Original Article

Comparison of valporic acid efficacy in familial versus sporadic cases of juvenile myoclonic epilepsy

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Background: Juvenile myoclonic epilepsy is a heterogeneous syndrome, both in genetic and clinical aspects. Aims: This study was conducted to compare the efficacy of valproic acid in familial versus sporadic cases of this syndrome. Settings and Design: Seventy patients with JME were identified; 24 patients (34.3%) had positive history of JME in their first degree relatives (group I) and 46 patients (65.7%) were sporadic (group II). Materials and Methods: Valproic acid was started for the patients with upward titration. The cases were followed for one year after final titration of the drug with regular blood monitoring. Patients, who had no myoclonic, absence and grand mal seizures within one year, were considered excellent responders. Statistical Analysis: We used Student T-test and Fisher’s exact test for quantitative and qualitative variables respectively. Logistic Regression test was used to evaluate the predictive factors for final treatment outcomes. Results: Mean dosage of valproic acid was 800 mg/d in both groups (13 mg/kg and 12.4 mg/kg respectively). Mean therapeutic levels of the drug in group I and II were 74 µg/ml and 78.4 µg/ml respectively. Excellent responders’ rate was 66.7% in group I and 76.1% in group II. History of absences and older age at the onset of grand mal seizures decreased excellent responders’ rate in both groups. Conclusions: Considering response to valproic acid, there is no significant difference in familial versus sporadic cases of JME, whereas history of absences and older age at the onset of grand mal seizures decreased excellent responders’ rate in both groups.

Key words: Juvenile myoclonic epilepsy, valproate, epilepsy treatment

Introduction

Juvenile myoclonic epilepsy (JME) is a common form of idiopathic generalized epilepsies, having an overall prevalence of 4-10%.\(^1,2\)

It is the most common form of idiopathic generalized epilepsies, especially in women. Isolated myoclonic jerks of arms, shortly after awakening are characteristic. Generalized tonic - clonic seizures often occur and one third of cases also have absences. Seizure occurrence is more likely with sleep deprivation, fatigue and alcohol withdrawal.\(^3\)

Onset is usually in adolescence but seizures may begin or be diagnosed after the age of twenty.\(^4,5\)

A family history of epilepsy is common and there is evidence for linkage of the disease to chromosomes 6p and 15q.\(^6,7\)

The EEG background is typically normal and the characteristic interictal EEG findings are generalized 4-6 Hz polyspike and slow wave complexes, however, many patients have 3-4 Hz spike and slow wave complexes. More than half of patients may show normalization of EEG after drug therapy.\(^1\)

Valproic acid is currently the drug of choice and is reported to control the seizures in 80% of patients.\(^8\) Previous studies showed that those with all three seizure types are more likely to be poor responders\(^9,10\) and as JME is both genetically and clinically heterogeneous,\(^3\) we conducted this study to see if there is any difference between familial and sporadic cases in response to valproic acid.

Materials and Methods

Seventy patients (48 F, 22 M) with JME were studied. Study protocol (after getting approval from university ethics committee) was sent to our colleagues in general neurology clinics of the hospital and subjects with impression of JME were referred to epilepsy clinic. Cases were included according to the following criteria:

1. History of myoclonic jerks with history of generalized tonic-clonic seizures or absence at times.
2. Age at the onset between 8-25 years old.
3. At least one EEG with fast spike - slow waves or poly spike -
slow wave complexes and normal background.

Patients with mental retardation, history of severe head injury, pregnancy during the study and structural brain lesions, revealed by MRI, were excluded. Informed consents were obtained from the cases before inclusion.

Demographic data, family history of seizures, details about myoclonic jerks, generalized tonic-clonic seizures, absences, valproate associated adverse effects, any discontinuation and reasons, number of seizures at base line, during titration and after stable valproate dose, results of MRI and EEG were all registered. The patients who had family history of JME in their first degree relatives were considered familial (group I) and sporadic cases defined as those who had no history of seizure in their families (group II). Sodium Valproate (Tablet 200 mg) 400-600 mg/day started in these patients, upward titration was performed over a six weeks period until the patients were seizure free, intolerable side effects occurred, or a maximum dose of 600 mg/kg was reached and they were included in the study groups after eight weeks of treatment.

