Focal EEG Findings in Juvenile Absence Syndrome and the Effect of Antiepileptic Drugs

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ABSTRACT
The presence of focal EEG abnormalities in juvenile absence syndrome (JAS) may cause it to be misdiagnosed as focal epilepsy. The purpose of our study was to determine the presence of focal EEG abnormalities in patients with JAS and to ascertain whether some clinical features or antiepileptic drugs (AEDs) have an effect on focality.

Serial EEGs of 52 consecutive patients with JAS were retrospectively analyzed. The patients were divided into two groups according to whether they were treated with valproic acid and/or lamotrigine (VA-LTG) or not during the times of these EEG recordings. The relationship between the presence of EEG focality and the use of AEDs in addition to other risk factors was examined.

Two or three consecutive EEGs (total 100) of the 52 patients were evaluated. Among these, the rates of focal EEG abnormalities were 18%, 36%, and 25% during the follow-up EEGs without AEDs (5/27) and first (18/45) and second EEGs (7/28) with AEDs, respectively. The last two EEGs showed a tendency towards a higher proportion of EEG focality in patients who received other AEDs (47%-45%) compared with those that received VA-LTG (13%-12%).

The proportion of JAS patients with focal EEG findings in serial EEGs tended to decrease with an increasing rate of VA-LTG use. As a hypothetical explanation, changes in EEG focality may reflect the effect of AEDs other than VA and/or LTG, in addition to a developing hyperexcitable cortical area.

INTRODUCTION
Electroencephalograms (EEG) along with clinical history may provide strong supportive evidence for the diagnosis of idiopathic generalized epilepsy (IGE). In particular, absences are easily studied with EEG; a first abnormal and characteristic EEG will be seen in more than 90% of untreated patients. However, focal EEG abnormalities that were reported commonly in juvenile myoclonic epilepsy (JME) may be rarely found in patients with absence epilepsy like juvenile absence epilepsy (JAS). Although JAS can be easily treated with antiepileptic drugs (AED) like valproic acid (VA) and lamotrigine (LTG), the misdiagnosis of these cases as focal epilepsy remains a problem.

To the best of our knowledge, there are only occasional cases of JAS with focal EEG findings reported in IGE groups. The purpose of our study was to determine focal EEG abnormalities in patients with JAS and to ascertain whether some clinical features or AEDs have an effect on focality.

MATERIALS AND METHODS
We included all patients with a clinical diagnosis of JAS who had undergone EEG recordings at our adult EEG laboratory between 1992 and 2006. Initially patients who had histories of well-documented absences and/or generalized seizures compatible with IGE, and evidence of typical generalized spike wave (GSW) discharges of JAS in their EEG (interpreted by authors S. S., A. C., F. I. T.) were included. Clinically and electrophysiologically, patients suspected of having other types of IGEs and partial epilepsy were excluded. Medical records as well as all available EEG tracings of these patients were reevaluated. Patients fulfilling all criteria for IGE-JAS as defined in the International Classification of Epilepsies and Epileptic Syndromes were identified by one of the authors (S. S.).

Inclusion and exclusion criteria were mainly according to the ILAE classification but definitions proposed by Panayiotopoulos for absence epilepsy were also considered for exclusion. Clinically patients who had typical absences beginning around puberty (9 to 17 years of age) with or without generalized tonic-clonic convulsions (GTCS) and infrequent myoclonic seizures were included. In addition, according to the suggestions made by Panayiotopoulos, patients who had absences with marked eyelid or perioral myoclonus, single or rhythmic limb and trunk myoclonic jerks, or absences with mild or clinically undetectable impairment of consciousness were excluded. All patients had typical 3-4 Hz GSW discharges in at least one EEG recording during follow-up. Patients with abnormal background patterns for their age or persistent lateralized-localized continuous slow activity in EEGs (except in those recorded after sleep deprivation) were excluded. Patients clinically diagnosed with JAS but whose EEG recordings did not have findings typical of JAS were excluded.

