DOCTORAL THESIS

Predictive factors of higher drug load for seizure freedom in idiopathic generalized epilepsy: Comparison between juvenile myoclonic epilepsy and other types

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Predictive factors of higher drug load for seizure freedom in idiopathic generalized epilepsy: comparison between juvenile myoclonic epilepsy and other types

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ABSTRACT

Purpose: Predictive factors of higher drug load for seizure freedom were investigated in idiopathic generalized epilepsy (IGE), focusing on the difference between juvenile myoclonic epilepsy (JME) and other types of IGE (non-JME IGE).

Methods: Twelve patients with JME and 12 patients with non-JME IGE, who achieved seizure freedom for 1 year or longer with appropriate antiepileptic drugs (AEDs) after video electroencephalography monitoring, were reviewed retrospectively. The sum of prescribed daily dose/defined daily dose ratio of all prescribed AEDs at the final visit was defined as total AED load. Patients requiring total AED load >1 were classified into the higher AED load group. Clinical background and the presence of interictal focal epileptiform abnormalities (FEAs) were compared between the higher and lower AED load groups.

Results: Higher AED load group of patients with JME had interictal FEAs and family history of epilepsy more frequently than the lower AED load group (p = 0.03 and p = 0.03). Similar comparison of patients with non-JME IGE showed no significant differences.

Conclusions: The presence of interictal FEAs and a family history of epilepsy are significantly associated variables for higher AED load for seizure freedom in patients with JME, but not in patients with non-JME IGE.

Keywords:
Juvenile myoclonic epilepsy
Idiopathic generalized epilepsy
Antiepileptic drug load
Focal epileptiform abnormalities
Impaired drug responsiveness

HIGHLIGHTS
- Predictive factors of higher AED load for seizure freedom in IGE were investigated.
- Focal epileptiform abnormalities indicated need for higher AED load in JME.
- Family history of epilepsy indicated need for higher AED load in JME.
- No clinical features indicated need for higher AED load in other types of IGE.
1. Introduction

Patients with juvenile myoclonic epilepsy (JME), a common subtype of idiopathic generalized epilepsy (IGE), generally respond well to lower dosages of appropriate antiepileptic drugs (AEDs), but some patients need more doses and higher dosages of AEDs or their JME remains intractable. Focal electroencephalography (EEG) abnormalities and family history of epilepsy are correlated with poor seizure prognosis in patients with JME (Jayalakshmi et al., 2010; Tekin Güveli et al., 2013), but the value of these predictive factors to indicate poor seizure outcome remains controversial (Baykan et al., 2008; Gelisse et al., 2001). Seizure outcome is commonly used to evaluate drug resistance in patients with epilepsy. Most patients with JME who remain seizure-free would be considered to have no drug resistance using this criterion. However, some such seizure-free patients needed higher drug load to control their seizures, which implies impaired drug responsiveness. The present study evaluated the predictive factors of higher drug load for seizure freedom in patients with IGE, to identify any differences between JME and other types of IGE (non-JME IGE).

2. Methods

2.1. Patients

We identified 37 patients with IGE including 18 with JME among 430 consecutive patients from the database of Tohoku University Hospital Epilepsy Monitoring Unit, Sendai, Japan. All patients underwent long-term video EEG monitoring (VEEG) for 4 or 5 days from September 2010 to December 2014. None of the 37 patients had received definitive diagnosis or had been seizure-free before VEEG evaluation. Twenty-four of the 37 patients with IGE who achieved seizure freedom for 1 year or longer with appropriate AEDs after VEEG were recruited for the present study, of whom 12 were diagnosed with JME. The other 8 and 4 patients were diagnosed with generalized tonic-clonic seizures alone and unspecified genetic generalized epilepsy, respectively. Eventually, these patients were classified as non-JME IGE. The
diagnosis of JME was based on the criteria of the International League Against Epilepsy (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). All patients also had: (i) no evidence of neurological or intellectual deficit; (ii) normal EEG background and generalized epileptiform abnormalities; and (iii) no potential epileptogenic lesion identified by 3-T magnetic resonance imaging and no focal hypometabolism by $^{18}$F-fluoro-deoxy-glucose positron emission tomography.