During drug escalation the patients were visited every 2-4 weeks and blood monitoring (CBC-LFT) was conducted. All the patients were followed for one year based on frequency of different types of seizures. Within one year following final titration of the drug, the patients were divided into two groups. Patients who had no myoclonic, absence and grandmal seizures were considered as excellent responders and the remaining patients were identified as non excellent responders.

We used student T-test for comparison of quantitative variables and Chi-square or Fisher’s exact test for qualitative ones. Variables that could be related to excellent response were subjected to analysis with a logistic regression procedure and forward stepwise selection. Dependent variables coded as zero for excellent response and one for other results. Odds ratio with 95% confidence interval assessed for one. Variables like age, sex, family history in the first degree relatives, history of absences, age at the onset of generalized tonic-clonic seizures, daily dose of valproic acid and its serum level (total of 7 variables) were included in the model as predictive factors. The maximum likelihood approach was used to estimate weights of the logistic parameters. Statistical analysis was performed using SPSS software (SPSS Inc, Chicago, IL).

Results

Seventy patients met selection criteria. 24 patients (34.3%) had history of JME in their first degree relatives (group I) and 46 patients (65.7%) were without positive family history (group II). The patients in group I (18 women, 6 men) ranged from 16 to 36 years, the group II (30 women, 16 men) ranged from 13 to 50 years. Both groups were comparable in age (mean 23.9 vs. 23.8), sex and age at the onset of myoclonic seizures (mean 14.8 vs. 14.5 years) age at the onset of absence seizures and also with respect to the frequency of their myoclonic, absence and grandmal seizures. We could not find any significant differences between age at the onset, type of seizures, response to treatment, serum valproate level and side effects of treatment in two groups [Tables 1 and 2]. Mean dosage of valproic acid was 800 mg/day (Range 400-1500) in both groups (13 mg/kg and 12.4 mg/kg respectively).

Mean therapeutic serum levels of the drug were 74 µg/ml (Range 50-99 µg/ml) in familial and 78.4 µg/ml (Range 54-131 µg/ml) in sporadic cases. During the study all the patients had more than 50% reduction in their seizures and excellent responders (seizure free) were 66.7% in group I and 76.1% in group II.

Sleep deprivation was the most common precipitating factor for seizures (72.9%) and the others, in order of decreasing frequencies, were stress, fatigue, drug withdrawal, hunger and alcohol [Table 3]. The mean daily dosage of valproic acid was 12.35 mg/kg (Range 7-25) in excellent responders and it was 13.1 mg/kg (Range 6-31) in non excellent responders.

Statistical analysis with logistic regression showed that history of absence seizures and age at the onset of generalized tonic-clonic seizures were predictive for non-excellent response to treatment (P= .01).

The odds ratio for absence seizures was 5.72 and for age at the onset of GTCS was 1.21

Discussion

Juvenile myoclonic epilepsy has been one of the most extensively studied epilepsy at the molecular levels as this syndrome has the advantage of being a common familial epilepsy with well defined clinical and EEG features. Despite being a familial disorder, significant number of cases (about one-half to one third) is sporadic. It is possible that the sporadic cases could be genotypically different or similar as compared with the familial ones. [11]

This study conducted to compare efficacy of valproic acid in familial versus sporadic cases. In our study 34.3% of the patients had family history of JME and 28% had a prior history of absence seizures. They were almost the same comparing to the other reports. [12,13]

Sporadic and familial cases of some neurological conditions may have differences in clinical manifestations and course. In Parkinson’s disease family history is accompanied by earlier age at the onset of disease and also slower motor and mental decline. [14]

Tordelli et al showed that age at the onset, is significantly lower in women with familial cluster headache comparing to sporadic cases [15] and familial Alzheimer disease has some special clinical and pathological characteristics. [16] On the other hand, in some diseases like migraine and multiple sclerosis the authors could not find any significant difference between familial and sporadic cases. [17,18]

As mentioned earlier, the over all clinical characteristics of familial and sporadic cases were similar. We could not find any significant difference between these two groups in response to valproic acid therapy, serum levels and side effects of the drug. This shows that
All the patients