We retrospectively analyzed patients’ charts to extract their demographic details and potential risk factors for epilepsy. The following variables were investigated: histories of febrile seizures, trauma, and perinatal injury; family history of epilepsy; abnormal neuroimaging findings; and name of the AEDs used after the diagnosis of epilepsy.

Medical records were also evaluated to establish the time of EEG records and AEDs used during these periods. The data about AEDs of all patients were available in the EEG reports and charts of the EEG laboratory. EEGs had mostly been recorded on an 8-channel EEG instrument with hyperventilation and intermittent photic stimulation for 20-30 min and/or 60 min after sleep deprivation. The EEGs of a few
Figure 1.
A-F are examples of focal EEG findings. A-C: Asymmetry in the amplitude and/or frequency of generalized discharges. D-E: focal spikes, sharp waves, or spike-wave complexes independent of generalized discharges. F: lateralized fragments of generalized spike-wave discharges.
patients had been recorded on a 32-channel instrument. All available EEG tracings of all patients were reviewed but only EEGs without any effect of AEDs and the first two EEGs recorded under the effect of AEDs were included in the analysis because of the small number of follow-up EEGs. EEGs were classified into three groups: (1) With typical generalized spike wave patterns. (All patients had typical GSW discharges in at least one of their EEGs. The nonlateralized fragments of GSW discharges that were mostly reported over the frontal midline region\(^1\) were also included in this group.) (2) With focal abnormalities (Figure 1); a. Intermittent localized or lateralized slow waves independent of generalized discharges; b. Focal spikes or sharp waves independent of generalized discharges; c. Lateralized and/or localized spikes, spike-slow wave, slow waves preceding generalized discharges; d. Asymmetry in the amplitude and/or frequency of generalized discharges; e. Lateralized fragments of GSW. (3) Normal.

During all these EEG series, the patients were divided into two groups based on whether they were treated with VA and/or LTG (with and without ethosuximide (ETX)) or with other AEDs like carbamazepine (CBZ), diphenylhydantoin (DPH), and phenobarbital (PHB). The two groups were compared statistically. A chi-square or Fisher’s exact test of independence was used for univariate analysis of the following categoric variables: histories of febrile seizures,

### Table 1

<table>
<thead>
<tr>
<th>EEG without effect of AEDs n:27</th>
<th>First EEG with effect of AEDs n:45</th>
<th>Second EEG with effect of AEDs n:28</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal or Typical EEG</strong></td>
<td>VA-LTG n:15 Other AEDs n:30</td>
<td>VA-LTG n:17 Other AEDs n:11</td>
</tr>
<tr>
<td>Normal</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Typical or fragmented</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>Focal EEG Abnormalities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent lat-loc slow waves</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Focal spike-sharp waves – SW complexes</td>
<td>1 1</td>
<td>1 1</td>
</tr>
<tr>
<td>Spike, SW and slow waves preceding GSW</td>
<td>4 4</td>
<td>4 4</td>
</tr>
<tr>
<td>Asymmetric GSW</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Lateralized-fragmented GSW</td>
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<td>2</td>
</tr>
</tbody>
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perinatal injury, and trauma; family history of epilepsy; and use of VA and/or LTG.

Fifty-two consecutive patients with a clinical diagnosis of JAS were included. Twenty of them were male. Mean age at the time of the first absence seizure was 13.05±2.60 years. Eight (15%) patients had a history of febrile convulsions and 19 (37%) had a history of mild head trauma. Perinatal injury was reported in 3 (6%) patients. There was a family history of epilepsy in 29 (56%) patients.

Twenty-three patients underwent computerized tomography (CT) of the head and 39 underwent cranial magnetic resonance (MR) imaging. All CTs were normal, but 3 of the 39 patients had pathological findings like lipoma on the corpus callosum, lacunar infarction on the thalamus, and arachnoid cyst in the left temporal region on MR imaging.

