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A predictive risk model for medical intractability in epilepsy

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ABSTRACT

Objective: This study aimed to investigate early predictors (6 months after diagnosis) of medical intractability in epilepsy.
Methods: All children <12 years of age having two or more unprovoked seizures 24 h apart at Xinhua Hospital between 1992 and 2006 were included. Medical intractability was defined as failure, due to lack of seizure control, of more than 2 antiepileptic drugs at maximum tolerated doses, with an average of more than 1 seizure per month for 24 months and no more than 3 consecutive months of seizure freedom during this interval. Univariate and multivariate logistic regression models were performed to determine the risk factors for developing medical intractability. Receiver operating characteristic curve was applied to fit the best compounded predictive model.
Results: A total of 649 patients were identified, out of which 119 (18%) met the study definition of intractable epilepsy at 2 years after diagnosis, and the rate of intractable epilepsy in patients with idiopathic syndromes was 12%. Multivariate logistic regression analysis revealed that neurodevelopmental delay, symptomatic etiology, partial seizures, and more than 10 seizures before diagnosis were significant and independent risk factors for intractable epilepsy. The best model to predict medical intractability in epilepsy comprised neurological physical abnormality, age at onset of epilepsy under 1 year, more than 10 seizures before diagnosis, and partial epilepsy, and the area under receiver operating characteristic curve was 0.7797. This model also fitted best in patients with idiopathic syndromes.
Conclusion: A predictive model of medically intractable epilepsy composed of only four characteristics is established. This model is comparatively accurate and simple to apply clinically.

1. Introduction

Nearly 20% of 326,000 children with epilepsy in the United States are found to have medically intractable epilepsy [1]. In clinical practice, the goal of epilepsy treatment is to achieve seizure freedom without disturbing side effects. It is important to predict as soon as possible which children will become seizure-free and which are likely to develop medically intractable seizures [2]. Although some studies investigated the prognostic factors for intractable epilepsy, most of them were of case–control designs [3–12]. This type of study does not allow estimation of the risk of developing intractable epilepsy in patients with a given risk factor. Up to now, only few prospective cohort studies are available [2,7,9,10]. In these studies, a range of factors, such as age at onset, neurological physical abnormality, electroencephalograph (EEG), and other characteristics were studied to predict the seizure outcome yet with great variability. Further, some pitfalls have been found in the designs. Several studies did not include patients younger than 2 years old [7], and this group of children may be particularly at risk of developing intractable epilepsy. Other studies used broad criteria for defining intractable epilepsy [9]. Therefore, a prospective cohort study with a comparatively larger population is needed to identify factors predicting long-term seizure outcome. The objective of the present work was to investigate the value of potential prognostic factors identifiable at 6 months from diagnosis in a prospectively followed cohort of children younger than 12 years old with recent-onset epilepsy [2].

2. Methods

2.1. Definitions and classification criteria

Seizures were considered unprovoked when they occurred in the absence of any known proximate precipitant. Epilepsy was defined as the occurrence of two or more unprovoked seizures. More than one seizure within a period of 24 h was considered to be a single seizure. Status epilepticus was defined as a seizure lasting more than 30 min or recurrent seizures lasting a total of more than 30 min without the

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patient fully regaining consciousness. The type of seizure was classified according to the 1981 International League Against Epilepsy (ILAE) criteria [13]. We considered that a patient had various seizure types when he/she had both partial and generalized seizures, various types of partial seizures (for example, simple partial and secondarily generalized seizures), or various types of generalized seizures (for example, absences and generalized tonic–clonic seizures). Epilepsies were categorized according to their etiology as idiopathic, cryptogenic, or symptomatic, following the ILAE criteria. In particular, epilepsies were classified as symptomatic when they occurred in a patient with a history of a static encephalopathy of pre- or perinatal origin or a prior neurological insult such as central nervous system infection, stroke, or significant head trauma [14]. Classification of patients by epileptic syndrome was also performed according to the 1989 ILAE revised classification [13]. Into the category "without unequivocal partial or generalized seizures", we classified all patients with apparently generalized tonic–clonic seizures and a normal EEG. Intractable epilepsy was defined as failure, due to lack of seizure control, of more than 2 antiepileptic drugs (AEDs) at maximum tolerated doses, with an average of more than 1 seizure per month for 24 months and no more than 3 consecutive months of seizure freedom during this interval [2]. Drugs withdrawn due to intolerable adverse effects in patients without recurrences were not taken into account.