2.2. VEEG data

The 21-channel EEG recording was performed according to the international 10-20 system using a long-term VEEG system (Neuro Fax EEG-1200, Nihon Kohden, Tokyo, Japan). The VEEG data were retrospectively reviewed to evaluate the presence of focal epileptiform abnormalities (FEAs). A board-certified clinical neurophysiologist (K.J.) reviewed the long-term EEG recordings using the bipolar and referential montages. Sleep stages were scored based on the American Academy of Sleep Medicine criteria (Iber et al., 2007). The interictal EEG findings were determined according to the International Federation of Clinical Neurophysiology glossary of terms (Noachtar et al., 1999). A single focal spike or a focal spike preceding a generalized spike and wave complex was defined as FEA (Figs. 1 and 2). To consider spikes as focal, we modified the previously reported method (Japaridze et al., 2016). Spikes were considered focal only if seen over one side of bipolar montages and if the distribution of the negative potentials over the head was strictly unilateral and confined to 1 to 3 adjacent regions. Bilateral distribution and multifocal distribution were excluded.

2.3. AED load

The prescribed daily dose (PDD)/defined daily dose (DDD) ratio (PDD/DDD) (Canevini et al., 2010) was calculated for each AED, and the sum of each ratio for prescribed AEDs at the final visit was defined as the total AED load. Serum drug levels were used to determine the
appropriate PDD in each patient. The DDD corresponds to the assumed average maintenance
daily dose of a drug used for its main indication (World Health Organization, 2017). Patients
were classified into higher and lower AED load groups based on total PDD/DDD values (total
PDD/DDD >1 and ≤1, respectively). Clinical features such as age, duration of epilepsy, sex,
family history of epilepsy among first to fourth degree relatives, seizure types, interictal FEAs,
prescribed AEDs at the final visit, and AED load were compared between these two groups.

2.4. Statistical methods

Data are given as median (range) values. Welch’s t test for continuous variables and Fisher’s
exact probability test for categorical variables were used. p < 0.05 was considered statistically
significant. All statistical calculations used computer software JMP Pro 12 (SAS Institute, Cary,
NC, USA).

3. Results

3.1. Comparison between patients with JME and non-JME IGE

Table 1 compares the clinical features of patients with JME and non-JME IGE. The age at
admission was significantly higher in the non-JME IGE group than in the JME group.
Myoclonic seizures were only seen in patients with JME. Interictal FEAs were observed during
both wakefulness and non-rapid eye movement sleep. Interictal FEAs during sleep were
observed at significantly higher rate in the non-JME IGE group compared to the JME group,
although no significant difference was found in the occurrence of interictal FEAs between these
groups. No significant differences were found in any other clinical features such as sex, age at
onset, duration of epilepsy, age of admission, family history of epilepsy, history of absence
seizures, prescribed AEDs, and PDD/DDD. No recruited patients had prominent psychiatric
issues.

Table 2 shows the median PDD and the number of patients, as well as DDD values for
individual AEDs. There were no significant differences in AED load between these two groups.

3.2. Comparison between higher and lower AED load groups

Tables 3a and 3b compare the clinical features between the higher and lower AED load groups, in patients with JME and non-JME IGE, respectively. Patients with JME in the higher AED load group had more interictal FEAs, family history of epilepsy, and ratio of patients taking lamotrigine than in the lower AED load group, although no significant differences were found in sex, age at onset, duration of epilepsy, age of admission, seizure types, ratio of interictal FEAs during sleep, and other prescribed AEDs. No significant difference was found in any clinical features in patients with non-JME IGE between the higher and lower AED load groups.

4. Discussion

The present study defined impaired drug responsiveness as higher AED load needed to achieve seizure freedom, and specifically investigated the difference in predictive factors of impaired drug responsiveness between JME and non-JME IGE. The present results showed that the presence of interictal FEAs and family history of epilepsy were associated with higher AED load needed for seizure freedom in patients with JME, but not in patients with non-JME IGE.

The presence of focal EEG abnormalities, combination of all 3 seizure types, family history of epilepsy, psychiatric disorders, delayed diagnosis, poor medication adherence, and psychosocial problems are all reported predictive factors for poor seizure outcome in patients with JME (Tekin Güveli et al., 2013; Baykan et al., 2008; Gelisse et al., 2001; Dasheiff and Ritaccio, 1993; Hirano et al., 2008), and can be classified into predictive factors for true- and pseudo-drug resistance. Poor medication adherence and psychosocial problems are predictive factors for pseudo-drug resistance. Patients with JME who suffered recurrence of seizures despite excellent initial response to AEDs had poor medication adherence or psychosocial
problems (Hirano et al., 2008). In contrast, presence of focal EEG abnormalities, combination of all 3 seizure types including absence seizures as well as myoclonic and generalized tonic-clonic seizures, family history of epilepsy, psychiatric disorders, and delayed diagnosis are predictive factors for true-drug resistance.

