INTRODUCTION

Assessment of the risk profile of a child with epilepsy may be used to tailor the treatment strategies. If known at onset, this risk profile can be used to identify children who might benefit from vigorous treatment.\(^1\)\(^2\) Although the prognosis for the majority of epileptic children is good, up to 30-35% of such children do not have complete remission despite appropriate therapy with antiepileptic drugs (AEDs), a condition known as 'intractable epilepsy'.\(^3\)-\(^7\) The potential of a "Prognostic Group Specific Management Approach" should be explored so that effective management plans could be used in a more rational and targeted fashion. However, determining the prognosis of patients when they first present with epilepsy is a difficult task.\(^8\)\(^9\) The characteristics of patients are ill-defined and epileptic children with good and bad prognosis may be difficult to differentiate from each other at onset.\(^10\) The potential predictors of intractable epilepsy are age at onset, seizure etiology, EEG abnormalities at onset, number of seizures before treatment started, and early response to antiepileptic drugs (AEDs).

There is hardly any local data of epileptic children upon which the predictability of intractable epilepsy can be based. To resolve this issue, it remains essential to gather follow-up data of local patients and look for factors upon which predictability of prognosis can be based. Anticipation of the prognosis at onset is helpful in offering the best available evidence-based management.

The objectives of this study were to determine the prognosis of seizures in epileptic children and identify early predictors of intractable childhood epilepsy.

PATIENTS AND METHODS

It was a case-control study conducted from February 2005 to April 2007. Children diagnosed to have epilepsy and being followed-up at the epilepsy centre of the Children's Hospital, Lahore, were included in the study. During the first visit, an extensive questionnaire was completed, containing pre-defined variables like gender, age of onset, number of seizures before starting the treatment, history of neonatal seizures, EEG findings, early response to antiepileptic drug(s), epilepsy type, seizure type and status epilepticus before commencing
treatment etc. that may help predicting the intractability. Confirmation of the diagnosis of epilepsy by the paediatric neurologist was required for inclusion. The standard surface EEG records were performed by a qualified EEG technologist. Neuroimaging (CT/MRI brain) was performed when indicated to look for underlying structural abnormalities and such patients were excluded from the study. Information obtained from history, physical examination and EEG findings was used to classify epilepsy as idiopathic, symptomatic (excluded from the study) or cryptogenic (epilepsy with mental retardation without apparent etiology) according to ILAE.3

All patients were prescribed the appropriate antiepileptic drugs (AEDs) according to the type of seizures; characteristics, efficiency, side-effects and interaction profile of the available drugs.11,12 Patients were started on standard protocol of monotherapy (most commonly valproate, phenytoin, carbamazipine or phenobarbitone). Patients were subsequently evaluated at the epilepsy clinic after 4 weeks of commencement of treatment and then 3-4 monthly thereafter. A combination of drugs was used in patient, whose epilepsy remained uncontrolled despite treatment with two single drugs.13,14 Dosage and compliance were monitored at the out-patient-clinics and adjusted as dictated by clinical circumstances, whereas patients having poor compliance or follow-up were excluded from study at the time of final analysis.

Seizures were classified as generalized convulsive (e.g. tonic, tonic-clonic or myoclonic) or non-convulsive (e.g. absence) seizures and partial seizures, depending on the clinical presentation and the result of the studies described above. Outcome was defined as controlled or intractable epilepsy. Epilepsy was defined as “intractable” when despite taking adequate treatment for at least two years, patients continued to have significant seizures and were taken as cases.16-19 Adequate treatment was described as using at least three antiepileptic drugs either alone or in combination with proper compliance and dosage. ‘Control’ was defined as an epileptic having no seizures for a minimum of one year at last follow-up visit. ‘Early response’ was defined as at least 75% reduction in seizure frequency and severity by 4 months of starting treatment.15 Final evaluation of seizure control was done at minimum of 2 years of follow-up period. Demographic details, clinical characteristics and other relevant data was analyzed using statistical package SPSS (version 12.0). For categorical variables, Chi-square test or Fischer’s exact test was applied and a p-value of < 0.05 was considered significantly. A univariate comparison between ‘controls’ and ‘cases’ was done for each possible predictor to calculate Odds Ratio (OR) and 95% Confidence Interval (CI).