Valproic acid in familial and sporadic cases of JME

Table 1: Mean daily dose of valporic acid and serum levels in familial and sporadic cases of JME

<table>
<thead>
<tr>
<th>Variables</th>
<th>All the patients</th>
<th>Familial JME</th>
<th>Sporadic JME</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean daily dose of valporic acid mg/kg</td>
<td>12.6</td>
<td>13.06</td>
<td>12.37</td>
<td>0.56 (student T-test)</td>
</tr>
<tr>
<td>Mean daily dose of valporic acid mg/day</td>
<td>800</td>
<td>800</td>
<td>800</td>
<td>0.95 (student T-test)</td>
</tr>
<tr>
<td>Mean serum level of valporic acid µg/ml</td>
<td>76.91</td>
<td>74.08</td>
<td>78.33</td>
<td>0.29 (student T-test)</td>
</tr>
</tbody>
</table>

Table 2: Side effects of valporic acid in familial and sporadic JME

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Total % (N=19)</th>
<th>Familial % (N=5)</th>
<th>Sporadic % (N=14)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain</td>
<td>27.1 (N=19)</td>
<td>20.8 (N=5)</td>
<td>30.4 (N=14)</td>
<td>0.39 (Chi-square test)</td>
</tr>
<tr>
<td>Hair loss</td>
<td>18.6 (N=13)</td>
<td>20.8 (N=5)</td>
<td>17.1 (N=8)</td>
<td>0.75 (Fisher's exact test)</td>
</tr>
<tr>
<td>Tremor</td>
<td>17.1 (N=12)</td>
<td>20.8 (N=5)</td>
<td>15.2 (N=7)</td>
<td>0.73 (Fisher's exact test)</td>
</tr>
<tr>
<td>Acne</td>
<td>10.0 (N=7)</td>
<td>8.3 (N=2)</td>
<td>10.9 (N=5)</td>
<td>1 (Fisher's exact test)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8.6 (N=6)</td>
<td>4.2 (N=1)</td>
<td>10.9 (N=5)</td>
<td>1 (Fisher's exact test)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>1.4 (N=1)</td>
<td>0</td>
<td>2.1 (N=1)</td>
<td>1 (Fisher's exact test)</td>
</tr>
<tr>
<td>Menstrual irregularities</td>
<td>14.6 (N=7)</td>
<td>11.1 (N=2)</td>
<td>16.1 (N=5)</td>
<td>1 (Fisher's exact test)</td>
</tr>
</tbody>
</table>

Table 3: Aggravating factors in patients with familial and sporadic JME

<table>
<thead>
<tr>
<th>Aggravating factors</th>
<th>Total % (N=51)</th>
<th>Familial % (N=17)</th>
<th>Sporadic % (N=34)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep deprivation</td>
<td>72.9 (N=51)</td>
<td>70.8 (N=17)</td>
<td>73.9 (N=34)</td>
<td>0.78 (Chi-square test)</td>
</tr>
<tr>
<td>Stress</td>
<td>52.9 (N=37)</td>
<td>54.2 (N=13)</td>
<td>52.2 (N=24)</td>
<td>0.87 (Chi-square test)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32.9 (N=23)</td>
<td>25 (N=6)</td>
<td>37 (N=17)</td>
<td>0.31 (Chi-square test)</td>
</tr>
<tr>
<td>Hanger</td>
<td>27.1 (N=19)</td>
<td>25 (N=6)</td>
<td>28.3 (N=13)</td>
<td>0.77 (Chi-square test)</td>
</tr>
<tr>
<td>Light</td>
<td>11.4 (N=8)</td>
<td>8.3 (N=2)</td>
<td>13 (N=6)</td>
<td>0.7 (Fisher's exact test)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>2.9 (N=2)</td>
<td>0</td>
<td>4.3 (N=2)</td>
<td>1 (Chi-square test)</td>
</tr>
<tr>
<td>Menstruation</td>
<td>22.9 (N=11)</td>
<td>22.2 (N=4)</td>
<td>23.3 (7)</td>
<td>1 (Fisher's exact test)</td>
</tr>
<tr>
<td>Drug withdrawal</td>
<td>31.4 (N=22)</td>
<td>37.5 (N=9)</td>
<td>28.3 (N=13)</td>
<td>0.12 (Chi-square test)</td>
</tr>
</tbody>
</table>

Valproate is equally effective in both groups and positive family history does not affect the prognosis.