Some case series of JME have compared good and poor seizure outcome groups, after excluding patients with pseudo-drug resistance. Focal EEG abnormalities and family history of epilepsy were found to be correlated with poor seizure outcome in one study (Tekin Güveli et al., 2013), but were not associated with poor seizure outcome in other studies (Baykan et al., 2008; Gelisse et al., 2001). Therefore, the predictive power of these factors for poor seizure outcome remains controversial. Consequently, predictive factors for drug resistance have not been fully clarified in patients with JME.

Seizure outcome is commonly used to evaluate drug resistance in patients with epilepsy. Up to 85% of patients with JME become seizure-free with adequate medication with AEDs (Höfler et al., 2014). Therefore, patients without seizures would generally be considered to have no drug resistance. However, some patients require multiple AEDs to achieve seizure freedom, whereas others only require low doses of single AED. In addition, classification based on seizure outcome cannot easily differentiate patients with pseudo-drug resistance from patients with true-drug resistance. Therefore, the present study enrolled only seizure-free patients and defined impaired drug responsiveness as low effectiveness of AEDs. The AED load is a standardization method for overall evaluation of dose numbers and dosages of AEDs. We compared the dose numbers and dosages of AEDs in the same outcome group to evaluate drug resistance based on total AED load required for seizure freedom.

This study specifically investigated the difference in predictive factors for impaired drug responsiveness between JME and non-JME IGE. A previous study reported an association between the presence of focal EEG abnormalities and other clinical factors in patients with IGE including JME (Esmail et al., 2016), but did not compare JME and non-JME IGE.
JME is a well-defined clinical syndrome but may be distinct from other IGE syndromes (Zifkin et al., 2005). A comprehensive review of neuropsychological and imaging data showed functional and structural abnormality in the frontal cortex in patients with JME (Wandschneider et al., 2012). Patients with JME might show FEAs with aspects of focal epilepsy, whereas patients with non-JME IGE show FEAs as a fragment of generalized spikes. Fragmentation of generalized discharges in IGE including JME is sometimes observed during sleep (Hrachovy and Frost, 2006). Our study showed that the rate of interictal FEAs during sleep was significantly higher in the non-JME IGE group than in the JME group. This finding may suggest that FEAs during sleep imply fragmentation of generalized discharges, whereas FEAs during wakefulness imply focal functional abnormality, although further investigation is required to establish this hypothesis.

JME is also characterized by high genetic involvement (Marini et al., 2004). An interesting case illustrates the close relationship between FEAs and a family history of epilepsy. A 16-year-old girl with JME had a family history of epilepsy and presented with focal as well as generalized EEG abnormalities occurring both interictally and ictally (Bartocci et al., 2007). Molecular genetic analysis identified polymorphism of the EFHC1 and GABRA1 genes. Mutations of EFHC1 and GABRA1 genes occur in autosomal dominant JME (Cossette et al., 2002; Suzuki et al., 2004). Such polymorphism of these genes might have caused FEAs as well as a family history of epilepsy in this patient.

Several limitations of this study should be acknowledged. First, larger sample size is needed for multivariate analysis, because interictal FEAs and family history of epilepsy may be related. We excluded patients who had not achieved seizure freedom with appropriate AEDs after VEEG, because patients with pseudo-drug resistance were difficult to distinguish from those with true-drug resistance. Further study is required to establish the predictive factors of true-drug resistance. In addition, a comparative study between JME and other specific diagnoses of IGE is also required, because non-JME IGE is extremely heterogeneous. Future multicenter
studies should meet these requirements. Finally, our patients with higher AED load may simply be overtreated. Some of them might continue to achieve seizure freedom with lower doses or fewer drugs, but general application of this approach will raise ethical problems.

5. Conclusion

The present study investigated predictive factors for higher AED load in seizure-free patients with IGE to evaluate impaired drug responsiveness in IGE, especially focusing on the difference between JME and non-JME IGE. The presence of interictal FEAs and a family history of epilepsy are significantly associated variables of higher AED load for seizure freedom in patients with JME, but not in patients with non-JME IGE.

Conflict of interest

KJ has received honoraria for presentations from UCB Japan and Otsuka Pharmaceutical Co., Ltd. NN has received a scholarship donation from Otsuka Pharmaceutical Co., Ltd. and received a grant from Ricoh Co., Ltd. for a donated fund laboratory and received honoraria for presentations from Daiichi Sankyo Co., Ltd. and Eisai Co., Ltd. The remaining authors have no conflicts of interest. 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.

