Early clinical predictors of intractable epilepsy in childhood

Semra SAYGI[1],*, İlknur EROL[2], Füsun ALEHAN[1]

[1]Department of Pediatrics, Division of Child Neurology, Faculty of Medicine, Başkent University, Ankara, Turkey
[2]Department of Pediatrics, Division of Child Neurology, Faculty of Medicine, Başkent University, Adana, Turkey

Aim: In this retrospective study, we evaluated the clinical responses to antiepileptic drug (AED) therapy in pediatric epilepsy patients treated at a single center.

Materials and methods: We identified 28 children with intractable epilepsy and 213 patients with drug-responsive epilepsy.

Results: Univariate analysis showed that age at onset, high (daily) initial seizure frequency, infantile spasm, history of neonatal seizures, abnormal neurodevelopmental status, neurological abnormalities, mental retardation, remote symptomatic etiology, and abnormal brain imaging results were significant risk factors for the development of intractable epilepsy (P < 0.05). Multivariate logistic regression analysis revealed that high (daily) initial seizure frequency and remote symptomatic etiology were significant and independent risk factors for intractable epilepsy (P < 0.05).

Conclusion: Our study suggests that the risk of developing intractable epilepsy in childhood may be predicted, to some extent, by the early clinical course. Early identification of patients at high risk of developing intractable epilepsy will guide appropriate therapy and reduce exposure to ineffectual treatments.

Key words: Intractable epilepsy, childhood

1. Introduction
Epilepsy, characterized by recurrent, spontaneous, and unprovoked seizures, afflicts 3.5–7.2 out of every 1000 children (1). Although the majority of epilepsy patients can attain seizure-free status under the appropriate drug regime, approximately 10%–20% of patients will continue to have seizures despite treatment with widely effective antiepileptic drugs (AEDs).

Medically refractory epilepsy is defined as inadequate seizure control despite therapy with at least 3 AEDs at maximally tolerated doses for 1–2 years (2). The identification of risk factors for intractability in childhood epilepsy has become a major research focus, but very few data exist for the Turkish population (3,4).

We performed a retrospective case-control study in Turkish children and adolescents with epilepsy to identify early predictors (at the time of initial diagnosis) associated with later intractable epilepsy.

2. Materials and methods
The study included children from 1 month old to 18 years of age. All were diagnosed with epilepsy by the same epileptologist (FA) and antiepileptic drug therapy was initiated at the Başkent University Hospital in Ankara, Turkey, between March 2000 and March 2008. Medical records were reviewed to retrieve the following information: sex, age at onset of seizures, initial seizure type, initial seizure frequency, history of febrile/neonatal seizures, history of status epilepticus, perinatal history, neurodevelopmental and cognitive status, family history of seizure disorders, parental consanguinity, neurological abnormalities, brain imaging findings, electroencephalography (EEG) records, and etiology. This study was approved by the local research ethics committee.

Twenty-one–channel EEG was performed in all patients for the diagnosis and classification of epilepsy, and 1.5-T magnetic resonance imaging (MRI) was used for routine evaluation of all patients presenting with seizures.

We evaluated the drug treatment efficacy for each patient and selected a group showing poor response and another group exhibiting well-controlled epilepsy. Statistical comparisons were used to identify early predictors of intractability. In this study, we excluded children whose seizures were poorly controlled but had low serum drug concentrations or poor compliance.

* Correspondence: semra_saygi@yahoo.com

2.1. Definitions

Epilepsy syndromes were classified according to the International League Against Epilepsy (ILAE) classification (5). Seizures were classified according to ILAE definitions based on clinical descriptions and EEG recordings.

The definition of intractable epilepsy was at least 1 seizure per month over an observation period of 1 year, despite medical therapy with 3 or more AEDs in maximally tolerated doses administered singly or in combination. Any drug used acutely to treat breakthrough seizure or status epilepticus in the emergency department was not counted as 1 of the 3 AEDs. The control group consisted of children with well-controlled epilepsy defined as at least 1 seizure-free year at the last follow-up.

Mental retardation was diagnosed on the basis of clinical estimation supplemented by neuropsychological evaluation when available. Neuroimaging findings were classified as normal, abnormal, or incidental. Etiologic determination was divided into 3 categories: idiopathic, symptomatic, and cryptogenic epilepsy. Symptomatic epilepsy was defined as seizures associated with an identifiable pathology in the brain. Cryptogenic epilepsy was presumed to be nongenetic and a consequence of an underlying but undetermined lesion. Idiopathic epilepsies were presumed to be genetic in origin and the diagnosis was based on clinical and EEG findings.

