PREDICTIVE FACTORS OF PEDIATRIC INTRACTABLE SEIZURES

Javad Akhondian MD*, Farhad Heydarian MD**, Seyed-Ali Jafari MD**

Background: This study was performed in children aged <15 years, at the Pediatric Neurology Clinic of Imam Reza Hospital affiliated to Mashhad University of Medical Sciences. The objective of this study was to recognize the main predisposing factors that result in uncontrolled seizures in patients so that we can start the treatment accurately.

Methods: There were two groups of patients; group I, consisted of 51 patients, with minimum refractory seizures of one episode per month while taking at least two antiepileptic drugs, and group II, comprised of 80 well-controlled patients chosen at random, who had no fit within 6 months after starting the treatment.

Results: Factors affecting the occurrence of refractory seizures included age <1 year, multiple seizures before starting the treatment, male gender, myoclonic seizures, neurologic defects, neonatal and daily seizures, and first abnormal electroencephalogram and brain computerized tomography scan.

Conclusion: There are several factors that can predict development of uncontrolled seizures. Knowledge of these factors helps us to discriminate our patients and pay more attention to those at risk of developing uncontrolled seizures.

Keywords: Electroencephalogram (EEG) • intractable seizures • status epilepticus

Introduction

Epilepsy is one of the most important childhood diseases. Fortunately, most of the patients are treatable, with good outcome. However, 10 – 30% of epileptic patients are resistant to therapy, a condition the so called “intractable seizures.” This condition associates with many adverse effects on life quality. Identifying those children who are prone to develop uncontrolled seizures is thus critical for parental counseling and selecting patients for more intensive investigations and treatment, such as early consideration of epilepsy surgery.

Patients and Methods

In this case-control study, those children under the age of 15 years, visited at the Children’s Neurology Clinic of Imam Reza Hospital affiliated to Mashhad University of Medical Sciences, northeastern Iran were investigated. We classified the state of seizure control into two types: “well-controlled,” defined as no seizure episode during six months after the start of treatment and “intractable seizure,” defined as a seizure frequency of at least one attack per month during six months, despite receiving two anticonvulsant drugs. After taking a detailed history and physical examination, an anticonvulsant drug was administered. All patients were visited twice a month.

A comparison was performed between various factors (Table 1). Classification of the seizure type was made according to the revised International Classification of Epileptic Seizures. The patients were stratified according to their...
frequency of attacks at the onset of disease as follow: a) daily attacks, b) more than one attack in a week, c) one to four attacks per month, and d) the interval between attacks of more than one month.

We analyzed the predisposing risk factors between the two groups with Pearson $\chi^2$ and Fisher’s exact test, using the SPSS statistical software.

**Results**

There were 51 patients with intractable (case) and 80 with well-controlled (control) seizures. Characteristics of patients are shown in Table 2.

There were 39 males (76.5%) and 12 females (23.5%) in the case group and 42 males (52.5%) and 38 females (47.5%) in the control group ($P = 0.006$).

In the case group, the onset of seizure in 64.7% of patients was <1 year of age and in 35.3% was above this age ($P < 0.001$).

In the case group, 13.7% and in the control group, 12.5% of patients had a positive family history for epilepsy ($P = 0.839$).

In the case group, 19.6% of patients had focal seizure at the onset of disease, 66.7% had generalized, and 13.7% had myoclonic seizures. In the control group, 22.5% of patients had focal seizure, 75% had generalized, and 2.5% had myoclonic seizure at the onset of disease ($P = 0.047$).

Forty-one (80.4%) of 51 patients in the case group and 7 out of 80 (8.8%) patients in the control group had neurologic defects ($P < 0.001$).

A history of neonatal seizure was found in 17.6% of patients in the case group and 5% of patients in the control group ($P = 0.018$).

The first electroencephalogram (EEG) was abnormal in 96.1% of patients in the case group and in 83.8% of patients in the control group ($P = 0.031$).

An abnormal brain computed tomography was demonstrated in 52.9% of the case group patients, and in 13.6% of the control patients ($P = 0.002$).

A history of status epilepticus was found in 11.8% and 11.3% of patients in the case and control groups, respectively ($P = 0.92$).

The mean age at presentation was 19.6 months in the case group and 46.5 months in the control group ($P = 0.002$).

The onset of seizure in males was 16.7 months in the case group and 44.2 months in the control group, respectively ($P = 0.216$) in females, however, this was 27.8 and 44.2 months in the case and control groups, respectively ($P = 0.216$).

