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Original Article

Predictors of Intractable Childhood Epilepsy

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ABSTRACT

Our study sought to identify early predictive factors of medically intractable childhood epilepsy. A cohort of epileptic children from the city of Mersin was retrospectively investigated. All patients received care from the same Department of Pediatric Neurology. The epileptic cohort was divided into a drug-responsive epilepsy group and an intractable epilepsy group. Intractable epilepsy is defined as continued seizures in children despite adequate therapy with two or more antiepileptic drugs for more than 18 months. Strong univariate association was observed between intractability and several factors: age of onset, high initial seizure frequency, symptomatic etiology, mixed seizure types, previous history of status epilepticus, febrile and neonatal seizures, mental and motor developmental delay, multiple seizures in 1 day, electroencephalogram abnormalities, magnetic resonance imaging findings, and specific epileptic syndromes. Logistic regression analysis revealed that a previous history of epilepticus status, abnormal electroencephalogram results, and multiple seizures in 1 day comprise independent predictors of medically intractable childhood epilepsy. We suggest that medical intractability in childhood epilepsy can be predicted by monitoring these factors. Along with early prediction, alternative therapies may be designed to provide patients better seizure control and quality of life.

Introduction

Epilepsy is the most common neurologic disorder of childhood. All over the world, approximately 10.5 million children are diagnosed with active epilepsy, amounting to 25% of the worldwide population with epilepsy [1]. Each year, 3.5 million new cases of epilepsy are reported. Forty percent of this group will be less than 18 years of age at their time of diagnosis, and more than 80% of them will live in developing countries [1].

Unfortunately, 6-14% of these children will develop intractable epilepsy. They will not respond well to antiepileptic drugs, and will continue to manifest seizures [2]. Intractable epilepsy can be defined as inadequate seizure control despite appropriate medical therapy with at least two antiepileptic drugs at maximally tolerated doses for more than 18 months, or adequate seizure control with unacceptable drug-related side effects [3].

Several studies specifically addressed the risk factors associated with medical intractability and its predictors [3-7]. To the best of our knowledge, our present study is the largest to be performed on a population of Turkish children with epilepsy.

The early identification of intractability may be useful in designing alternative therapies such as anti-inflammatory agents or surgical interventions. It would also be essential in parental counseling and individual support.

Study Design and Methods

Definitions and medical records

Medical records were obtained from children diagnosed with epilepsy under the control of the Department of Pediatric Neurology at the Faculty of Medicine, Mersin University (Mersin, Turkey). Information was abstracted retrospectively from the patient's medical records. To obtain missing information, telephone contact was initiated by a pediatric neurologist. An experienced pediatric neurologist neurologically

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and systemically examined all patients. If any suspicion of additional behavioral problems arose, patients were directed to a pediatric psychiatrist for a more definite diagnosis.

Epilepsy was defined as two or more nonprovoked seizures. Intractable epilepsy can be defined as inadequate seizure control despite appropriate medical therapy with at least two antiepileptic drugs in maximally tolerated doses for more than 18 months, or adequate seizure control with unacceptable drug-related side effects [3]. Adequate therapy, under the observation of a pediatric neurologist, refers to the maximum dose for seizure control until signs of clinical or laboratory toxicity become evident [3]. A drug used to treat status epilepticus in an emergency setting was not counted as an antiepileptic drug in the present context. Drug-responsive epilepsy involved a seizure-free period of at least 2 years during therapy with a maximum of two antiepileptic drugs.

Children monitored for at least 2 years were included in the study. We excluded patients with shorter periods of follow-up or for whom inadequate follow-up was available. We also excluded children who did not undergo an initial electroencephalogram and magnetic resonance imaging evaluation. All patients were evaluated initially in our clinic. Electroencephalograms and magnetic resonance imaging were performed at our hospital. Most of the children received multiple electroencephalogram and magnetic resonance imaging scans. We only used information obtained from the first evaluation of each patient after the diagnosis of epilepsy. The same pediatric neurologist reviewed the electroencephalogram records of patients. Experienced radiologists analyzed the magnetic resonance imaging scans.

Seizures and epileptic syndromes were classified according to the diagnostic scheme of the International League Against Epilepsy from 1989 [8-10]. Etiologically, patients were divided into three groups, i.e., symptomatic, idiopathic, and remote symptomatic (cryptogenic) [8-10].