History of status epilepticus was defined as at least 1 prolonged seizure lasting more than 30 min, or a series of shorter seizures extending over 30 min or more during which time the child never fully regained consciousness (6).

Potential predictive factors tested included age at onset, initial seizure type, initial seizure frequency before treatment, history of febrile seizures, history of neonatal seizures and status epilepticus, perinatal history, neurodevelopmental delay, family history of seizure disorders, parental consanguinity, neurological deficits, mental retardation, abnormal brain imaging findings, and etiology.

2.2. Data analysis

Data were analyzed with SPSS 15.0 for Windows (SPSS, Chicago, IL, USA). Categorical variables were analyzed by chi-square and chi-square test trend univariate comparison. $P < 0.05$ was considered significant. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from the estimated individual cell probabilities. Forward logistic multivariate regression was used to test candidate risk factors.

3. Results

During the retrospective study period (2000–2008), 28 pediatric patients were treated who met our definition for intractable drug-refractory epilepsy (35.7% female, mean age ± SD: 9.90 ± 5.07 years; 64.3% male, 7.39 ± 5.19 years). For comparison, 213 patients were included with well-controlled seizures (42.7% female, 8.21 ± 4.49 years; 57.3% male, 7.40 ± 4.43 years). There was no significant difference in sex ratio or age between the 2 groups. The mean duration of follow-up was 2.6 ± 1.4 years for the drug-responsive patients and 3.1 ± 1.6 years for the drug-resistant (intractable) group.

The demographic characteristics of patients with well-controlled and intractable epilepsy are presented in Table 1.

A much smaller fraction of patients in the intractable group had an idiopathic etiology (10.7%) compared to the well-controlled group (64.8%) (Table 1). The proportions in each etiological category are shown in Table 1, while the specific causes of symptomatic epilepsy are presented in Table 2.

A history of status epilepticus and febrile seizures, family history of seizure disorders, and parental consanguinity were not found to be significant predictors of intractable epilepsy in our study ($P > 0.5$).

On univariate analysis, age at onset of younger than 1 year (OR = 2.057, 95% CI 1.491–2.838), high (daily) initial seizure frequency (OR = 9.994, 95% CI 3.419–29.209), positive history of neonatal seizures (OR = 5.128, 95% CI 1.845–14.285), developmental delay (OR = 8.6, 95% CI 3.63–20.4), mental retardation (OR = 9.803, 95% CI 3.921–24.390), symptomatic epilepsy (OR = 14.285, 95% CI 4.048–50), abnormal brain imaging results (OR = 4.76, 95% CI 2.044–10.989), and infantile spasms (OR = 15.151, 95% CI 2.873–76.923) were found to be significant risk factors in the intractable group ($P < 0.05$) (Table 3).

On multivariate analysis, high (daily) initial seizure frequency (OR = 8.2, 95% CI 2.48–26.99) and symptomatic etiology (OR = 12.345, 95% CI 3.3–45.45) were independent predictors of intractability (Table 4).

4. Discussion

There is no widely accepted definition for drug-refractory epilepsy. Current working definitions usually stipulate unresponsiveness to a number of AEDs within a specified treatment duration, so it is difficult to identify intractability in infants and very young children (7).

The reported prevalence of epilepsy varies by region in Turkey, from 6.10 to 10.20 per 1000 (8), but there are no reliable estimates of the number of Turkish children with intractable epilepsy. Therefore, we conducted a statistical analysis of candidate risk factors for intractable epilepsy at a central treatment facility in Turkey.

Early identification of children at high risk of developing intractable epilepsy is critical for parental counseling and for selecting the most promising treatments. The timely selection of an effective alternative will prevent the adverse effects of recurrent seizures on

Table 1. The demographic characteristics of patients.