**Table 1. Factors examined.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Uncontrolled ($n = 51$)</th>
<th>Well-controlled ($n = 80$)</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (&lt;1 year)</td>
<td>64.7</td>
<td>22.5</td>
<td>6.31</td>
<td>2.9 – 13.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Seizure frequency</td>
<td>66.7</td>
<td>22.5</td>
<td>6.8</td>
<td>3.14 – 15.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal EEG at onset (%)</td>
<td>96.1</td>
<td>83.8</td>
<td>4.75</td>
<td>1.02 – 22.03</td>
<td>0.031</td>
</tr>
<tr>
<td>Sex (male) (%)</td>
<td>76.5</td>
<td>52.5</td>
<td>2.94</td>
<td>1.34 – 6.42</td>
<td>0.006</td>
</tr>
<tr>
<td>Positive history of status epilepticus (%)</td>
<td>11.8</td>
<td>11.3</td>
<td>1.05</td>
<td>0.35 – 3.15</td>
<td>0.92</td>
</tr>
<tr>
<td>Neurologic defects (%)</td>
<td>80.4</td>
<td>88.8</td>
<td>42.7</td>
<td>15.1 – 120.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neonatal seizures (%)</td>
<td>17.6</td>
<td>5</td>
<td>4.07</td>
<td>1.18 – 14.02</td>
<td>0.018</td>
</tr>
<tr>
<td>Abnormal brain CT scan (%)</td>
<td>52.9</td>
<td>13.6</td>
<td>7.12</td>
<td>1.87 – 27.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Positive family history of epilepsy (%)</td>
<td>13.7</td>
<td>12.5</td>
<td>1.11</td>
<td>0.39 – 3.14</td>
<td>0.83</td>
</tr>
</tbody>
</table>

**Table 2. Characteristics of patients with refractory and well-controlled seizures.**
Discussion

One of the most complex problems in pediatric neurology is uncontrolled seizure that constitutes 10 – 30% of epilepsies.\textsuperscript{3, 8, 10} Difference between the reported frequencies of uncontrolled seizures may be not only due to various geographic and socioeconomic states, but also for lack of a standard definition of uncontrolled seizures as well.\textsuperscript{11 – 14}

Patients who suffer from 20 generalized seizures before starting the treatment are at risk for development of intractable seizures and relapse two to five years after tapering of drugs. Failure to achieve remission may be attributed to poor compliance in use of drugs, relapse after tapering of drugs, lack of treatment, or deficiency of trace elements such as selenium.\textsuperscript{14 – 18} The lack of a three-month seizure-free period after six months of treatment is a major prognostic factor.\textsuperscript{2}

There was a significant correlation between sex and the occurrence of refractory seizures (Table 2). In other words, we found that male gender is a risk factor for developing intractable seizures, which is in contrast to the findings of another study.\textsuperscript{10} Our results showed that another risk factor is the onset of seizure before the age of one year, which is similar to other studies.\textsuperscript{11, 12, 20, 21} However, in some reports, no relationship was found.\textsuperscript{19, 22} Argue about the role of age at onset of seizures and the chance of intractability can be partially attributed to the type of study—community or hospital-based studies.\textsuperscript{22} A family history of epilepsy is not a risk factor, based on our findings.

Myoclonic seizure is a risk factor, and similar findings for uncontrolled seizures are reported by Chawla et al.\textsuperscript{20} Neurologic defect is a risk factor for the appearance of intractable seizure, according to our study, which is in agreement with the findings of Ko et al.\textsuperscript{11} Other risk factors are neonatal and daily occurrence of seizures.

If there is no success in control of seizures in the first year of its onset, the chance of remission is approximately 60%. The outcome is obviously better with increasing the age at the onset of seizures.\textsuperscript{14, 23, 24} In other studies, the frequent seizure at the first visit is confirmed as a risk factors for development of refractory seizures.\textsuperscript{11, 19, 22, 25, 26} This may be a result of underlying brain structural defects.\textsuperscript{19}

The first abnormal EEG is another predictive factor for occurrence of uncontrolled seizures, as shown by Ko et al.\textsuperscript{11} However, another study revealed no correlation between abnormal EEG and development of intractable seizure.\textsuperscript{22}

According to our results, which are similar to other reports,\textsuperscript{11} an abnormal brain CT scan is yet another measure to predict development of refractory seizures.

A positive history of status epilepticus is not an important factor for predicting development of intractable seizures, based on our findings. This is, however, in contrast to findings of other studies.\textsuperscript{11, 22}

A review of our findings reveals that various factors are involved in development of refractory seizures, which include neurologic defects, myoclonic seizure, first abnormal EEG and brain CT scan, male gender, neonatal seizure, and an age under one year at the beginning of seizures.

Other factors, which have been studied and could not be identified as risk factors for development of uncontrolled seizures were prior status epilepticus and positive family history of epilepsy.

References

11 Ko TS, Holmes GL. EEG and clinical predictors of medically intractable childhood epilepsy. Clin...


