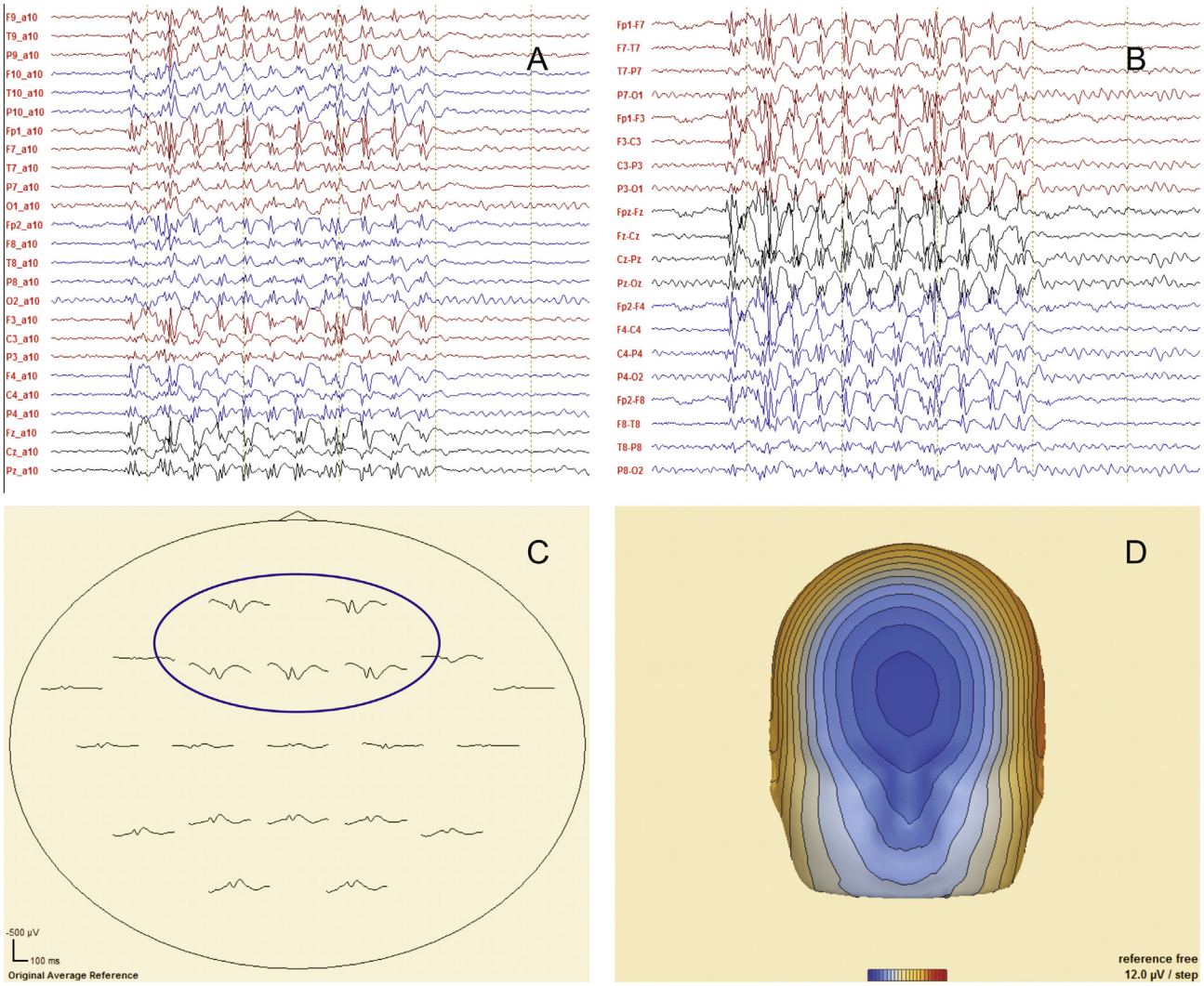

Fig. 1. Bilateral synchronous ("generalized") spike/polyspike-and-slow-wave discharges. (A) Common average montage. (B) Longitudinal bipolar montage. (C) Top-plot view; the blue ellipsoid shows the spatial distribution of the first spike-and-slow-wave complex of the train. (D) 3D voltage-map (front-view) of the first peak, illustrating the bilateral, symmetric and synchronous distribution of the discharge; color-codes in (D): blue for negative, red for positive potentials. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

in frontal and in temporal regions. However, single focus was identified in a significant proportion (35.6%) of the patients.

