

## Risk Factors in Childhood Intractable Epilepsy

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### ABSTRACT

**Objective:** Intractable epilepsy is defined as a continuation of a seizure although antiepileptic drugs prescribed in accordance with the seizure type has been administered with adequate timing and dosage. Factors such as sex, age at onset of the seizure, family history, previous febrile seizure, mental and motor retardation, type of seizure, electroencephalography, and abnormal findings in neuroradiological imaging may cause resistance in treating epilepsy. Determining the risk factors of intractable epilepsy may be useful in the early diagnosis, prognosis, and treatment of the disease. This study aimed to determine the possible risk factors for the development of intractable epilepsy.

**Methods:** A questionnaire was completed face to face by the families of 210 patients with childhood epilepsy who applied to the Department of Child Neurology, Gaziantep University School of Medicine between January 2018 and September 2018 and were followed up. Data analysis was performed to determine the risk rates for the development of intractable epilepsy.

**Results:** Early-seizure onset, abnormal neurological examination, microcephaly, symptomatic and cryptogenic epilepsy, electroencephalography abnormality, pathology, and specific epileptic syndrome were found to be the effective risk factors for the development of intractable epilepsy.

**Conclusion:** The lack of the clear understanding of the definition of intractable epilepsy in the literature and the inability to clearly define its limits lead to contradicting results on the risk factors for it. Determining the exact criteria to evaluate the risk of developing intractable epilepsy in future studies and patient follow-up will guide the diagnosis, treatment, and prognosis of patients with intractable epilepsy.

**Keywords:** Epilepsy, intractable epilepsy, intractable childhood, risk factor

### INTRODUCTION

Epilepsy is a common childhood neurological disease (1). Risk factors for childhood epilepsy include head trauma, encephalitis, perinatal hypoxia, congenital structural disorders, and febrile convulsions (2, 3). Intractable epilepsy is defined as a continuation of a seizure even after an antiepileptic drug prescribed in accordance with the type of seizure has been administered with adequate timing and dosage. However, there is no consensus on the number of drugs used and the frequency and duration of seizures in the definition of intractable epilepsy (4, 5). Many factors—including sex; age onset of the seizure; family history; previous febrile seizure; neonatal seizure; mental and motor retardation; type of seizure; status epilepticus; presence of specific epileptic syndromes or abnormal findings in electroencephalography (EEG) and radiological imaging; and multiple seizure types—may cause resistance to epilepsy treatment (6-8). It is thought that determining the risk factors for intractable epilepsy may be useful in the early diagnosis, prognosis, and treatment of the disease. This study aimed to determine the risk factors that can be prevented in intractable epilepsy and the possible risk factors that effectively predict the prognosis of epilepsy.

### METHODS

In this prospectively planned study, a questionnaire consisting of 21 items was prepared taking previous studies into account (3, 4, 6, 8). The questionnaire was completed by the families of 210 patients with childhood epilepsy who applied to the Pediatric Neurology Department of Gaziantep University Faculty of Medicine between January 2018 and September 2018 and were followed up. Prior verbal consent was obtained from the families. The questionnaire was constructed by examining patient medical records.

### Ethics Statement

The study was conducted in accordance with the principles of the Declaration of Helsinki, and previous permission was obtained from the Clinical Research Ethics Committee of the University of Gaziantep (Decision number 2018/23).

### Statistical Analysis

The suitability of the data to fit a normal distribution was tested using the Shapiro–Wilk test, and Mann–Whitney U test was used to compare the variables that did not fit the normal distribution

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in 2 independent groups. The chi-square test was used to test the relationships between categorical variables. Binary logistic regression analysis was used to determine the variables that may have had an impact on epilepsy resistance and to estimate the risk ratio and 95% confidence intervals. Descriptive statistics are presented as mean±standard deviation for numerical variables and numbers with percentages for categorical variables. SPSS for the Windows version 22.0 package program was used for statistical analysis (IBM SPSS Corp.; Armonk, NY, USA), and  $p < .05$  was considered statistically significant.

## RESULTS

In this study, a questionnaire was distributed to 210 patients with epilepsy who applied to the Department of Child Neurology, Faculty of Medicine, University of Gaziantep between January 1, 2018 and September 1, 2018. A total of 122 patients (49 girls and 73 boys) who met the criteria were included in the study. The mean age of the patients was  $110.50 \pm 48.79$  months (minimum-maximum: 1-204). There were 21 girls and 42 boys in the group with intractable epilepsy and 28 girls and 31 boys in the group with epilepsy. There was no significant difference between the sex in both groups ( $p = .113$ ).

We found that early seizure onset, abnormal neurological findings, microcephaly, symptomatic and cryptogenic epilepsy, EEG abnormalities, pathology in radiological imaging of the central nervous system (CNS), and specific epileptic syndrome were effective risk factors in the development of intractable epilepsy. Idiopathic epilepsy, CNS infections, febrile seizures, head trauma, consanguineous marriage, a family history of seizures, neonatal jaundice, maternal pre-eclampsia or gestational diabetes, infection during pregnancy, an appearance, pulse, grimace, activity, and respiration (APGAR) score  $\leq 6$ , exposure to smoking, type and frequency of seizures, and seizure onset were not effective risk factors for the same (Table 1).

