Prognostic Role of Focal Clinical Findings and Electroencephalographic Features of Patients With Juvenile Myoclonic Epilepsy

Juvenil Miyoklonik Epilepsi Hastalarında Fokal Klinik Bulgular ve EEG Özelliklerinin Prognostik Rolü

Yasemin BİÇER GÖMCELİ, Gülnihal KUTLU, Beyhan GÖNÜLAL, Levent Ertuğrul İNAN

Department of Neurology, Antalya Education and Research Hospital, Antalya
Department of Neurology, Ankara Education and Research Hospital, Ankara

Summary

Objectives: Our aim was to investigate the relationship between the focal clinical findings and electroencephalographic (EEG) features of patients with juvenile myoclonic epilepsy (JME) and their prognosis.

Methods: We retrospectively studied the clinical and EEG features of 110 patients with JME and classified each seizure type and its evolution according to the semiologic seizure classification. Focal semiologic features and focal interictal EEG findings were defined in each patient.

Results: Fifteen patients (13.6%) had focal clinical features, and 13 patients (11.8%) had isolated focal EEG abnormalities. Regarding their prognosis, patients were classified into three groups: seizure free, good prognosis, or poor prognosis. Ten patients had a poor prognosis, and 9 (90%) of those patients exhibited focal clinical features, focal EEG features, or both.

Conclusion: Our study supported that focal clinical features, except the presence of auras, and focal or asymmetrical features plus generalized EEG abnormalities, especially isolated focal EEG features, as suggestive of a poor prognosis.

Key words: Electroencephalography; focal features; juvenile myoclonic epilepsy; prognosis.

Özet

Amaç: Bu çalışmada juvenil myoklonik epilepsi (JME) hastalarında fokal klinik bulgular ve elektroencefalografik (EEG) özelliklerinin prognoz ile ilişkilerini araştırmayı amaçladık.

Gereç ve Yöntem: Geriye dönük olarak 110 JME hastasının klinik ve EEG özellikleri incelendi ve her bir nöbet tipi ve gelişimi semiyolojik nöbet sınıflamasına göre sınıflandırıldı. Fokal semiyoljik özellikler ve fokal interiktal EEG bulguları olan hastalar belirlendi.

Bulgular: On beş hastada (%13.6) fokal klinik özellikler, 13 hasta (%11.8) izole fokal EEG anormaliteleri mevcuttu. Hastalar prognoz özelliklerine göre; nöbet, işi, iyi prognoz ve kötü prognoz olarak üç gruba sınıflandırıldı. Kötü prognozu olan 10 hastanın 9’unda (%90) fokal klinik özellikler, fokal EEG özellikleri veya ikisi birden mevcuttu.

Sonuç: Bizim çalışmamız auralar haricindeki fokal klinik özelliklerin, jeneralize EEG anormaliteleri ile birlikteli fokal veya asimetrik EEG özelliklerinin ve özellikle de izole fokal EEG anormalitelerinin kötü prognozu öngörebileceğini desteklemektedir.

Anahtar sözcükler: Elektroencefalografı; fokal özellikler; juvenile myoclonic epilepsy; prognoz.

Accepted (Yayın kabul tarihi): 05.2.2012

e-mail (e-posta): yasemingomceli@hotmail.com

© 2012 Türk Epilepsi ile Savaş Derneği
© 2012 Turkish Epilepsy Society
Introduction

Juvenile myoclonic epilepsy (JME) is a hereditary, idiopathic, generalized form of epilepsy and is estimated to account for approximately 10% of all epilepsies, with a range of 4% to 11%.[1] Seizures have an age-related onset and are characterized by the triad of myoclonic jerks on awakening, generalized tonic-clonic seizures (GTC), and typical absence seizures. In classical cases of JME, the seizures are usually bilateral and symmetrical, and the electroencephalographic (EEG) findings reveal generalized interictal epileptiform discharges and a generalized seizure pattern that is bilaterally synchronous.[2]

The presence of focal EEG abnormalities and focal clinical features often cause difficulties and errors in the diagnosis of JME.[3] Despite well-defined clinical and EEG features of patients with JME, only a few reports have addressed the prognosis for these patients.[4-8]

In this study, we aimed to investigate the relationship between the focal clinical findings and EEG features of patients with JME and their prognosis.

