Clinical Profile and Prediction of Response to Treatment in Childhood Epilepsy - A Single-Centre Experience from Eastern India

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ABSTRACT

BACKGROUND

Though epilepsy remains a significant problem for children and adolescents in our country, studies delineating the clinical profile and response to treatment in childhood epilepsy are lacking. The current study was carried out for obtaining a baseline profile and to predict the response to treatment in childhood epilepsy in India that may be helpful in planning management strategies from a public health point of view.

METHODS

Patients with clinical suggestion of active epilepsy (N = 141) from one month to 12 years, were enrolled into the study over a period of 1 year (February 2010 to January 2011) from the out-patient department and epilepsy clinic of Bangur Institute of Neurology. Detailed history was taken along with neurological examination. Electroencephalography (EEG) and neuroimaging (MRI / CT scan) were done on all patients. Each patient included in the study was kept in follow-up for a period of 6 months and their response to the treatment was recorded.

RESULTS

About 48.9 % (N = 69) patients had localisation related epilepsy while the rest had generalised epilepsy. Of those with generalised epilepsy, generalised tonic-clonic seizures (GTCS) was by far the most common type. Of those with focal EEG activity, the highest proportion (50 %), were localised to the temporal lobe. Symptomatic aetiology accounted for 59.6 % (N = 84) of the patients. 20.6 % (N = 29) had poor response to treatment at 6 months follow-up. Abnormal neuroimaging (OR = 6.708) and abnormal EEG (OR = 6.357) were effective factors in predicting poor response to treatment.

CONCLUSIONS

Our study highlights the need to link specialised epilepsy services with primary health centres for early detection and treatment. EEG is an essential cost-effective modality in determining seizure localisation and response to treatment.

KEYWORDS

Paediatric, Epilepsy, Clinical Profile, Response to Treatment

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BACKGROUND

The incidence of epilepsy is approximately 1 %.[1] "Approximately 4 - 10 % of paediatric population encounters at least a single seizure within the first 16 years of life".[2] A recent meta-analysis of twenty Indian studies on the prevalence of epilepsy revealed an overall prevalence of 5.33 per 1000 population.[3] Response to treatment depends on a variety of factors including aetiology, family history, age at seizure onset, EEG and neuroimaging abnormalities even in patients with good drug compliance. "Previous studies have shown that the age at onset of seizure, cognitive status and neonatal seizures were important predictive factors".[4,5] Eliciting the baseline profile and predicting the response to treatment in patients with epilepsy may be helpful in planning management strategies from a public health point of view. Though epilepsy remains a significant problem for children and adolescents in our country, studies delineating the clinical profile and response to treatment are lacking in our country. We wanted to determine the clinical profile and prediction of response to treatment in childhood epilepsy.

METHODS

This prospective observational study was carried out in neurology department of Bangur Institute of Neurosciences (BIN), which is a tertiary level referral centre of Eastern India located in Kolkata.

Inclusion Criteria

All consecutive patients who attended with history suggestive of clinically active epilepsy were enrolled over a period of 1 year (N = 141), from 1st of February 2010 to 31st of January 2011, in the age group of one month to 12 years from the out-patient department and epilepsy clinic of the institute. Active epilepsy was defined as a person with epilepsy who has had at least one epileptic seizure in the previous 5 years regardless of anti-epileptic drug (AED) treatment.[6]

Exclusion Criteria

Patients less than 1 month of age, metabolic cause, inborn errors of metabolism, acute symptomatic seizure, storage disorder, neurodegenerative disorder or those with history suggestive of intoxication were excluded from the study. Patients with poor drug compliance were also excluded from the study.

Clear history was obtained from both patients and parents with prior informed consent. A detailed history including age at onset, developmental history, family history of epilepsy (same or other type and febrile seizures), anti-epileptic drug usage and compliance to drugs were taken. After enrolment and initial data recording, each patient was followed up for 6 months and their response to treatment was recorded as good or poor. The good response was defined as absence of clinical seizures after initiation of appropriately chosen anti-epileptic drugs (less than or equal to 2 AEDs) during the follow-up period. The studied factors were age at seizure onset, sex, family history of seizure, developmental status, EEG findings, neuroimaging (MRI / CT) findings and aetiology.

The study was carried out with hospital ethical committee clearance (IEC NO: INST. / IEC / 814).

Description of Seizures

Detailed description of seizures included data of the first attack, the age at onset [infancy (> 1 month – 1 year), toddlers and pre-schoolers (1 year - 5 years) and childhood (> 5 years)], semiology of the attacks, duration, timing and frequency of attacks were taken so as to delineate whether patient was in status or not. History regarding AED usage was also taken to determine the compliance and response to the treatment.