In total 119 EEGs were evaluated. Twenty-seven patients had their first EEG without any effect of AEDs. Six of them underwent no follow-up EEG examination. Forty-five patients had their first follow-up EEG with AEDs and 28 patients had their second follow-up EEG with AEDs. Thirteen patients had their third follow-up EEG while on AEDs and 6 patients had their fourth follow-up EEG while on AEDs, but these last two follow-up EEGs with 19 EEG recordings were not included in the statistical analysis.

RESULTS

Among the 52 patients, 19 (37%) had intermittent focal EEG abnormalities at some time during the follow-up period. On the other hand, among the 100 EEGs of the 52 patients included in the statistical analysis, the rates of focal abnormalities were 18%, 36%, and 25% during the follow-up EEGs while not on AEDs and the first and second EEGs while on AEDs, respectively. The presence of focal EEG abnormalities at any time during follow-up was not significantly related to the presence of febrile convulsions, a history of trauma or perinatal injury, a family history of epilepsy, or pathological findings on neuroimaging.

Initially 37 of the 52 patients (71%) were taking AEDs other than VA and LGT (with or without OAT). Of the 48 patients whose medical records contained information about their AEDs, 41 (85%) were taking only VA and/or LGT at the last follow-up. The relation between use of VA and/or LGT and AEDs and presence of focal EEG findings at different times during follow-up was examined (Table 1). The proportion of focal abnormalities on the first EEG in patients who received VA and LGT was 2/15 (13%). However, in patients who received AEDs other than VA and LGT this proportion was higher: 14/30 (47%). The difference in terms of the presence of focal EEG findings between the groups who received VA and/or LGT and other AEDs was nearly significant (p=0.046) (Table 2). On the second EEG while on AEDs the difference was not statistically significant (p=0.076), but there was a tendency towards a higher proportion of focal EEG findings in patients who received AEDs other than VA and/or LGT (5/11, 45%) compared with those that received VA and/or LGT (2/17, 12%).

Also, when the patients with clear lesions on MR imaging have been excluded, the difference in the presence of focal findings between the groups who received VA-LTG and other AEDs became more significant statistically at the first follow-up (p=0.015).

Furthermore, the relation between the presence of focal EEG findings and the condition of the patients, such as being drowsy or not, was examined. Seventeen EEGs were obtained after sleep deprivation (ASD). Only 5 of them had focal EEG abnormalities. At different times during follow-up, the relation between the presence of focal findings and condition of the patients during EEG (ASD or not) recordings was not related statistically (p=1.0, p=0.42, p=0.55).

DISCUSSION

Juvenile absence epilepsy often presents with absence seizures before GTCS and myoclonic seizures during puberty. These patients might have been unaware of these absences before the first GTCS. In addition to patients’ unawareness, the misdiagnosis of absences as complex partial seizures by physicians also may lead to delayed or inefficient treatment of absences. In addition to these problems, in clinical findings focal abnormalities on EEG may also affect treatment adversely. This was evidenced in our group, with 71% of patients receiving AEDs other than VA and/or LTG. In a number of studies about IGEs involving JME patients these are reported as a common finding at a rate of 30.3%-36.7%. The consideration of rare focal EEG findings of IGEs with absence seizures changed after the study by Lombroso. In a longitudinal study following the routine EEGs of 58 patients, intermittent focal delta and theta waves or focal spikes and sharp waves in 60%-67% of patients with absence seizures were reported. Lombroso also suggested that focality rarely presented in the early EEGs (13%), but tended to develop in subsequent recordings (56%). Betting et al. also reported that atypical focal abnormalities increased from 28% to 42% in serial EEGs of patients with absences in a group of IGEs. In our JAS group 18% of patients had EEG focalties in the first EEG without any effect of AEDs, but this rate increased to 36% and 25% in the first and second follow-up EEGs while on AEDs.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Presence of focal EEG findings and relation of these with AEDs</th>
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<tbody>
<tr>
<td>EEG</td>
<td>Presence of focal EEG findings</td>
</tr>
<tr>
<td>1st EEG</td>
<td>2</td>
</tr>
<tr>
<td>2nd EEG</td>
<td>2</td>
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VA: Valproic acid, LTG: Lamotrigine, AED: Antiepileptic drugs
In the literature, the increasing proportion of EEG fociality during the follow-up of patients with IGE absences was interpreted as microdysgenesis or the development over time of localized, self-sustaining hyperexcitability in low-threshold cortical structures subjected to repeated generalized spike-wave activity. Autopsy studies in patients with IGE also documented focal microdysgenesis in several cases. MR imaging studies also support these findings, showing an increase of cortical gray matter in the mesial frontal lobes in JME patients and the reduction in N-acetyl aspartate in these cortical regions of patients with generalized epilepsy. However, in our patients there was no relationship between structural findings and EEG fociality based on nonstandardized neuroimaging studies.