Materials and Methods

We retrospectively analyzed 2581 charts of patients in our Epilepsy Department, with the aim of identifying patients with a diagnosis of JME. Between May 1995 and October 2008, 144 patients of our Outpatient Department were diagnosed with JME. The criteria for exclusion were insufficient clinical data; irregular follow-up, treatment, or lifestyle; association of partial seizures; and follow-up period <1 year. Among the 144 patients with JME, 110 of them had regular follow-ups for at least 1 year and were included in this study. Four of the 144 patients had additional partial seizures, which was confirmed with long-term video-EEG monitoring, and were excluded from the study. All the patients were seen by the same neurologists with an interest in epilepsy, and the diagnosis of JME was confirmed based on the clinical and EEG findings, using the following International League Against Epilepsy classification criteria for epilepsies and epileptic syndromes: myoclonic jerks with or without an association to generalized tonic-clonic (GTC) seizures or absence seizures, onset in puberty, and normal neurological examination.[9] A detailed history of the type and frequency of the seizures was obtained from the patients, parents, and other relatives. We classified each seizure type and its evolution according to the semiologic seizure classification. Focal semiologic features included auras, asymmetrical or unilateral myoclonic jerks, focal tonic seizures, focal clonic seizures, asymmetrical tonic limb posturing, and version before the tonic phase of the GTC seizures. All of the patients had regular follow-up visits every 3-6 months at our Epilepsy Department. Each visit included a neurological examination, survey of the frequency of each seizure type, and routine blood analysis.

The EEG evaluation was performed and analyzed at the same institution. The standard placement of 10-20 electrodes was used for the EEG recordings. The standard recording phase lasted 20 min and the hyperventilation phase lasted 4 min. Intermittent photic stimulation was performed with frequencies of 5, 10, 15, and 20 flashes/s, and 0.5 and 70 Hz filters were used. The interictal EEG findings for each patient were analyzed for any focal or generalized features. Focal interictal EEG findings were defined as isolated regional slow waves and regional epileptiform discharges (sharp, spike, spike-wave complexes, or polyspikes), whereas generalized features were defined as generalized irregular slow waves and generalized epileptiform activity. Focal or lateralized epileptiform abnormalities (hemispheric predominance) and generalized epileptiform abnormalities on the EEGs of the patients were also defined.

Results

We included 110 consecutive patients (85 female and 25 male) with a clinical diagnosis of JME. The mean age at first evaluation was 24.7 years (range, 14 to 58 years). The mean age at onset of epilepsy was 14.5 years (range, 5 to 25 years). The mean delay between the first seizure and the diagnosis of JME was 5.4±4.2 years.

Nine of the 110 patients (8.2%) had a history of febrile convulsions and 30 of the 110 patients (27.3%) had a history of epilepsy in their first-degree relatives. No patient had a history of any major disease, and the neurological examinations were normal in all cases. Brain magnetic resonance imaging (MRI) was performed on 33 patients, and brain computerized tomography (CT) was performed on 43 patients.

Seizures

The most common clinical presentation was myoclonic and GTC seizures together (66 patients, 60%), whereas
myoclonic seizures alone existed in 13 patients (11.8%). Table 1 shows the seizure types of the 110 patients included in this study.

Eighty-three patients (75.5%) had typical generalized seizures, whereas 27 patients (24.5%) had seizures with focal clinical features. Twelve patients had an aura before the symmetrical GTC seizures, without any other focal clinical features. Therefore, these 12 patients were identified as distinctive. Except for the patients with these isolated auras, 15 patients had focal clinical features. Asymmetrical myoclonic seizures were recorded in 8 patients, asymmetrical tonic limb posturing during GTC seizures were recorded in 3 patients, auras and versive head and eye deviations during GTC seizures were recorded in 1 patient, and head and eye deviations during GTC seizures without auras were described in 3 patients.