Investigations

Detailed neurological examination was done for each patient. Scalp EEG was recorded in both awake and sleep state for all patients with standard machine (RMS). Neuroimaging (CT / MRI) was done in all patients.

Types of Seizures

Epilepsy was classified as generalised, localisation-related and unclassified according to the International League Against Epilepsy classification. Based on the aetiology, epilepsy was categorised into idiopathic and symptomatic. Idiopathic epilepsy has a presumed genetic origin. Symptomatic epilepsies are those where there is history of prior brain injury with an established risk factor for seizures like neonatal hypoxia, previous central nervous system (CNS) infection and head injury). Sometimes epilepsies are designated as cryptogenic when they have no discernible cause.

Statistical Analysis

Statistical analysis was done using SPSS 13 and logistic regression model was used to determine the predictive power of the factors studied in relation to the response to treatment. P-value of <.05 was considered significant.

RESULTS

Socio-Demographic Data

The socio-demographic and the clinical profile of the study sample have been summarised in Table 1. The age range of our sample was 3 months to 12 years with a mean age of 50.24 months with greater number of males (male: female ratio = 1.82: 1). Of them 7.1 % (N = 10 / 141) were below 12 months, 26.2 % (N = 37 / 141) were between 12 - 60 months and 66.7 % (N = 94 / 141) were above 60 months. About 55 % patients hailed from rural areas, 68.1 % were

from lower middle class and only 3.5 % from upper socioeconomic group. 47.9 % had adequate school performance and 33 % had no formal education. None of the parents had history of consanguineous marriage. Positive family history of epilepsy was reported in 1.4 % (N = 2 / 141) and febrile seizures in about 7 % (N = 10 / 141) cases.

Types of Epilepsy

Epilepsy was classified into three groups: generalised, localisation-related, and unclassified (not known whether generalised or localised to start with). Nearly half of the patients (48.9 %, N = 69) had localisation related epilepsy. Approximately 57.9 % (N = 40 / 69) of these children were clinically diagnosed as generalised epilepsy but EEG revealed that it is focal in origin followed by secondary generalisation. Focal epilepsy with secondary generalisation was the commonest type of localisation-related epilepsy encountered in our patients. Clinically, temporal lobe epilepsy was the commonest type of localisation-related epilepsy (N = 32, 46.3 %) followed by parietal (N = 11, 15.9 %), frontal (N = 10, 14.5 %) and occipital (N = 5, 7.2 %).

Epileptic EEG activity in focal epilepsy were identified in 54.5 % (N = 36 / 66) of the patients. Of those with focal EEG activity, maximum cases (50 % (N = 18 / 36) were of temporal lobe origin, while those from frontal lobe (25 %, N = 9 / 36), parietal (16.6 %, N = 6 / 36) and occipital lobes (8.3 %, N = 3 / 36) were less common.

Nearly 50 % patients had generalised epilepsy (N = 71 / 141). Among the generalised epilepsies GTCS was the commonest type of seizure observed occurring in 74.6 % (N = 53 / 71) patients. Myoclonic epilepsies had earlier age at onset followed by Lennox-Gastaut. Among all patients, age-specific epileptic syndromes were identified in 22 (15.5 %) which included: Lennox-Gastaut (N = 8, 5.6 %), West Syndrome (N = 5, 3.5 %), juvenile myoclonic epilepsy (N = 3, 2.1 %) and rolandic epilepsy (benign epilepsy with centro-temporal spikes), childhood absence, benign childhood epilepsy with occipital paroxysms (N = 2, 1.4 % each). Lennox-Gastaut syndrome was the most frequent type of childhood epilepsy syndrome observed in our study.

Underlying pathology for epilepsy were identified in 59.5 % (N = 84 / 141) of patients (remote symptomatic epilepsy) while the aetiology couldn't be determined (idiopathic) in 40.4 % (N = 57 / 141) patients. 35.7 % (N = 30 / 84) of the symptomatic epilepsies were due to previous CNS infections. 53.3 % (N = 16 / 30) of the CNS infection cases were due to neurocysticercosis. Perinatal complications were found in 53.6 % (N = 45 / 84) and developmental disorder of brain contributed to about 13.09 % (N = 11 / 141) and head trauma in 2.4 % (N = 2 / 84) cases.

Interictal EEG

Interictal EEG record was normal in 53.2 % (75 / 141) patients at presentation.