RESULTS

Overall 506 epileptic children were enrolled at the clinic between February 2005 and April 2007. Sixty four patients were excluded from the study for failing to fulfill the inclusion criteria. Forty were lost to follow-up and 24 had poor compliance. The remaining 442 (61% male and 39% female) patients constituted the study population. Of those, 117 (26%) patients showed good control of epilepsy (controls), while 325 (74%) patients had intractable epilepsy according to the study criteria (Table I).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases n=325 (%)</th>
<th>Controls n=117 (%)</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>226 (70%)</td>
<td>43 (37%)</td>
<td>3.92</td>
<td>2.52-6.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at onset &lt; 1 year</td>
<td>148 (46%)</td>
<td>16 (14%)</td>
<td>5.27</td>
<td>2.98-9.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at onset 5-7 years</td>
<td>35 (11%)</td>
<td>38 (32%)</td>
<td>0.25</td>
<td>0.14-0.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt; 10 seizures before starting treatment</td>
<td>110 (34%)</td>
<td>14 (12%)</td>
<td>3.76</td>
<td>2.05-6.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of neonatal seizures</td>
<td>46 (14%)</td>
<td>5 (4%)</td>
<td>3.69</td>
<td>1.43-9.53</td>
<td>0.004</td>
</tr>
<tr>
<td>Cryptogenic epilepsy</td>
<td>191 (59%)</td>
<td>15 (13%)</td>
<td>9.69</td>
<td>5.39-17.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal EEGs</td>
<td>204 (63%)</td>
<td>22 (19%)</td>
<td>7.28</td>
<td>4.34-12.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Early response to AED</td>
<td>79 (24%)</td>
<td>88 (75%)</td>
<td>0.10</td>
<td>0.06-0.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Absence seizures</td>
<td>2 (1%)</td>
<td>29 (25%)</td>
<td>0.019</td>
<td>0.004-0.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myoclonic seizures</td>
<td>13 (4%)</td>
<td>0</td>
<td>1.37</td>
<td>1.29-1.45</td>
<td>0.02</td>
</tr>
<tr>
<td>Status epilepticus before presentation</td>
<td>32(9%)</td>
<td>5 (4%)</td>
<td>2.44</td>
<td>0.93-6.43</td>
<td>0.07</td>
</tr>
<tr>
<td>History of head trauma</td>
<td>41 (13%)</td>
<td>4 (3.5%)</td>
<td>4.07</td>
<td>1.42-11.64</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Sixty three percent (74/117) of the controlled epileptic children were female, compared to 70% (226/325) with intractable epilepsy being male [OR 3.92, 95% CI 2.52-6.12; p-value < 0.001]. Of the total, 164 patients had onset of epilepsy under one year of age and these infants showed more chance of intractable epilepsy [46% (148/325) cases vs. 14% (16/117) control; OR 5.27, 95% CI 2.98-9.34; p-value < 0.001]. Onset of epilepsy beyond infancy showed less chances of intractable epilepsy, more so when onset was between 5-7 years of age, Table II (OR 0.25, 95% CI 0.14-0.42; p-value < 0.001).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases n=325 (%)</th>
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<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset &gt; 7 years</td>
<td>72 (22%)</td>
<td>29 (25%)</td>
<td>0.86</td>
<td>0.52-1.4</td>
<td>0.56</td>
</tr>
<tr>
<td>Generalized seizures at onset</td>
<td>160 (49%)</td>
<td>50 (43%)</td>
<td>1.29</td>
<td>0.85-1.98</td>
<td>0.22</td>
</tr>
<tr>
<td>Family history of epilepsy</td>
<td>30 (9%)</td>
<td>14 (12%)</td>
<td>0.74</td>
<td>0.38-1.46</td>
<td>0.39</td>
</tr>
</tbody>
</table>
Of 325 children with intractable epilepsy (cases), 110 (34%) had more than 10 seizure episodes before treatment was started compared to 14 (12%) children in control group (OR 3.76, 95% CI 2.05-6.88; p-value < 0.001). History of neonatal seizures was a risk factor [14% cases vs. 4% controls; OR 3.69, 95% CI 1.43-9.53; p-value 0.004]. Forty five (10%) patients had history of head injury and it was a poor prognostic variable (13% cases vs. 3% controls; OR 4.07, 95% CI 1.42-11.64; p-value 0.005). Statistically, family history of epilepsy did not show any impact on intractability of seizures (OR 0.74, 95%, CI 0.38-1.46; p-value 0.39).