Both of the epileptic groups were evaluated for general characteristics and seizure details. These included sex, age, age at onset of seizures, seizure type at onset, initial seizure frequency, multiple seizures per day, etiology, previous history of status epilepticus, febrile and neonatal seizures, family history, mental and motor developmental delay, electroencephalogram abnormalities, magnetic resonance imaging findings, specific epileptic syndromes, and behavioral problems.

Out of 676 patients with a diagnosis of epilepsy, 256 were considered to manifest intractable epilepsy. Fifty-six of these patients were not eligible for this study because their follow-up data were insufficient, or their clinical or electroencephalogram data were incomplete. Of the 420 patients with drug-responsive epilepsy, 208 had received 2 years of follow-up and were included in the study. Data regarding the 200 patients with a diagnosis of intractable epilepsy were compared with the data of the 208 patients with drug-responsive epilepsy.

Data analysis

Data were processed and analyzed using SPSS software, version 11.5 (Statistical Package for Social Sciences, Inc. Chicago, IL), and MedCalc version 11.0.1 (MedCalc Software, Mariakerke, Belgium). Descriptive statistics, the Pearson χ^2 test, likelihood ratios, continuity corrections, and the Fisher exact test were used to analyze data where applicable. The level of significance was set at $P < 0.05$. Finally, all variables demonstrating a significant association with outcomes were entered into a logistic regression model to determine independent predictors of intractable epilepsy.

Results

Patient profiles

Two hundred patients comprised the group with intractable epilepsy, and 208 patients comprised the group with drug-responsive epilepsy. In both groups, males were significantly more numerous than females. No differences in age and sex between the two groups were evident.

Clinical features

A comparison of the two groups in regard to clinical factors revealed several statistically significant differences (Table 1). In more than half of the patients in the group with intractable epilepsy, onset occurred before age 1 year. This finding indicates that the risk of intractability decreased with age. Seizure frequency was also compared between the two groups, and was significantly higher in the group with intractable epilepsy. Generalized seizures were more frequent in the group with drug-responsive epilepsy. Among specific epileptic syndromes, infantile spasms and Lennox-Gastaut syndrome were observed only in the group with intractable epilepsy. Previous neonatal seizures, a history of status epilepticus, motor and mental deficiency, a history of febrile seizures, and microcephaly were also much more common in the group with intractable epilepsy and demonstrated statistical significance. On the other hand, family history and behavioral problems were reported more commonly in the group with intractable epilepsy, but failed to achieve statistical significance.

Electroencephalogram and magnetic resonance imaging features

Electroencephalogram recordings were obtained using a 21-channel electroencephalograph, with scalp electrodes placed according to the international 10-20 system. All records were obtained while the patients were asleep. According to the electroencephalogram records, an initial abnormality seemed to be significantly important in the development of intractability ($P < 0.001$). Although focal and multifocal spikes comprised the most common abnormalities in both groups, they were significantly more common in the group with intractable epilepsy. Moreover, burst suppression was evident only in the group with intractable epilepsy.

Both groups were also compared in terms of magnetic resonance imaging findings. Abnormal magnetic resonance imaging findings were also more frequent in the group with intractable epilepsy, and achieved statistical significance ($P = 0.002$) (Table 1).

In multivariable analysis, a previous history of status epilepticus, electroencephalogram abnormalities, and multiple seizures in 1 day remained significant predictors for developing intractable epilepsy (Table 2).

Table 1. Clinical features of patients

Clinical Factors	Intractable Epilepsy n (%)	Drug-Responsive Epilepsy n (%)	*P* Value
Age of onset <12 months	109 (54.5)	59 (28.4)	<0.001
Multiple seizures in a day	28 (14)	0	<0.001
Generalized seizures	45 (22.5)	106 (51)	<0.001
Specific epileptic syndrome	23 (11.5)	0	<0.001
Neonatal seizure	28 (14)	10 (4.8)	<0.001
Febrile seizure	90 (45)	66 (31.7)	0.006
Status epilepticus	64 (32)	2 (1)	<0.001
Motor deficiency	164 (82)	60 (28.8)	<0.001
Mental deficiency	167 (83.5)	63 (30.3)	<0.001
Microcephaly	58 (29)	21 (10.1)	<0.001
Symptomatic etiology	82 (41)	38 (18.3)	<0.001
MRI abnormality	92 (46)	64 (30.8)	0.002