**EEG**

At least two EEGs were obtained from all the patients. The number of EEGs per patient ranged from 2-6 (mean, 3.2), with a total of 352 tracings. Sleep EEGs were performed in 86 patients. Table 2 summarizes the EEG findings.

The EEGs showed characteristic generalized abnormalities in 55 of the 110 patients (50%). Generalized typical abnormalities and additional focal or lateralized (hemispheric predominance) abnormalities were observed in 20 patients (18.1%). Isolated focal abnormalities were observed in 13 patients (11.8%). None of these 13 patients had any clinical focal semiologic features. The EEG was always normal in 17 patients.

**Treatment**

Ninety-eight patients (89%) received monotherapy and 12 patients received polytherapy. The most common single-drug regimen utilized valproic acid (91 patients, 82.7%). Table 3 shows the drug regimens used with the patients.

**Prognosis**

The average follow-up period was 3.5 years (range, 1 to 12 years) at our epilepsy unit. Regarding the prognosis, patients were divided into three groups. Patients were considered to be ‘seizure free’ if they had not had a seizure for at least 1 year. Patients were classified as having a ‘good prognosis’ if they only had isolated, rare myoclonic jerks in response to severe precipitant factors. Patients were classified with a ‘poor prognosis’ if their seizures continued, with or without a reduction in frequency. Eighty-two of the 110 patients (74.5%) were seizure free, 18 patients (16.4%) had a good prognosis, and the remaining 10 patients (9.1%) had a poor prognosis. All patients with isolated myoclonic jerks (13 of the 110 patients) and additional absence seizures (11 of the 110 patients) were considered seizure free. Seven of the 10 patients with a poor prognosis had focal clinic features or isolated focal EEG abnormalities. Furthermore, 1 of the 10 patients with a poor prognosis had focal plus generalized EEG abnormalities, and 1 of the 10 patients with a poor prognosis had focal clinic features along with focal plus generalized EEG abnormalities. Auras were recorded in 14 patients, which occurred prior to typical symmetrical GTC seizures in 13 of these patients; all 13 of these patients were seizure free. Except for isolated auras, focal clinical features were observed most frequently in patients with a poor prognosis. Focal epileptiform abnormalities were observed the least in patients of the seizure-free group (2 of 82 patients). The frequencies for the focal clinical and EEG abnormalities are summarized in Table 4.

Despite adequate treatment, 10 of the 110 patients were medically intractable. Table 5 shows the demographic

---

**Table 1. Types of seizures of patients**

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoclonic jerks only</td>
<td>13 (11.8%)</td>
</tr>
<tr>
<td>Myoclonic + GTC seizures</td>
<td>66 (60%)</td>
</tr>
<tr>
<td>Myoclonic + Absence seizures</td>
<td>11 (10%)</td>
</tr>
<tr>
<td>Myoclonic + Absence + GTC seizures</td>
<td>20 (18.2%)</td>
</tr>
</tbody>
</table>

GTC: Generalized tonic-clonic.

**Table 2. EEG findings of patients**

<table>
<thead>
<tr>
<th>EEG</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized epileptiform activity</td>
<td>55 (50%)</td>
</tr>
<tr>
<td>Generalized irregular slow waves</td>
<td>3 (2.7%)</td>
</tr>
<tr>
<td>Generalized + focal epileptiform activity</td>
<td>20 (18.1%)</td>
</tr>
<tr>
<td>Focal epileptiform activity</td>
<td>13 (11.8%)</td>
</tr>
<tr>
<td>Focal irregular slow waves</td>
<td>2 (1.8%)</td>
</tr>
<tr>
<td>Normal</td>
<td>17 (15.4%)</td>
</tr>
</tbody>
</table>
data, clinical and EEG findings, and treatment of the patients with a poor prognosis.