In the present study we also examined the effect of risk factors other than neuroimaging findings on the focality of EEG. The presence of focal abnormalities of EEG was not related to histories of febrile convulsion, perinatal injury, or trauma, or family history of epilepsy. However, the rate of focal EEG abnormalities changed during follow-up; it increased from 18% to 36% after treatment with AEDs in the first EEG. Patients taking AEDs other than VA or LTG had a higher rate of focal EEG findings than those taking VA or LTG (47% vs. 13%) and the difference was almost significant (p=0.046). Furthermore, with the decreasing rate of focal EEG findings from 36% to 25%, use of AEDs other than VA or LTG decreased from 30/45 (67%) to 11/28 (39%) on the second EEGs with AEDs. That decreasing rate of focal EEG abnormalities may be related to the decreasing use of AEDs other than VA-LTG.

The effect of AEDs on the focality of EEGs in IGE was not examined in previous studies. As a hypothetical explanation, changes in the focal EEG rate in our serial EEG recordings may reflect the effect of treatment with AEDs other than VA-LTG on EEGs in addition to a developing hyperexcitable cortical area. On the other hand, it could be the cause of these patients being started on the wrong drugs due to focal EEG findings. In contrast, the focal abnormalities in the first EEGs while not on AEDs (18%) were lower than in those while on AEDs (36%).

Activating procedures like sleep deprivation increase the probability of registering typical or atypical interictal epileptiform activity. In our study the increased rate of focal epileptiform abnormalities may have been related to changes in the conditions of patients, such as being drowsy or not. However, we compared the presence of focal EEG abnormalities in three follow-up EEGs with the condition of patients, and found no statistically significant result, but this is a limitation of all retrospective studies. Standardized follow-up EEG recordings in similar conditions may strengthen the results. The other limitation was related to the possibility of interpretation of fragmented GSW discharges as focal abnormalities. These were not clearly defined in the literature. For that reason we excluded nonlateralized bilateral frontal spike wave discharges in focal EEG abnormalities.

As a consequence, inexperienced clinicians wrongly interpreting absence seizures as complex partial seizures or failing to appreciate that focal EEG abnormalities are not rare in JAS may seriously affect patients’ treatment and management. Unlike partial epilepsies, seizures in IGE seem to be more vulnerable to aggravation by AEDs. CBZ and DPH are generally safe drugs, but they may aggravate some forms of IGE. Seizure exacerbation seems to result from an adverse interaction between the model of action of these drugs and the pathogenetic mechanisms underlying specific seizure types or syndromes. However, this result was not seen in all patients with IGEs who were taking CBZ and DPH. This may be explained by genetic differences. In future clinical and genetic research on IGEs the investigation of molecular-biochemical lesions may be helpful for understanding how AEDs affect them.

REFERENCES