Alcohol is considered as a common precipitating factor in other studies but it was one of the unusual precipitants in our cases. This may be explained by cultural differences, low prevalence of alcohol consumption and lack of reporting.

An interesting point was that the mean daily dose of valproate in excellent responders was 12.35 mg/kg (Rang 7-25), which is less than the standard recommended dose of 20-40 mg/kg. This may be due to differences in drug metabolism or protein binding. Controlling seizures with lower dosage has also been described in some other studies which help in reducing the toxic effects and increasing compliance of patients.[13]

It should be mentioned that history of absences and age at the onset of GTCS independently affect response to valproic acid. For history of absence seizures the odds ratio was 5.72 (1.51-21.69 CI= 95% P= 0.01). This means that a patient with history of absence seizures has approximately 5.7 times more chance to be in non excellent responders. For the age at the onset of GTCS the odds ratio was 1.21 (1.07-1.37 CI= 95% P= 0.02). This also shows that one year increase in age at the onset of GTCS increases this probability by 1.7 times. Other studies also reported that history of absences, or suffering from three seizure types in JME, increase probability to be a non responder to valproate therapy.[9,10]

Lack of genetic study and information about protein binding or drug metabolism in excellent and non excellent responders are our main limitations in this study.

Recognition of clinical subtypes among JME patients (especially excellent responders) could have therapeutic implications and help to improve the characterization of JME phenotypes. Conducting molecular studies in these subgroups may yield valuable information and we suggest more evaluations regarding genetic analysis and response to treatment in this syndrome.

Acknowledgements

We would like to acknowledge Dr. P. Tadj for her valuable assistance in statistical analysis and Mr. Hejrani for secretarial helps.

References

Invited Comments

Typically presenting in the early teenager years, Juvenile Myoclonic Epilepsy (JME) is a common epilepsy syndrome with a prevalence of 4-10% of all patients with epilepsy.[1] Patients with JME present with multiple seizure types including generalized tonic-clonic, absence and myoclonic jerks. At least 40% of patients with JME report a family history of JME. Genetic studies have indicated several potential loci, with the most commonly accepted site identified as chromosome 6p12-p11.[2] The mainstay of therapy for JME is valproate (VPA), with 80% of patients achieving seizure freedom and up to 90% achieving > 50% reduction in seizure frequency.[3]

In this issue, the authors describe their experience using VPA in 46 patients with sporadic JME, as compared to 24 patients with familial JME.[4] The authors prospectively evaluated a cohort of 70 patients with JME treated with VPA for one year. They obtained blood VPA levels and clinical responses and they defined excellent responders as those who were seizure free on treatment. They found no statistical difference in the number of patients who were excellent responders with sporadic JME (76.1%) as compared to those with familial JME (66.7%) with a family history of JME in a first degree relative. Mean drug level of VPA and mg/kg/day of dosage was also similar. History of absence seizures and increased age at the onset of grand mal seizures decreased the number of excellent responders (response rates) in both groups. This is in slight contrast to other reports which have shown poor responders to have all three sub-types of seizures, abnormal photo-paroxysmal response and psychiatric co-morbidities.[1]

This study has some limitations. Most importantly, the authors do not provide information as to whether the patients recruited in the study had new-onset seizures and were drug-naive or if the patients were previously treated. In addition, no information is provided on how seizure counts were monitored in the sub-types with absence seizures. A 24-hour ambulatory EEG is far more sensitive in assessing success to treatment in patients with absence seizures, since clinical observations may be misleading. Also, seizure freedom as an indicator of successful response to therapy may be misleading; a 50% reduction in seizure frequency may be a more accepted way to assess efficacy of therapy. Interestingly, the mean dose of medication in both groups (12-13 mg/kg/day) is significantly lower than what is used in clinical practice.

Overall, this study provides valuable information. In spite of JME being both clinically and genetically heterogeneous, both groups responded equally to VPA therapy. Further research is warranted to investigate whether similar observations occur in other epilepsy syndromes and neurological conditions with a genetic predisposition.

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