**Discussion**

Typical cases of JME manifest as bilateral symmetrical seizures and abnormal EEG patterns. Clinical or EEG focal- ity, asymmetry, or both may lead to misdiagnosis of JME in some patients.

The most important element in the diagnosis of JME is the patient’s history. Myoclonic jerks are seen in 100% of the cases of JME and are necessary for the diagnosis. Myoclonic jerks are brief, bilateral, usually symmetrical, and predominantly involve the shoulders and arms. Some jerks occur unilaterally, which may mislead doctors toward a diagnosis of focal motor seizures. Predominantly unilateral jerks were reported by 8 of our patients (7.2%), and 5 of these patients had been misdiagnosed as having focal motor seizures. GTC seizures occurring in patients with JME are often characterized by an absence of auras, symmetry, remarkable violence, and a long-duration tonic phase. Atypical focal clinical features, such as version of the head or eyes or both, focal tonic seizures, focal clonic seizures, asymmetrical tonic limb posturing, versive or circling seizures, have been associated with some patients with JME. In our study, asymmetrical tonic limb posturing during GTC seizures were recorded in 3 patients, and versive head and eye deviations during GTC seizures were recorded in 4 patients. None of our patients had circling seizures.

EEGs were important for confirming or suggesting the appropriate diagnosis for the patients with JME. EEG abnormalities have classically been reported as characterized by generalized polyspike and slow-wave discharges that predominate in the frontal regions. Other EEG findings include spike and wave complexes, single spikes, and irregular slow-wave complexes. Asymmetrical generalized discharges and focal abnormalities (either independent or associated with generalized paroxysms) may be observed in some patients with JME. These focal abnormalities may present as focal slow waves, spikes, or sharp waves, which may lead to a misdiagnosis of partial epilepsy. Several authors reported focal or asymmetrical EEG abnormalities or both; however, the mechanisms for these abnormalities are unclear. One possible mechanism for repeated generalized epileptiform activities associated with focal cortical pathology is microdysgenesis. An alternative explanation is provided by the telencephalic theory which states that the cortex is diffusely excitable.

Thirty-five of our 110 patients (31.8%) had focal EEG abnor-

---

**Table 3. Treatment schedule of the patients**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Monotherapy</th>
<th>Polytherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA</td>
<td>91 (82.7%)</td>
<td>VPA+LTG</td>
</tr>
<tr>
<td>LTG</td>
<td>4 (3.6%)</td>
<td>VPA+TP</td>
</tr>
<tr>
<td>TP</td>
<td>1 (0.99%)</td>
<td>VPA+LVT</td>
</tr>
<tr>
<td>LVT</td>
<td>2 (1.8%)</td>
<td>VPA+CLN</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>VPA+LTG+CLN</td>
</tr>
<tr>
<td></td>
<td>98 (89.0%)</td>
<td>12 (11.0%)</td>
</tr>
</tbody>
</table>

CLN: Clonazepam; LTG: Lamotrigine; LVT: Levetiracetam; TP: Topiramate; VPA: Valproic acid.

---

**Table 4. Focal clinical features and focal plus generalized EEG abnormalities of the patients.**

<table>
<thead>
<tr>
<th>Seizure Free (n=82)</th>
<th>Good Prognosis (n=18)</th>
<th>Poor Prognosis (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCF (15/110)</td>
<td>8 (9.7%)</td>
<td>4 (22.2%)</td>
</tr>
<tr>
<td>FEA (13/110)</td>
<td>2 (2.4%)</td>
<td>7 (38.8%)</td>
</tr>
<tr>
<td>FEA+GEA (20/110)</td>
<td>11 (13.4%)</td>
<td>7 (38.8%)</td>
</tr>
</tbody>
</table>

FCF: Focal clinical features; FEA: Focal epileptiform abnormalities; GEA: Generalized epileptiform abnormalities.
malities. Twenty of these 35 patients had focal abnormalities associated with generalized epileptiform abnormalities, 13 had isolated focal epileptiform abnormalities, and 2 of them had focal irregular slow waves.