Abbreviation:
MRI = Magnetic resonance imaging

Table 2. Independent predictors after logistic regression analysis

Predictors	Odds Ratio	95% CI
Age of onset	1.06	0.47-2.39
Generalized	0.23	0.03-1.52
Neonatal seizure	0.82	0.22-3.01
Status epilepticus	15.18	2.82-81.87
Motor deficiency	2.05	0.31-13.47
Mental deficiency	6.09	0.87-42.82
EEG findings	0.19	0.09-0.41
MRI findings	0.34	0.04-3.11
Microcephaly	0.55	0.21-1.46
Symptomatic etiology	6.04	0.64-57.09
Multiple seizures in a day	22.30	9.36-53.15

Abbreviations:
CI = Confidence interval
EEG = Electroencephalogram
MRI = Magnetic resonance imaging

Discussion

This retrospective report indicates that several factors are strongly associated with intractability in childhood epilepsy. Although our findings require verification with prospective studies, we demonstrated strong univariate associations with several predictors. Moreover, our study indicates that a previous history of status epilepticus, electroencephalogram abnormalities, and multiple seizures in 1 day comprise independent predictors of intractable childhood epilepsy.

According to previous studies, age at onset was among the most important predictors of intractable childhood epilepsy. In Chawla et al. [5], the age at onset among 66% of their patients fell within the first decade of age. Similarly, 53% of the patients in the study of Ohtsuka et al. [7] were diagnosed before age 12 months. In accordance with these authors, 54.5% of patients in the group with intractable epilepsy in our study were diagnosed during their first decade of age. This finding supports the hypothesis that early-onset seizures indicate a predisposition to epileptogenesis in the developing brain, which can cause medical intractability.

Initial seizure frequency was identified as a significant predictive factor in our study, in accordance with another recent study [5]. Moreover, after multivariate analysis, our study indicates that multiple seizures in 1 day constitute an independent predictor.

Previous studies also addressed the prognostic significance of seizure type. Chawla et al. [5] observed an association between myoclonic seizures and intractability on multivariate analysis. Controversially, Berg et al. [4] did not observe a significant association between initial seizure type and refractoriness. Eriksson and Koivikko [11] stated that the presence of mixed seizure types, myoclonic seizures, and infantile spasms may cause poor seizure control. In our study, generalized seizures occurred significantly more often in the drug-responsive epilepsy group. Moreover, in accordance with the findings of Eriksson and Koivikko [11], mixed seizures comprised the most common type in our group with intractable epilepsy.

The other important predictive factor addressed in most studies involved a history of neonatal seizures [3-5]. These can be associated with the strong epileptic foci induced by neuronal damage during this period of rapid brain development. Furthermore, most of these children demonstrate a history of prenatal asphyxia, congenital malformations, and other factors that play an important role in the development of intractable epilepsy.

A history of status epilepticus is also frequently associated with refractoriness [3,4,7]. Controversially, in a few studies, no significant association was evident between intractability and a history of status epilepticus [5]. In some studies, status epilepticus was not considered as a predictive factor, although it was emphasized as a criterion for measuring the severity of underlying disease [12]. In accordance with recent studies, a history of status epilepticus in our study was significantly more frequent in the group with intractable epilepsy, and remained an independent predictor. Nevertheless, we cannot distinguish with certainty whether a history of status epilepticus was a predictor of medical intractability or a result of the severity or poor control of the disease. The predictive value in a history of status epilepticus should be verified in prospective studies.

The association between febrile seizures and medical intractability was investigated in many studies. Most studies indicated a lack of association between febrile seizures and medical intractability [4-7]. In our study, febrile seizures and especially prolonged febrile seizures were more common in the group with intractable epilepsy.

Studies investigating the association between family history and intractability were unable to address the statistical significance of this association [2,4].

Mental and motor deficiencies were identified as significant predictors of intractability in previous studies [3,4,7]. Likewise, our study observed a strong relationship between mental-motor deficiency and intractability.