Supplementary material 2 shows data separately for JME and JAE patients. Focal slowing in the occipital region was found more often in JAE than in JME patients (16% vs. 3%; $p < 0.01$). None of the other focal EEG characteristics differed significantly between JME and JAE patient-groups (Table 2 and Supplementary material 2).

Out of 118 recordings with focal EEG features, in only four recordings the focal findings were seen exclusively during drowsiness. In 91 recordings, the focal features occurred exclusively in awake state. In 23 patients, they occurred both in awake state and in drowsiness.

3.3. Initial therapeutic choices in patients who were previously treated

Among the 72 patients who had already been treated at the time of the first consultation in our institute, there was a significantly higher incidence of IAT for the patients with focal EEG features as compared to those without focal EEG features ($p < 0.001$).This was most striking for patients with focal slowing (Supplementary material 3).

The high incidence of IAT among the patients with focal EEG features was related to the initial misdiagnosis of these patients. None of the patients on IAT was seizure-free.

3.4. Therapeutic response to AT: one year follow-up

All drug-naïve patients ($n = 96$) were prescribed AT in our institution. The AEDs were changed to AT for all patients previously on IAT ($n = 34$). In addition, AEDs were changed for 10 patients while dose was adjusted for 12 patients on AT ($n = 38$) (Supplementary material 4).

Data on therapeutic response after one-year were available for 118 patients. Forty-two patients (25%) were lost to follow-up. Eight patients (4.8%) had the initial EEGs less than one year from the last follow-up. Most of the patients (107 = 90.7%) were seizure free at the one-year follow-up. There was no difference in the therapeutic response to AT between patients with and without focal EEG features. None of the described focal EEG features affected the therapeutic response (Table 3).

Therapeutic response one year after starting AT was similar, regardless whether they were initially drug-naïve, on AT or on IAT (Supplementary material 5).