Acknowledgements

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**LEGENDS**

**Fig. 1.** Typical examples of interictal focal epileptiform abnormalities in a 14-year-old female with juvenile myoclonic epilepsy. Left: Focal left frontal spike (filled circle) in the average reference montage. Right: Focal left frontal spike (filled circle) in the bipolar montage. Spikes were considered focal only if seen over one side of bipolar montages and if the distribution of the negative potentials over the head was strictly unilateral and confined to 1 to 3 adjacent regions.

**Fig. 2.** Typical examples of interictal focal epileptiform abnormalities in a 14-year-old female with juvenile myoclonic epilepsy. Left: Focal left frontal spike (filled circle) preceded a generalized spike and wave complex in the average reference montage. Right: Focal left frontal spike (filled circle) preceded a generalized spike and wave complex in the bipolar montage. Spikes were considered focal only if seen over one side of bipolar montages and if the distribution of the negative potentials over the head was strictly unilateral and confined to 1 to 3 adjacent regions.
Table 1

Comparison of clinical features between patients with juvenile myoclonic epilepsy (JME) and other types of idiopathic generalized epilepsy (non-JME IGE).

<table>
<thead>
<tr>
<th></th>
<th>JME (n=12)</th>
<th>Non-JME IGE (n=12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male), %</td>
<td>33.3</td>
<td>66.7</td>
<td>0.11</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>14.0 (4–19)</td>
<td>14.0 (9–18)</td>
<td>0.67</td>
</tr>
<tr>
<td>Duration of epilepsy, y</td>
<td>5.5 (1–11)</td>
<td>8.0 (0–46)</td>
<td>0.10</td>
</tr>
<tr>
<td>Age of admission, y</td>
<td>19.5 (14–26)</td>
<td>24.5 (17–56)</td>
<td>0.05*</td>
</tr>
<tr>
<td>Family history of epilepsy, %</td>
<td>58.3</td>
<td>25.0</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Seizure types, %

<table>
<thead>
<tr>
<th></th>
<th>JME (n=12)</th>
<th>Non-JME IGE (n=12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>25.0</td>
<td>33.3</td>
<td>0.67</td>
</tr>
<tr>
<td>GTCS</td>
<td>100.0</td>
<td>91.7</td>
<td>1</td>
</tr>
<tr>
<td>MS</td>
<td>100.0</td>
<td>0</td>
<td>0*</td>
</tr>
<tr>
<td>Interictal FEAs (wakefulness/sleep), %</td>
<td>58.3 (18/14)</td>
<td>50.0 (7/20)</td>
<td>0.7 (0.03*</td>
</tr>
</tbody>
</table>

Prescribed AEDs, † %

<table>
<thead>
<tr>
<th></th>
<th>JME (n=12)</th>
<th>Non-JME IGE (n=12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>33.3</td>
<td>41.7</td>
<td>1</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>58.3</td>
<td>33.3</td>
<td>0.41</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>66.7</td>
<td>75.0</td>
<td>0.67</td>
</tr>
<tr>
<td>PDD/DDD †</td>
<td>0.70 (0.13–2.53)</td>
<td>1.03 (0.13–1.53)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Age, duration, and PDD/DDD are median (range). Welch’s t-test was used for comparison of clinical features. *p < 0.05.

†At the final visit.

AS, absence seizure; GTCS, generalized tonic-clonic seizure; MS, myoclonic seizure; FEAs, focal epileptiform abnormalities; AEDs, antiepileptic drugs; PDD/DDD, sum of the daily dose/defined daily dose ratio for prescribed antiepileptic drugs.
Table 2

Defined daily dose (DDD) values based on the assignment made by the World Health Organization (2017) and prescribed daily dose (PDD) for individual antiepileptic drugs in the present study.

<table>
<thead>
<tr>
<th>Antiepileptic drugs</th>
<th>DDD, mg</th>
<th>PDD, mg; n</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>JME</td>
<td>Non-JME IGE</td>
</tr>
<tr>
<td>Clobazam</td>
<td>20</td>
<td>5; 1</td>
<td>–</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>8</td>
<td>1 (0.5–1.5); 2</td>
<td>0.5; 1</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>300</td>
<td>275 (200–400); 4</td>
<td>200 (50–400); 5</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1500</td>
<td>1000 (500–2000); 7</td>
<td>1250 (1000–2000); 4</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>100</td>
<td>–</td>
<td>60; 1</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>300</td>
<td>–</td>
<td>150; 1</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>1500</td>
<td>500 (400–800); 8</td>
<td>400 (200–800); 9</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>200</td>
<td>200; 1</td>
<td>–</td>
</tr>
</tbody>
</table>

PDD is median (range). Welch’s t-test was used for comparison of PDD.