In accordance with our study, Berg et al. [4] and Chawla et al. [5] reported that microcephaly occurred with significant frequency in groups with intractable epilepsy.

Electroencephalographic factors were also observed to be prognostic in different studies. The findings are contradictory regarding the existence of an association and regarding the types of abnormality [3,4,6,7]. Berg et al. observed that focal slowing predicted poor prognosis [3]. In our group with intractable epilepsy, the most common electroencephalogram findings comprised multifocal spikes, and secondarily focal spikes, similar to the results of Ohtsuka et al. [7].

Another predictor mentioned in most related studies involved abnormal magnetic resonance imaging findings [4]. Likewise, in our study, abnormal magnetic resonance imaging findings occurred significantly more often in the group with intractable epilepsy.

One of the factors more consistently linked with the risk of intractable epilepsy in previous studies concerned etiology. In Chawla et al., a symptomatic etiology was evident in 80% of patients in their group with intractable epilepsy, whereas a symptomatic etiology was observed in only 2.8% of the patients in their group with drug-responsive epilepsy ($P < 0.001$) [5]. In a prospective evaluation of 613 patients by Berg et al., a symptomatic etiology was significantly frequent in their group with intractable epilepsy [3]. Similarly, in our study, a symptomatic etiology was evident in 41% of the group with intractable epilepsy, whereas a symptomatic etiology was evident in only 18.3% of the drug-responsive epilepsy group.

The presence of specific epileptic syndromes, especially among catastrophic epilepsies, was also addressed as an

important factor in predicting poor prognoses [4], in accordance with our study.

Also in accordance with our study, Gururaj et al. observed no association between coexisting behavioral problems and intractability [13].

This study contains some weaknesses and limitations. First, we used a strict definition of drug-responsive epilepsy, involving freedom from seizures for 2 years. Some authors limit this period to 12 months. Our definition of medical intractability may also be open to question. Some authors define medical intractability as the failure of three or more antiepileptic drugs. We preferred a definition involving two or more antiepileptic drugs, because a very small number of patients can become seizure-free with three antiepileptic drugs. One limitation of this study involves its methodology. This study is retrospective, and should be verified with prospective studies. Moreover, ours is a tertiary referral hospital, and thus a population bias may have occurred.

Nevertheless, the predictive factors of medical intractability may be helpful in designing new alternative therapies and improving both individual and parental quality of life.

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References

[1] Forsgren L. Incidence and prevalence. In: Wallace SJ, Farrell K, editors. Epilepsy in children. 2nd ed. London: Arnold; 2004. p. 21–5.

[2] Arts WF, Brouwer OF, Peters AC, et al. Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch Study of Epilepsy in Childhood. Brain 2004;127:1774–84.

[3] Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rappaport S, Beckerman B. Early development of intractable epilepsy in children: A prospective study. Neurology 2001;56:1445–52.

[4] Berg AT, Levy SR, Novotny EJ, Shinnar S. Predictors of intractable epilepsy in childhood: A case-control study. Epilepsia 1996;37: 24–30.

[5] Chawla S, Aneja S, Kashyap R, Mallika V. Etiology and clinical predictors of intractable epilepsy. Pediatr Neurol 2002;27:186–91.

[6] Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342:314–9.

[7] Ohtsuka Y, Yoshinaga H, Kobayashi K. Refractory childhood epilepsy and factors related to refractoriness. Epilepsia 2000;41: 14–7.

[8] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981;22:489–501.

[9] Engel J Jr, International League Against Epilepsy (ILAE). A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: Report of the ILAE Task Force on Classification and Terminology. Epilepsia 2001;42:796–803.

[10] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsy and epileptic syndromes. Epilepsia 1989;30: 389–99.

[11] Eriksson KJ, Koivikko MJ. Prevalence, classification and severity of epilepsy and epileptic syndromes in children. Epilepsia 1997;38: 1275–82.

[12] Maytal J, Shinnar S, Moshe SL, Alvarez LA. Low morbidity and mortality of status epilepticus in children. Pediatrics 1989;83: 323–31.

[13] Gururaj A, Sztriha L, Hertecant J, Eapen V. Clinical predictors of intractable childhood epilepsy. J Psychosom Res 2006;61: 343–7.