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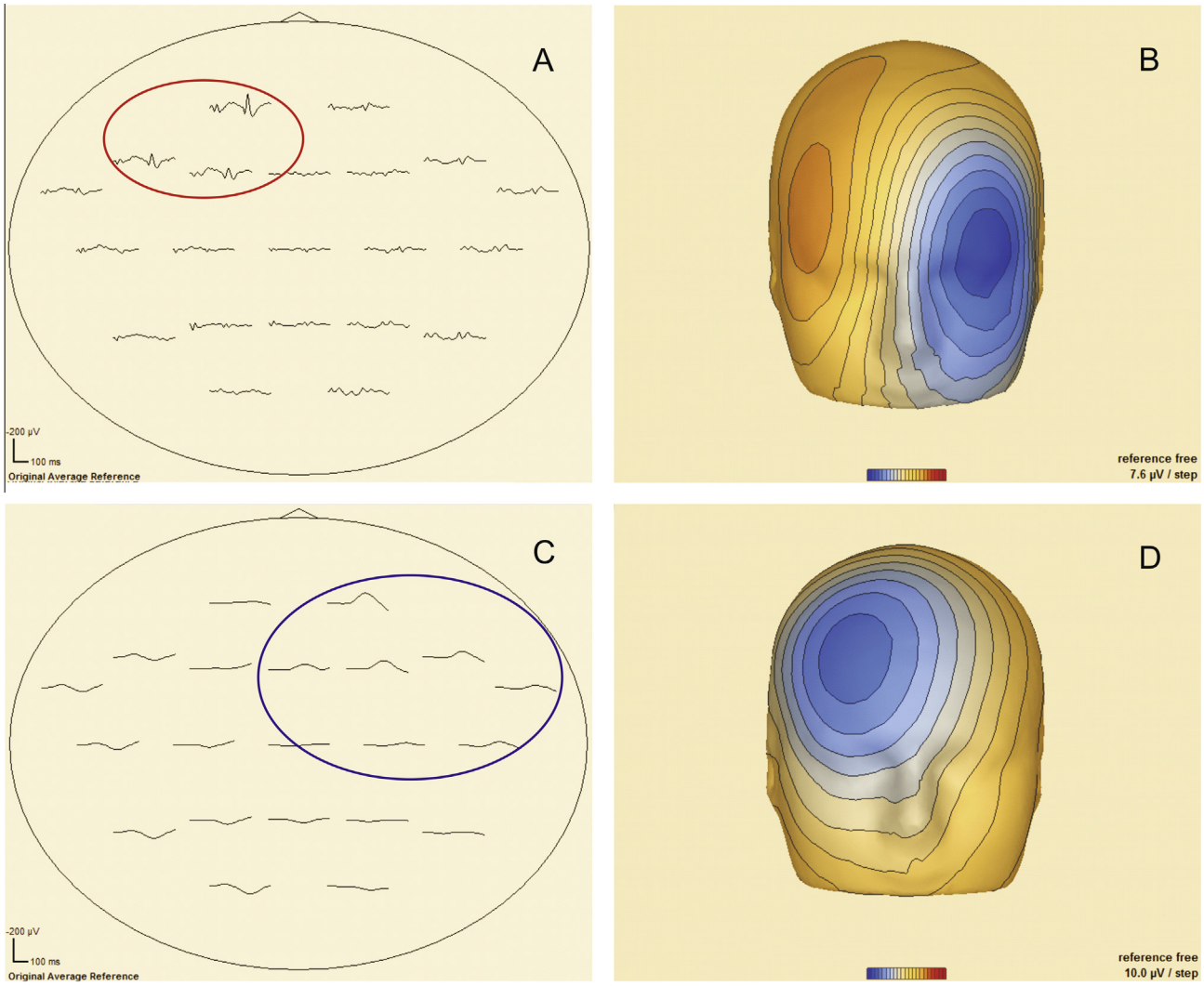

Fig. 2. Focal epileptiform discharge (A-B) and focal slowing (C-D). A and C are top-plot views, where the distribution of the focal discharges is marked with red (A) and blue (C) ellipsoids. B and D are 3D voltage-maps (front-view) illustrating the focal distribution of the discharges; color-codes in B and D: blue for negative, red for positive potentials. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Incidence and types of focal EEG features.

	Total (n = 168)	JME (n = 110)	JAE (n = 58)	Drug-naïve (n = 96)
Any focal feature	118 (70.2%)	75 (68.2%)	43 (74.1%)	67 (69.8%)
Focal EDs	89 (53.0%)	56 (50.9%)	33 (56.9%)	51 (53.1%)
Focal slowing	80 (47.6%)	50 (45.5%)	30 (51.7%)	41(42.7%)

3.5. Exacerbation on initial IAT

Thirteen out of 34 patients who initially were on IAT experienced seizure-exacerbation (38%). The occurrence of exacerbation was not influenced by the presence or absence of any focal EEG feature (Supplementary material 6).

3.6. Photosensitivity

Sixty-seven patients (39.9%) had photoparoxysmal response (45.5% in the JME and 29.3% in the JAE groups). This was significantly reduced among patients on AT (seven out of 38: 18.4%) as compared with patients on IAT (15 out of 34: 44%) and compared with drug-naïve patients (45 out of 96 patients: 46.9%) ($p < 0.01$). The presence or absence of focal features was not related to the photosensitivity (Supplementary material 7).