JME, juvenile myoclonic epilepsy; Non-JME IGE, other types of idiopathic generalized epilepsy.
### Table 3a

Comparison of clinical features between higher and lower antiepileptic drug load groups in juvenile myoclonic epilepsy (JME).

<table>
<thead>
<tr>
<th></th>
<th>PDD/DDD(\dagger) ≤1, n=7</th>
<th>PDD/DDD(\dagger) &gt;1, n=5</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male), %</td>
<td>14.3</td>
<td>60.0</td>
<td>0.22</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>15 (9–19)</td>
<td>12 (4–15)</td>
<td>0.29</td>
</tr>
<tr>
<td>Duration of epilepsy, y</td>
<td>5 (1–11)</td>
<td>6 (1–11)</td>
<td>0.73</td>
</tr>
<tr>
<td>Age of admission, y</td>
<td>20 (14–26)</td>
<td>18 (15–22)</td>
<td>0.33</td>
</tr>
<tr>
<td>Family history of epilepsy, %</td>
<td>28.6</td>
<td>100</td>
<td>0.03*</td>
</tr>
<tr>
<td>Seizure types, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td>42.9</td>
<td>20.0</td>
<td>0.58</td>
</tr>
<tr>
<td>GTCS</td>
<td>100.0</td>
<td>100.0</td>
<td>1</td>
</tr>
<tr>
<td>MS</td>
<td>100.0</td>
<td>100.0</td>
<td>1</td>
</tr>
<tr>
<td>Interictal FEAs (wakefulness/sleep), %</td>
<td>28.6 (5/5)</td>
<td>100 (13/9)</td>
<td>0.03* (0.71)</td>
</tr>
<tr>
<td>Prescribed AEDs, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>0</td>
<td>80.0</td>
<td>0.01*</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>42.9</td>
<td>80.0</td>
<td>0.29</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>71.4</td>
<td>60.0</td>
<td>0.71</td>
</tr>
</tbody>
</table>

### Table 3b

Comparison of clinical features between higher and lower antiepileptic drug load groups in other types of idiopathic generalized epilepsy (non-JME IGE).

<table>
<thead>
<tr>
<th></th>
<th>PDD/DDD(\dagger) ≤1, n=6</th>
<th>PDD/DDD(\dagger) &gt;1, n=6</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male), %</td>
<td>66.7</td>
<td>66.7</td>
<td>1</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>14 (9–18)</td>
<td>15 (8–17)</td>
<td>0.88</td>
</tr>
</tbody>
</table>
Duration of epilepsy, y 8.5 (2–46) 8 (0–34) 0.94
Age of admission, y 24.5 (18–56) 22 (17–45) 0.97
Family history of epilepsy, % 16.7 33.3 1
Seizure types, %
  AS 16.7 33.3 1
  GTCS 80.0 100.0 1
  MS 0 0 1
Interictal FEAs (wakefulness/sleep), % 33.3 (2/5) 66.7 (5/15) 0.57 (1)
Prescribed AEDs, † %
  Lamotrigine 33.3 50.0 0.62
  Levetiracetam 16.7 50.0 0.55
  Valproic acid 83.3 66.7 0.55

Age and duration are median (range). Welch’s t-test was used for the comparison of age at onset and age at admission. Fisher’s exact probability test was used for comparison of sex, family history of epilepsy, history of absence seizure, and interictal focal epileptiform abnormalities.

* p < 0.05.

† At the final visit.

AS, absence seizure; GTCS, generalized tonic-clonic seizure; MS, myoclonic seizure; FEAs, focal epileptiform abnormalities; AED, antiepileptic drug; PDD/DDD, sum of the daily dose (PDD)/defined daily dose (DDD) ratio (PDD/DDD) for prescribed antiepileptic drugs; FEAs, focal epileptiform abnormalities.
【論文目録】

Ⅰ 主論文

Predictive factors of higher drug load for seizure freedom in idiopathic generalized epilepsy: Comparison between juvenile myoclonic epilepsy and other types

Ⅱ 副論文

なし

Ⅲ 参考論文

外傷性皮質病変と海馬硬化を伴う内側側頭葉てんかんの1手術例
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*臨床神経学*, 第57巻第11号, 頁698–704, 2017

多小脳回患者で認められた正中神経刺激体性感覚誘発反応における異常ダイポール回転現象
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*日本生体磁気学会誌*, 第30巻第1号, 頁122–123, 2017