Response to Treatment

Regarding response to treatment in the 6 months follow-up period, 79.4 % (N = 112 / 141) of the patients responded well to treatment while 20.6 % (N = 29 / 141) responded poorly. Out of the 29 patients responding poorly to treatment, 62.1 % (N = 18 / 29) had radiological changes of hypoxic ischaemic encephalopathy, particularly periventricular leucomalacia and 20.6 % (N = 6 / 29) had developmental disorder of brain (4 had cortical dysplasia, 2 had mesial temporal lobe sclerosis).

Table 2 summarises the distribution of effective factors studied in predicting the response to treatment. Except family history of epilepsy / febrile seizures, all other parameters considered in our study were statistically significant.

Univariate logistic regression analysis, revealed younger age at first seizure onset (< 5 years), female sex, associated delayed development, abnormal neuroimaging (MRI / CT), abnormal EEG and symptomatic epilepsies as statistically significant independent predictors of poor treatment response (Table 3)

Multivariate logistic regression analysis, however, showed abnormal neuroimaging (OR = 6.708, 95 % CI = 1.475 - 30.519, P-value = 0.014) and abnormal EEG (OR = 6.357, 95 % CI = 2.040 - 19.804, P-value = 0.001) as statistically significant predictors of poor response to treatment (Table 4).

	Variables	N	%
Age	Less than 1 year	10	7.1
	1 to 5 years	37	26.2
	More than 5 years	94	66.7
Sex	Male	91	64.5
	Female	50	35.5
Socioeconomic status	Lower middle	96	68.1
	Middle	40	28.4
	Upper	5	3.5
Response to treatment	Good	112	79.4
	Poor	29	20.6
Aetiology	Symptomatic	84	59.6
	Idiopathic	57	40.4
Type of epilepsy	Localisation related	69	48.9
	Generalised	71	50.3
	Unclassified	1	0.7

Table 1. Clinical Profile of Study Sample (N = 141)

Factors		Response to Treatment Good (N = 112)	Poor (N = 29)	P-Value
Age at 1st seizure onset	≤ 5 years	66 (58.9 %)	25 (86.2 %)	0.006*
	> 5 years	46 (41.1 %)	4 (13.8 %)	
Sex	Male	77 (68.7 %)	14 (48.3 %)	0.043*
	Female	35 (31.3 %)	15 (51.7 %)	
Development	Delayed	29 (23.2 %)	22 (75.9 %)	< 0.001*
	Normal	83 (76.8 %)	7 (24.1 %)	
Family history of epilepsy / febrile seizures	Present	10 (8.9 %)	2 (6.9 %)	0.727
	Absent	102 (91.1 %)	27 (93.1 %)	
Neuroimaging (MRI / CT)	Abnormal	36 (32.1 %)	24 (82.7 %)	< 0.001*
	Normal	76 (67.9 %)	5 (17.3 %)	
EEG	Abnormal	45 (40.2 %)	21 (72.4 %)	0.002*
	Normal	67 (59.8 %)	8 (27.6 %)	
Aetiology	Idiopathic	55 (49.1 %)	2 (6.9 %)	< 0.001*
	Symptomatic	57 (50.9 %)	27 (93.1 %)	

Table 2. Association of Different Factors with Response to Treatment (N = 141)

*indicates statistically significant association at P < 0.05

Factors	OR	CI (95 %)	P-Value
Age at 1st seizure onset (≤ 5 years)	4.356	1.420 - 13.359	0.010*
Sex (female)	2.357	1.027 - 5.410	0.043*
Delayed development	8.995	3.479 - 23.254	< 0.001*
Family history of epilepsy / febrile seizures	1.324	0.274 - 6.402	0.727
Abnormal neuroimaging	10.133	3.575 - 28.725	< 0.001*
Abnormal EEG	3.908	1.593 - 9.591	0.003*
Aetiology (symptomatic)	13.026	2.955 - 57.414	0.001*

Table 3. Univariate Analysis of Factors in Predicting Poor Response to Treatment (N = 141)

*indicates statistical significance at P < 0.05

Factors	OR	CI (95 %)	P-Value
Age at 1st seizure onset (≤ 5 years)	2.633	0.622 - 11.143	0.189
Sex (female)	2.169	0.747 - 6.293	0.154
Delayed development	1.996	0.540 - 7.347	0.300
Family history of epilepsy / febrile seizures	0.547	0.074 - 4.028	0.554
Abnormal neuroimaging	6.708	1.475 - 30.519	0.014*
Abnormal EEG	6.357	2.040 - 19.804	0.001*
Aetiology (symptomatic)	2.389	0.306 - 18.628	0.406

Table 4. Multivariate Analysis of Factors in Predicting Poor Response to Treatment (N = 141)