4. Discussion

In a prospective, large-scale study, we have evaluated the focal EEG features in patients with JAE and JME, and we assessed whether they were related to the therapeutic response at one-year follow-up.

We found that more than two-thirds of the patients had focal EEG features. This is in agreement with previously reported rate of focal abnormalities in IGE, which varies between 7% and 65% (Aliberti et al., 1994; Panayiotopoulos et al., 1994; Lombroso, 1997; Grünewald et al., 1992; Leutmezer et al., 2002; Baise-Zung

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Table 2
Characteristics of focal EEG features (morphology and location).

Spatial features		Morphology of the focal EEG features		
		Any (n = 118)	Epileptiform discharges (n = 89)	Slowing (n = 80)
Distribution	Single	42 (35.6%)	40 (44.9%)	37 (46.3%)
	Bilateral independent	19 (16.1%)	13 (14.6%)	19 (23.8%)
	Multifocal	57 (48.3%)	36 (40.4%)	24 (30.0%)
Location	Frontal	80 (67.8%)	62 (69.7%)	38 (47.5%)
	Temporal	80 (67.8%)	49 (55.1%)	59 (73.8%)
	Central	11 (9.3%)	9 (10.1%)	4 (5.0%)
	Parietal	15 (12.7%)	12 (13.5%)	6 (7.5%)
	Occipital	23 (19.5%)	14 (15.7%)	12 (15.0%)

Table 3
Focal EEG features and therapeutic response at one-year follow-up.

	Total	Seizure-free	>50% reduction	No/minor change
All patients	118	107 (90.7%)	8 (6.8%)	3 (2.5%)
Any focal feature	80	71 (88.8%)	6 (7.5%)	3 (3.8%)
Focal EDs	60	52 (86.7%)	5 (8.3%)	3 (5.0%)
Focal slowing	54	49 (90.7%)	3 (5.6%)	2 (3.7%)
No focal features	38	36 (94.7%)	2 (5.3%)	0 (0%)

et al., 2006; Atakli et al., 1998; Dhanuka et al., 2001; Usui et al., 2005; Jayalakshmi et al., 2006; Asconapé and Penry, 1984; Durón et al., 2005). Focal changes were found in 56% of a large cohort of IGE patients, and in 65% of those who had absence epilepsies (Lombroso, 1997). Even higher percentage (11 of 13 AE patients, 85%) of focal alterations in IGE has been reported recently (Koutroumanidis et al., 2012). We looked prospectively and specifically for the focal features in our study, and that can explain why the incidence of focal features is higher than in some of the previous studies.

A previous paper suggested that AEDs could have caused the appearance of focal EEG features in patients with IGE (Tezer et al., 2008). In order to investigate this, we included both drug-naïve patients and patients who had already been treated with AEDs. We found that the two subgroups had similarly high incidence of focal features, therefore it is highly unlikely that focal EEG features are induced by the AEDs (Table 1).

In our study, special emphasis was given to excluding patterns of unclear significance/normal variants (Edwards and Kutluay, 2011). To distinguish epileptiform discharges from non-epileptiform sharp transients, we used Gloor's criteria (Gloor, 1977). Focal slowing was distinguished from posterior slow waves of youth, fronto-central theta and mid-central theta activity (Edwards and Kutluay, 2011).

The focal EEG features we are reporting in this study were not induced by sleep: none of these standard, awake recordings contained sleep – stage N2, N3 or REM.

Focal EEG features in our patients comprised both epileptiform discharges and focal slowing. In most of the patients, the focal EEG features were multifocal and located to the frontal and temporal regions. Both epileptiform discharges and slow-waves have been previously reported as focal abnormalities in IGE patients (Panayiotopoulos et al., 1994; Lombroso, 1997; Matur et al., 2009), the most frequent location being frontal and temporal (Lombroso, 1997; Matur et al., 2009; Leutmezer et al., 2002; Koutroumanidis et al., 2012; Aguglia et al., 1999). Data regarding spatial distribution of focal abnormalities in IGE are scarce (Koutroumanidis et al., 2012). They occurred in more than one area in six of 13 children with CAE and were restricted to a single area in five. Considering both topography and laterality, multifocal spikes occurred in eight of the 11 children with these abnormalities (73%), or in 62% of the total children.