Despite the well-known clinical features of patients with JME, there is insufficient data regarding the risk factors associated with the intractable nature of this disorder. Seizures are generally well controlled with appropriate medication in approximately 90% of patients. However, it is of vital importance to identify what characteristics distinguish the patients that fall into the remaining 10% of the patient population and how we can determine their prognosis.

Few studies address what features are associated with poor seizure control in patients with JME. Jain et al. studied 15 patients with JME with myoclonic jerks alone and hypothesized that those patients presenting with early morning myoclonic jerks only may represent a benign variant of the disorder. Our results supported the findings of this report because 13 patients (11.8%) in the present study had myoclonic seizures alone, and all of them were considered seizure free. Matsuoka reported an excellent prognosis for 32 patients diagnosed with JME that had absence seizures and myoclonic jerks. The seizures were well controlled in the patients with absence seizures compared to patients with generalized tonic-clonic seizures or patients with generalized tonic-clonic seizures plus absence seizures. Gelisse et al. studied 155 patients with JME and found two independent situations that were significantly associated with poor therapeutic control of the disorder: the coexistence of all three seizure types (myoclonic jerks, absence seizures, and GTC seizures) and the existence of psychiatric problems. There were no cases of drug resistance in the patients that experienced isolated myoclonic jerks only or a combination of myoclonic jerks and absence seizures. In accordance with the findings of these reports, additional absence seizures were observed in 11 patients in our study (10%), and all of them were considered seizure free. Six of 10 intractable patients with JME in the present study had GTC seizures, and the remaining 4 patients had all three types of seizures. Ours was a retrospective study, so we cannot provide details regarding the neuropsychological status of the patients.

Dasheiff and Ritacco identified 12 patients with intractable JME who had a long duration of epilepsy (the diagnosis and treatment were delayed) and a high percentage of asymmetrical or focal discharges with scalp EEGs. The average duration of epilepsy in these patients was 21 years. Those authors thought that JME was not necessarily a benign epilepsy and suggested that alternative therapies, such as epilepsy surgery, may be indicated. Fernando-Dongas et al. studied 33 patients with JME and found that 23 patients were sensitive to valproic acid (VPA) and 10 pa-

Table 5. Clinical characteristics of the 10 patients with a poor prognosis

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/Sex</th>
<th>Types of Seizures</th>
<th>Clinical Features</th>
<th>EEG</th>
<th>Treatment</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19/M</td>
<td>MJ+GTC</td>
<td>Typical</td>
<td>FEA</td>
<td>VPA</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>29/M</td>
<td>MJ+GTC</td>
<td>Typical</td>
<td>FEA+GEA</td>
<td>VPA+LTG+CLN</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>24/F</td>
<td>MJ+GTC+A</td>
<td>Typical</td>
<td>FEA</td>
<td>VPA+LTG</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>48/F</td>
<td>MJ+GTC</td>
<td>Typical</td>
<td>GEA</td>
<td>VPA+TP</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>30/F</td>
<td>MJ+GTC+A</td>
<td>Typical</td>
<td>FEA</td>
<td>LVT</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>24/F</td>
<td>MJ+GTC+A</td>
<td>Typical</td>
<td>FCF</td>
<td>GEA</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>16/F</td>
<td>MJ+GTC+A</td>
<td>FCF</td>
<td>GEA</td>
<td>VPA+LTG</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>17/F</td>
<td>MJ+GTC</td>
<td>FCF</td>
<td>GEA</td>
<td>VPA+LTG</td>
<td>16</td>
</tr>
<tr>
<td>9</td>
<td>42/F</td>
<td>MJ+GTC</td>
<td>FCF</td>
<td>GEA+GEA</td>
<td>VPA</td>
<td>18</td>
</tr>
<tr>
<td>10</td>
<td>19/F</td>
<td>MJ+GTC</td>
<td>FCF</td>
<td>GEA</td>
<td>VPA</td>
<td>18</td>
</tr>
</tbody>
</table>

A: Absence seizures; CLN: Clonazepam; F: Female; FCF: Focal clinic features; FEA: Focal epileptiform abnormalities; GEA: Generalized epileptiform abnormalities; GTC: Generalized tonic-clonic seizures; LTG: Lamotrigine; LVT: Levetiracetam; M: Male; MJ: Myoclonic jerks; TP: Topiramate; VPA: Valproic acid.