*indicates statistical significance at P < 0.05

DISCUSSION

Mean age of the study sample was 50.24 months (approximately 4 years), which consisted of a greater number of males (male: female = 1.82:1). "In a study of childhood epilepsy in Sudanese children, Mohammed et al.[7] found that the mean age at seizure onset was 3.48 years, whereas Banu et al.[8] found mean age of presentation of childhood epilepsy in Bangladesh to be 3 years". "In a study from Nepal by Shakya KN et al.[9] found that in 40 % cases, the first seizure occurred when aged between 2 - 5 years". Thus, the mean age of our study population is in broad agreement with other similar studies from developing countries. "Twenty-three percent of our study sample had their onset before 1 year of age while 48.3 % of children in the study by Mohammed et al.[7] and 56.3 % of study sample by Banu et al.[8] had onset of epilepsy before 1 year of age". "The delayed treatment seeking in our study sample which is also supported by the findings of Mohammed et al. and Banu et al. could be due to the fact that all the studies were carried out in tertiary centres where patients came after being referred from other centres". It may also reflect delayed treatment-seeking due to lack of awareness and resources in developing countries. Social factors like stigma towards the girl child can be a determining factor for this apparent male predominance observed in our study.

In this study aetiology for epilepsy was identified in 59.6 % (N = 84 / 141) patients (symptomatic epilepsy) while the aetiology could not be determined in 40.6 % (N = 57 / 141) of patients comprising the idiopathic / cryptogenic epilepsy group. "Banu et al.[8] in their study of paediatric epilepsy in Bangladesh found almost identical figures, i.e. idiopathic epilepsy in 39 % and symptomatic epilepsy in 61 %. Similar figures were also reported in a Chinese study".[10]

When classified according to the seizure focus, localisation-related epilepsy represented nearly half of the patients (48.9 %, N = 69), generalised epilepsy constituted 50.3 % (N = 71) and the remaining 0.7 % (N = 1) case was unclassified. Similar figures were reported from a Spanish study".[11] Approximately 57.9 % (N = 40 / 69) of these children were clinically diagnosed as generalised epilepsy but EEG revealed that it is focal in origin followed by secondary generalisation. "In the study conducted by Nicoletti et al.[12] the percentage of patients with focal seizures (with or without secondary generalisation) increased from 33.9 % to 53.2 % when EEG findings were taken into consideration. "Banu et al.[8] found partial epilepsy in 25 % of Bangladeshi children but when EEG findings were taken into account, 45 % had localisation related epilepsy". Thus, we can argue that EEG is a relatively affordable investigation which is essential in determining seizure focus which in turn helps in formulating the management plan of epilepsy. Thus, we can emphasize the need to establish EEG services in various rural hospitals across the country.

The current study aimed to predict the response to treatment at 6-month follow-up based on the factors deemed effective in the disease. Abnormal EEG and abnormal neuroimaging in both univariate and multivariate analyses were associated significantly with poor treatment response. Also, significant relationship was found between poor treatment response and early age at seizure onset (< 5 years), female sex, delayed development and symptomatic epilepsies in single-variable analysis in the current study. Such relationships were however not observed in multivariate analysis. In the study conducted by Braathen G et al.[5] on 161 children with epilepsy, age at seizure onset and abnormal EEG in first 6 months after treatment initiation, were effective factors in treatment response. In another study conducted by Sillanp M et al.[4] disease onset in age less than 6 years and aetiology (symptomatic) were significant predictors of poor therapeutic response". MRI abnormalities came as significant predictor of poor outcome in the study conducted by Spooner C.G et al.[13] In a study conducted by Banu SH et al.[14] motor disorder and cognitive impairment were found to be effective factors in predicting the treatment response". Abnormal neuroimaging, mainly structural abnormality resulting from perinatal insults, coming as significant predictor of poor outcome in this study highlights the importance of implementing better maternal health and delivery practices at the grass-root level in developing countries like ours, as this has the potential to bring down both the disease prevalence and associated treatment related issues.

Collecting hospital-based data in a tertiary care set-up can represent more difficult and refractory cases due to referral bias. Small sample size and limited follow-up period were the other limitations of the current study.

CONCLUSIONS

This study points out the need to link specialised epilepsy services with primary health care centres for early detection and treatment. Abnormal EEG and neuroimaging being important predictors of treatment response have to be made available on a broader scale especially in rural hospitals. The results of this study proposed that community based epidemiological study is needed to clarify the prevalence of paediatric seizure disorders. It also highlights the need for rigorous implementation of standard delivery practices, upliftment of standard of general living which are the real

problems in any developing country. Regular campaigning is required against epilepsy to break the myth and stigma about epilepsy prevalent in the society. However, long term follow-up studies based in the community are required to validate the preliminary findings of our study.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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