		Intractable n (%)	Well-controlled n(%)	Total
Sex				
	Female	10 (35.7)	91 (42.7)	101
	Male	18 (64.3)	122 (57.3)	140
Age at onset (years)				
	0–1	17 (60.7)	41 (19.3)	58
	1–3	4 (14.3)	22 (10.3)	26
	3–5	3 (10.7)	27 (12.76)	30
	5–10	2 (7.1)	72 (33.8)	74
	10–18	2 (7.1)	51 (23.9)	53
Type of seizures				
	Gen./tonic/clonic/tonic-clonic	13 (46.4)	83 (38.9)	96
	Myoclonic	5 (17.9)	16 (7.5)	21
	Partial	4 (14.3)	72 (33.8)	76
	Absence	0	19 (8.9)	19
	Atonic	3 (10.7)	23 (10.8)	26
	Multiple	3 (10.7)	0	3
Initial seizure frequency				
	Daily	17 (60.7)	33 (15.5)	50
	1–4/monthly	5 (17.9)	97 (45.5)	102
	1–4/year	5 (17.9)	57 (26.8)	62
	<1/year	1 (3.6)	26 (12.2)	27
History of febrile seizure		1 (3.6)	33 (15.5)	34
History of status epilepticus		3 (10.7)	17 (7.9)	20
Neonatal seizures		7 (25)	13 (6.1)	20
Infantile spasms		4 (14.3)	8 (3.7)	12
Consanguinity		2 (7.1)	39 (18.3)	41
Family history of seizures		5 (17.9)	27 (12.7)	32
Abnormal neurologic examination		19 (67.9)	44 (20.7)	63
Mental retardation		21 (75)	50 (23.5)	71
Developmental delay		19 (67.9)	42 (19.7)	61
Brain imaging (MRI)				
	Abnormal	14 (50)	41 (19.3)	55
	Normal	12 (42.8)	167 (78.4)	179
	Incidental	2 (7.1)	5 (2.34)	7
Etiology				
	Symptomatic	18 (64.3)	58 (27.2)	76
	Cryptogenic	7 (25)	17 (7.9)	24
	Idiopathic	3 (10.7)	138 (64.8)	141

Table 2. Symptomatic etiology of epilepsy in intractable and well-controlled patients.

Etiology	Intractable n (%)	Well-controlled n (%)	Total
Perinatal	9 (50)	24 (41.4)	33
Vascular	0	2 (3.4)	2
Trauma	0	2 (3.4)	2
Stroke	2 (11.1)	11 (19)	13
Hypoglycemia	0	3 (5.2)	3
CNS infection	2 (11.1)	5 (8.6)	7
Chromosomal	0	3(5.2)	3
Neurocutaneous disease	2 (11.1)	2 (3.4)	4
Cortical dysplasia	1 (5.6)	2 (3.4)	3
Metabolic disease	1 (5.6)	2 (3.4)	3
Mesial temporal sclerosis	1 (5.6)	2 (3.4)	3

Table 3. Univariate comparison of the intractable and well-controlled groups.

		Intractable n (%)	Well-controlled n (%)	Odds ratio	95% CI	P
Time of first seizure	0-1	17 (60.7)	41 (19.3)	2.057	1.491–2.838	<0.001
Initial frequency	Daily	17 (60.7)	33 (15.5)	9.994	3.419–29.209	<0.001
Neonatal seizures		7 (25)	13 (6.1)	5.128	1.845–14.285	<0.001
Infantile spasm		4 (14.3)	8 (3.7)	15.151	2.873–76.923	<0.001
Abnormal neurologic examination		19 (67.9)	44 (20.7)	8.13	3.44–19.23	<0.001
Mental retardation		21 (75)	50 (23.5)	9.803	3.921–24.390	<0.001
Developmental delay		19 (67.9)	42 (19.7)	8.6	3.63–20.4	<0.001
Brain imaging (MRI)	Abnormal	14 (50)	41 (19.3)	4.76	2.044–10.989	<0.001
Etiology	Symptomatic	18 (64.3)	58 (27.2)	14.285	4.048–50	<0.001

Table 4. Multivariate analysis for predictor factors of intractable epilepsy.

		Intractable n (%)	Well controlled n (%)	Odds ratio	95% CI	P
Initial seizure frequency	Daily	17 (60.7)	33 (15.5)	8.2	2.48–26.99	<0.001
Etiology	Symptomatic	18 (64.3)	58 (27.2)	12.345	3.3–45.45	<0.001

behavior and intellectual development. Furthermore, early predictors of drug-refractory epilepsy will eliminate the chance of AED overdose and drug interactions resulting from polypharmacy.

There are few widely recognized factors predictive of drug-refractoriness. We analyzed a multitude of candidates by comparing intractable and drug-responsive cases of childhood epilepsy.

A significant finding was that more than half of the patients with intractable epilepsy had daily seizures at onset. Both univariate and multivariate analysis revealed a strong positive association between daily initial seizures and intractability, again in accord with previous studies (2,4,9–11). Symptomatic etiology was another significant factor influencing the drug response of our epileptic patients. The majority of patients in the intractable group (64.28%) had a symptomatic etiology, whereas the majority of patients in the well-controlled group had an idiopathic etiology.

In this study, 60.7% of intractable patients exhibited an age at onset of less than 1 year as compared to only 19.3% of drug-responsive patients. Age at onset of seizures was an even stronger predictive factor with increasing age, consistent with previous reports (2,4,9,10).