1Aura and versive head and eye deviations during GTC seizures.
2Asymmetric tonic limb posturing during GTC seizures.
3Asymmetric myoclonic jerks.
tients were resistant. The VPA-resistant group had a higher frequency of EEG asymmetries, atypical seizure characteristics including auras and post-ictal confusion, and intellectual deficiencies. The average duration of epilepsy for our patients was 11.2 years in the seizure-free group and 13.3 years in the poor prognosis group. The epilepsy duration for these two groups was not significantly different from one another, and we did not find any relationship between a long duration of epilepsy and poor prognosis in patients with JME. In our study, the EEG patterns revealed that 6 of 10 patients (60%) in the poor prognosis group and 13 of 82 patients (15.8%) in the seizure-free group had isolated focal epileptiform abnormalities, or focal or lateralized epileptiform plus generalized epileptiform EEG abnormalities. In accordance with these reports, we found that focal EEG abnormalities were associated with a poor prognosis. In our study, auras occurred before the GTC seizures in 13 of 110 patients (11.8%). Only 1 patient (of 10) in the poor prognosis group described versive head and eye deviations during GTC seizures that followed an aura. Therefore, we did not find any relationship between the presence of auras a poor prognosis for JME. None of our patients had post-ictal confusion following absence seizures or myoclonic seizures.

Gelisse et al.[7] investigated the influence of structural brain lesions on the prognosis for JME in 82 patients. These authors confirmed that structural brain lesions were unrelated to the prognosis for patients with JME, and neuroimaging procedures should not be performed routinely in typical cases. In our series, we had brain neuroimaging data for 76 patients (MRI for 33 patients, CT for 43 patients) and only 11 of the scans were considered abnormal. Five of the 10 patients with a poor prognosis received a cranial MRI, and the data from all of those patients were normal. Therefore, we cannot make any comment about a relationship between brain structure abnormalities and the prognosis for JME.

Nine of 10 patients (90%) with intractable JME in our series had abnormal focal clinical features, abnormal EEG features, or both. A few previous studies indentified focal clinical features in patients with JME,[8][11-13] only two of these studies discussed the effects of these features on patient prognosis. In these two studies, versive seizures or circling seizures in idiopathic generalized epilepsy did not coincide with a worsened prognosis,[13] and atypical seizure characteristics such as auras and post-ictal confusion were associated with the valproic acid-resistant patients with JME.[8] This is the first study in the English literature in which the results confirmed that the presence of focal clinical features (asymmetrical or unilateral myoclonic jerks, asymmetrical tonic limb posturing, version before the tonic phase of GTC) worsened the prognosis for patients with JME. In contrast to previous studies, we conclude that the presence of isolated auras did not affect the prognosis for JME. A relationship between focal or asymmetrical epileptiform abnormalities on EEGs and a poor prognosis for JME was determined in previous studies.[5,8] In our study, we found that focal or asymmetrical plus generalized EEG abnormalities, especially isolated focal EEG features, were suggestive of a poor prognosis.

We can summarize our results as follows: 1) Myoclonic jerks alone or together with absence seizures were associated with a good prognosis; the presence of GTC seizures or all three types of seizures were associated with a poor prognosis. 2) Typical clinical and EEG features were associated with a good prognosis; the presence of focal clinical or EEG abnormalities were associated with a poor prognosis. 3) Auras, although considered an atypical clinical feature, were not associated with a poor prognosis.

Focal clinical features, EEG abnormalities, or both in patients with JME are not uncommon. Clinicians should be aware of these atypical features and be aware of their negative influence on prognosis while following these patients.

References

4. Matsuoka H. The seizure prognosis of juvenile myoclonic epi-