PPR was significantly lower in patients on AT, as compared to patients on IAT and with drug-naïve patients. This is consistent with previous reports. It is known that adequate AED therapy may inhibit PPR, and lead to normal EEG tracings (Baise-Zung et al., 2006; Waltz, 2001). Overall, photosensitivity was less likely to be seen in the adequately treated people than in those with no treatment or inadequate treatment in our study.

After starting adequate therapy, our patients had an excellent therapeutic response: 90.7% of the patients became seizure-free. According to the literature-data, seizures are generally well controlled with appropriate medication in up to 90% of JME and in 70–80% of JAE patients (Panayiotopoulos, 2007).

In our study, none of the focal EEG features influenced therapeutic response: patients with focal features responded similarly well to adequate therapy as patients without focal features. This is consistent with two, smaller scale studies (Yoshinaga et al., 2004; Bartolomei et al., 1997) and in contradiction with three previous studies (Matsuoka, 1992; Matur et al., 2009; Tezer et al., 2008) addressing this issue.

In 23 patients with childhood absence epilepsy, occurrence of focal epileptic discharges did not directly correlate with a poor prognosis; the follow-up period ranged between two and 10 years (Yoshinaga et al., 2004). Presence of focal EEG abnormalities on waking and/or napping EEG recordings in 80 IGE patients with absence seizures (53 with CAE and 27 with JAE) appeared to be of no prognostic value; the follow-up was between one and nine years (Bartolomei et al., 1997).

Patients who had focal EEG discharges at the beginning of treatment had an unfavourable outcome in a study on 32 patients with JME (Matsuoka, 1992). The ratio of seizure-freedom was lower and the psychiatric problems were significantly higher in the group of patients having focal abnormalities in a study that included 50 adult patients with IGE and absence seizures (Matur et al., 2009). The occurrence of focal EEG features seemed to be related to the lack of adequate therapy in a series of 52 consecutive patients with JAE (Tezer et al., 2008).

As opposed to the previous papers, our study addressed this issue prospectively, in a large cohort, using pre-defined diagnostic criteria for the IGE types and EEG-criteria for focal features. The methodology (EEG recordings and the follow-up duration) were homogenous in our patient-population. With this study-design, we aimed at eliminating the limitations of the previous reports.

About one-fourth of patients were lost to follow-up. However, the ratio of dropouts was not different between the sub-groups of patients. Therefore, it is unlikely that this could have influenced the results.

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None of the patients initially on inadequate therapy (carbamazepine) was seizure-free, regardless of the presence or absence of focal features. Exacerbation was seen in 38% of the patients on inadequate therapy. However, this did not depend on the presence or absence of focal features.

We found that focal EEG features are common in patients with IGE. This challenges the concept of "generalized" epilepsy, and indicates that the dichotomy of focal versus generalized epilepsy is an oversimplification. The frequent incidence of focal epileptiform discharges (often multifocal) in addition to the bilateral, synchronous discharges, suggests that epileptiform activity in these patients originates at some point within, and rapidly engages, bilaterally distributed networks (Berg et al., 2010). There is mounting evidence indicating that in patients with idiopathic/genetic generalized epilepsy, ictogenesis occurs via neuronal networks which subserve normal physiologic functions (Avanzini et al., 2012).

Presence of focal EEG features was related to misdiagnosis and inadequate treatment. None of the patients on inadequate therapy was seizure-free. However, after changing to adequate therapy all patients had an excellent response, regardless of the presence of focal EEG features.

To avoid misdiagnosis and inadequate treatment it is important to increase awareness of focal EEG features, which are common in IGE. These patients have excellent response to therapy adequate for IGE, in spite of the focal EEG features.

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

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.clinph.2015.11.048.

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