2.2. Cohort selection

Xinhua Hospital affiliated to Shanghai Jiao Tong University is a grade A tertiary care hospital in Shanghai, China. All the patients who visited our hospital with new-onset epilepsy were recruited in this prospective study between June 1, 1992 and December 31, 2006. Because 12 years old is the upper age limit in the pediatric department, all the patients included in our study were less than 12 years of age. Patients with seizures limited to the neonatal period, those with inborn errors of metabolism, and those with neurodegenerative disorders and children already on antiepileptic treatment started at other centers were excluded. Consequently, all patients were directly referred by primary care pediatricians or were first seen in the emergency department of our hospital. The study was approved by the ethical committee of the hospital, and informed consent was obtained for study participation.

2.3. Initial evaluation

For every patient, family and medical histories were taken. A physical and neurological examination was performed. A family history of unprovoked seizures was defined as having a first-degree relative (parent or sibling) with seizures. If the neurologist clinically suspected the patient as having intellectual deficiency, intelligence quotient assessment was performed, and neurodevelopmental delay was diagnosed when abnormal. Motor deficit was considered as present if there was hemiplegia, quadriplegia, diplegia, spastic form, ataxia, or other movement disorders.

Electroencephalograph was performed for every patient to ascertain the diagnosis at the initial evaluation. When the standard EEG was normal, a sleep record or video-EEG was performed. The result of EEG was further classified as normal or abnormal; the latter category includes both epileptiform (focal or generalized spike–waves) and nonepileptiform (focal or generalized slowing) abnormalities. Computed tomography (CT), magnetic resonance imaging (MRI), chromosomal analysis, urine test screening, and neuropsychological assessment were performed when needed for a precise diagnosis. Computed tomography or magnetic resonance imaging was performed at least in the cases with abnormal findings in the neurological physical examination, partial seizures, and focal abnormalities on the EEG. Neuroimaging was classified as abnormal only when the observed abnormality was considered the cause of epilepsy (398/649 had CT and 128/649 had MRI examined).

2.4. Follow-up

All patients were followed through in-person interviews at 1-month intervals in the hospital and then at 3-month intervals during hospital visits until a remission of 3 years was attained without AEDs (i.e., 3 years without either relapses or treatment). Patients in remission were further followed up in person in the hospital until a follow-up of 2 years without antiepileptic treatment was completed. If the patient did not visit the hospital, he was contacted by telephone (accounted for 5%). Afterward, patients were instructed to contact us if a relapse occurred. Otherwise, the patient was considered to be in remission.

2.5. Predictors of intractability

The following variables, all measured at 6 months of follow-up, were explored: sex, age at onset of epilepsy in years, prior febrile seizures, prior neonatal seizures, family history of epilepsy in the first-degree relatives, etiology, neurodevelopmental delay, neurological physical abnormality, motor deficit, abnormal neuroimaging (compared with normal, not done is considered as missing in the analysis), status epilepticus at diagnosis, multiple seizures at diagnosis, abnormal EEG, various seizure types, number of seizures before diagnosis, and number of seizures during the first 6 months after diagnosis. For treated patients, the date of diagnosis was the same as the date of treatment onset.

2.6. Analysis

Univariate and multivariate analyses of potential predictors of developing medical intractability were carried out using the logistic model. The event under study was the diagnosis of intractable epilepsy. Cases were considered censored if, at the end of the study, the event under observation had not occurred. Calculations were performed by means of statistical software SAS for Windows, version 9.2. Receiver operating characteristic curve was applied to examine the best compounded prediction model.

3. Results

3.1. General characteristics of the population

A total of 668 children were enrolled in the study. Nineteen patients were lost to follow-up before completing a minimum follow-up period of 2 years within 2 years of diagnosis. Therefore, 649 patients were followed up for more than 2 years and finally entered the analysis. Overall, only about 3% of the patients were lost to follow-up from the initial sample. A total of 116 (18%) of the children were younger than 1 year of age at diagnosis of epilepsy, 495 (76%) were between 1 and 9 years old, and 38 (6%) were 10 years of age or older. The mean age of subjects at diagnosis was 5.1 $\pm$ 3.2 years. The majority of patients were male (79%). The mean follow-up period was 6.6 $\pm$ 3.2 years (range: 3–19 years). The frequencies of neurodevelopmental delay, motor deficit, symptomatic etiology, and abnormal neuroimaging in the intractable epilepsy were higher than their counterparts.

3.1.1. Overall risk of developing intractable epilepsy

At 2 years after diagnosis, 18% of the patients were diagnosed with medically intractable epilepsy, while 12% of the patients with idiopathic syndrome developed intractable epilepsy. No significant differences in sex, family history of seizures, preterm, febril convulsion, aura, and abnormal EEG were found between the remission group and the medical intractability group (Table 1). The prevalence of neurodevelopmental delay, neurological physical abnormality, symptomatic etiology, abnormal neuroimaging, and number of seizures before diagnosis was higher in patients with intractable epilepsy.