Several candidate factors associated with intractability in previous studies were either not associated with intractability in our study or were significant only under univariate analysis. In the intractable group, 46.4% of first seizures were generalized tonic-clonic/tonic/clonic compared to 38.9% in the well-treated group, indicating that initial seizure type had no predictive value. Camfield et al. (12) reported comparable results, whereas other studies concluded that myoclonic seizures, multiple seizure types, and atypical absence seizures were associated with the poorest drug responses (13). Infantile spasm was found to be associated with intractable epilepsy in univariate analysis, in agreement with the findings of Chawla et al. and Berg et al. (10,14), but this association was not retained in the multivariate analysis. Similarly, mental retardation was observed in 70.42% of intractable patients compared to 23.5% of well-controlled patients, but a significant association was obtained only by univariate analysis. Univariate comparisons between the 2 groups suggested that abnormal neurological development and mental status were relatively important predictive factors, in accordance with previous papers (2,4,7,10,14), but neither was significant by multivariate analysis. History

of neonatal seizures is considered an important predictor of intractability (11,14). In contrast, status epilepticus was not found to be an important predictive factor in our study, although there are contradictory reports in the literature. This raises the question of whether status epilepticus is a result or a cause of epilepsy. A history of febrile seizures was also unrelated to intractability in this study (2,14). Similarly, neither Sillanpaa (7) nor Chawla et al. (10) found a significant association between febrile seizures and drug-refractory status.

Abnormal brain imaging findings, which can often reveal the immediate causes of seizures, were observed in 50% of the intractable group but in less than 20% of the drug-responsive patients. Although significant on univariate analysis, again an abnormal brain imaging result was not significant on multivariable analysis. Perinatal causes, including hypoxic-ischemic encephalopathy (HIE) and hypoglycemia, as well as stroke, central nervous system (CNS) infection sequelae, mesial temporal sclerosis, cortical dysplasia, and neurocutaneous disease, were found in both the intractable and the controlled group, (2,10) but none were statistically associated with one group or the other given the small number of intractable patients.

It is well known that the most important cause of intractable epileptic foci is mesial temporal sclerosis (MTS) and that MTS is the best target for epilepsy surgery. In our study, only one patient was diagnosed with mesial temporal sclerosis. In accord with previous findings, perinatal HIE was the most common underlying disorder in our patents with symptomatic intractable epilepsy.

This study demonstrates that high initial seizure frequency and symptomatic etiology are significant and independent predictors of drug-refractory epilepsy in Turkish children. Indeed, our study suggests that the risk of developing intractable epilepsy can be predicted to some degree by the early course of the illness. Early identification of high-risk patients will guide appropriate treatments while avoiding the use of potentially dangerous and inefficacious AEDs.

References

1. Oskoui M, Webster RI, Zhang X, Shevell MI. Factors predictive of outcome in childhood epilepsy. J Child Neurol 2005; 20: 898–904.

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

3. Altunbasak S, Herguner O, Burgut HR. Risk factors predicting refractoriness in epileptic children with partial seizures. J Child Neurol 2007; 22: 195–9.

4. Seker Yilmaz B, Okuyaz C, Komur M. Predictors of intractable childhood epilepsy. Pediatr Neurol 2013; 48: 52–5.

5. Commission on Classification and Terminology of the International League Against Epilepsy (ILAE). Proposal for revised classification of epilepsy and epileptic syndromes. Epilepsia 1989; 30: 389–99.

6. Commission on Epidemiology and Prognosis of the International League Against Epilepsy. Guidelines for epidemiological studies on epilepsy. Epilepsia 1993; 34: 592–6.

7. Sillanpaa M. Remission of seizures and predictors of intractability in long-term follow-up. Epilepsia 1993; 34: 930–6.

8. Çalişir N, Bora I, Irgil E, Boz M. Prevalence of epilepsy in Bursa city center, an urban area of Turkey. Epilepsia 2006; 47: 1691–9.

9. Kwong KL, Sung WY, Wong SN, So KT. Early predictors of medical intractability in childhood epilepsy. Pediatr Neurol 2003; 29: 46–52.

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

11. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, Beckerman B. Early development of intractable epilepsy in children: a prospective study. Neurology 2001; 56: 1445–52.

12. Camfield C, Camfield P, Gordon K, Smith B, Dooley J. Outcome of childhood epilepsy. A population- based study with a simple scoring system for those treated with medication. J Pediatr 1993; 122: 861–8.

13. Eriksson KJ, Koivicco MJ. Prevalence, classification and severity of epilepsy and epileptic syndrome in children. Epilepsia 1997; 38: 1275–82.

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