Significant abnormalities of EEG were documented among 226 (51%) of the 442 patients. A higher proportion of patients with abnormal EEG continued to have seizures during the study period compared to patients with normal EEG (63% cases vs. 19% controls; OR 7.28, 95%, CI 4.34-12.18; p-value < 0.001).

Among the study population, 236 (53%) patients were classified to have idiopathic epilepsy and 206 (47%) patients had cryptogenic epilepsy. A higher proportion of patients with cryptogenic epilepsy continued to have seizures compared to patients with idiopathic epilepsy (59% case vs. 13% controls with cryptogenic epilepsy; OR 9.69, 95%, CI 5.39-17.4; p-value < 0.001).

Early response to single antiepileptic drug was documented in 167 (38%) epileptic children and there was a significant trend of higher proportion of ‘controls’ among patients who had early response to a single antiepileptic drugs (24% cases vs. 75% controls; OR 0.10, 95%, CI 0.06-0.17; p-value < 0.001).

At the time of presentation, 238 (54%) patients had generalized seizures [194 (44%) tonic-clonic, 31 (7%) absence, 13 (3%) myoclonic] and 204 (46%) epileptic children presented with partial seizures. Overall, there was no significant difference between the proportion of patients with generalized onset seizures and partial onset seizures concerning intractability (49% cases vs. 43% controls with generalized epilepsy and 46% cases vs. 32% controls with partial seizures; OR 0.81, 95% CI 0.49-1.34; p-value 0.38). Thirty one (7%) patients had absence seizures at onset and higher proportion of these patients were seizure-free at the time of final analysis (25% controls vs. 1% cases; OR 0.02, 95% CI 0.004-0.008; p-value < 0.001). Myoclonic seizures were present among 13 (3%) patients and all of these had intractable epilepsy (OR 1.37, 95% CI 1.29-1.45; p-value 0.02). Though absence and myoclonic were had intractable epilepsy (OR 1.37, 95% CI 1.29-1.45; p-value 0.004-0.008; p-value < 0.001). Myoclonic seizures had intractable epilepsy (OR 1.37, 95% CI 1.29-1.45; p-value 0.004-0.008; p-value < 0.001). Myoclonic seizures were present among 13 (3%) patients and all of these had intractable epilepsy (OR 1.37, 95% CI 1.29-1.45; p-value 0.02). Though absence and myoclonic were had intractable epilepsy (OR 1.37, 95% CI 1.29-1.45; p-value 0.004-0.008; p-value < 0.001).

We have documented that the history of neonatal seizures was a risk variable for drug resistant seizures as has been reported in other studies.5,23,25 Neurological findings (cryptogenic epilepsy) was a risk factor for
intractable childhood epilepsy in this study, which is in agreement with findings by Berg et al.25 who reported intractable seizures in 34.6% of children with symptomatic/cryptogenic and 2.7% with idiopathic generalized childhood epilepsy. An early response to drug therapy conveys a favourable prognosis and the present findings found that the response to the first antiepileptic drug was also a powerful prognostic factor (75% vs. 24%). This is also supported by other authors like Schmidth, Kawan and Dlugos.26-28

On the whole, generalized seizures were not strongly associated with intractability, in agreement with Stephen.29 In contrast, absence onset seizures were a strong favourable prognostic variable, which is in agreement with other studies.5,16-18 Similarly, all 13 children with myoclonic seizures had intractable epilepsy and it appears to be a strong predictor as has also been observed by others.6,25,30 A history of status epilepticus was an important factor for predicting development of intractable seizures, was in agreement with Ohtsuka,16 Ko and Holmes,31 but in contrast to the observations of Akhondian et al.22 A strong association was noted between intractability and initial abnormal EEG, which is in agreement with other studies.2,21-32

**CONCLUSION**

A large number of patients with childhood refractory epilepsy may be identified at the onset or in the early course of disease based on gender, age, onset of seizures. This type of seizure response to first drug etc. conceptual framework has important implications for formulation of a “Prognostic Group Base Approach” to the management of newly diagnosed childhood epilepsy. Early identification of anticipated intractable epilepsy would allow prompt referral to the specialist services, where the diagnosis can be confirmed, seizures and syndromes classified, AED therapy optimized and suitability for additional combination therapies assessed.

**REFERENCES**