## DISCUSSION

Epilepsy is one of the common neurological diseases of the CNS that are associated with recurrent seizure tendencies (9). Uncontrolled seizures in intractable epilepsy may cause many health problems, including aspiration, cardiac arrhythmia, renal failure, brain edema, electrolyte imbalance, sudden death from an unknown cause, and resistant status epilepticus (10). When these negative results are considered, it is important to determine the

factors that may predict the development of intractable epilepsy in children to reduce future health problems and provide adequate support to families.

The definition of intractable epilepsy in the literature is controversial. Significant differences in treatment, the number of drugs patients use, seizure frequency, and observation time were noted in different studies (4, 5, 11). Gururaj et al. (12) defined patients with intractable epilepsy as those who used at least 3 antiepileptic drugs individually or in combination, were followed for 2 years, and had at least 1 seizure a month.

There was no statistically significant difference between the 2 patient groups in terms of sex, which was not a significant risk factor for intractable epilepsy. Kwan and Brodie (13) also found that sex was not a risk factor for intractable epilepsy. In contrast, another study from India with 442 patients reported that the male sex was a significant risk factor for developing intractable epilepsy (14).

Several studies have reported that age at onset of seizures is a risk factor for intractable epilepsy (10, 15-18). Kwong et al. (15) found that the onset of seizures before a child reached the age of 1 was a risk factor for intractable epilepsy. Ohtsuka et al. (16) reported that the rate of first seizure in patients with intractable epilepsy who were aged  $< 1$  year was 53%. Similarly, this study found that the age at onset of seizures was a risk factor for intractable epilepsy; each monthly increase in age at onset of seizure decreased the risk of resistance by 0.984 units. In this study, the incidence of the first seizure was found to be 50.8% for patients with intractable epilepsy; in the literature, this rate varies between 50% and 60%, meaning that our finding is consistent with the literature (10). In this study, the rate of first seizure was found to be 32.2% for the group with epilepsy; in contrast, this rate was between 10% and 20% in the literature (10). The difference in the number of patients, different criteria for including patients in the intractable epilepsy group, and the cognitive level of the parents were thought to be responsible for this difference between our study and the literature. Age of seizure onset is likely to be a risk factor for intractable epilepsy because the CNS is damaged more and because the seizures are noticed late in a period of rapid neurological development.

Some studies report that abnormal neurological findings are a risk factor for intractable epilepsy (12, 17, 19). One such study found that neurological deficits and developmental delays were significant risk factors for intractable epilepsy (12). Similarly, this study also found that abnormal neurological findings were a significant risk factor for intractable epilepsy. Abnormal neurological findings indicate a pathology of the CNS in most children. Considering that pathological findings in CNS imaging and symptomatic epilepsy are risk factors for intractable epilepsy, it is considered that intractable epilepsy can be predicted in many patients if a neurological examination is performed correctly.

Other studies report that microcephaly is a significant risk factor for intractable epilepsy (10, 17, 20). In a study by Berg et al. (10) the rate of microcephaly occurrence was found to be 23.7%

### Main Points:

- Determining the risk factors for intractable epilepsy may be useful in the early diagnosis, prognosis, and treatment of the disease.
- The lack of a clear definition of intractable epilepsy in the literature and its limits have led to studies on the topic presenting differing findings.
- Early-seizure onset, abnormal neurological examination, microcephaly, symptomatic and cryptogenic epilepsy, electroencephalography abnormality, pathology, and specific epileptic syndrome may be the effective risk factors for the development of intractable epilepsy.

**Table 1.** Distribution of patients according to risk factors

Risk factors	Intractable epilepsy	Epilepsy	Total	RR (CI)	p
Age of seizure onset (month) (mean±SD)	26.98±29.04	48.27±43.5	37.3±38.11	0.984 (0.97–0.99)	.003*
Abnormal neurological examination	40	20	60	3.39 (1.61–7.14)	.001*
Microcephaly	9	1	10	9.66 (1.18–78.86)	.034*
<b>Epilepsy type</b>					
Idiopathic	27	40	67		.737
Symptomatic	23	13	36	3.21 (1.08–9.48)	.035*
Cryptogenic	13	6	19	2.62 (1.13–6.05)	.024*
EEG abnormality	47	31	78	2.65 (1.23–5.69)	.012*
Pathology in the CNS imaging	47	19	66	6.18 (2.81–13.59)	.001*
Specific epileptic syndrome	12	0	12	2.15 (1.76–2.64)	.001*
CNS infection	3	2	5		.704
Febrile seizure	17	25	42		.076
Head trauma	7	9	16		.502
Consanguineous marriage	26	26	52		.750
History of seizure in family	30	27	57		.830
Neonatal jaundice	13	14	27		.681
Pre-eclampsia	2	3	5		.598
Maternal gestational diabetes	2	3	5		.704
Pregnancy infection	3	2	5		.704
Drug using during pregnancy	3	4	7		.634
APGAR score ≤ 6	8	2	10		.080
Smoking exposure	13	14	27		.681
<b>Seizure type</b>					.916
Partial	15	15	30		
Generalized	46	44	90		
Other	2	0	2		
<b>Seizure frequency</b>					.283
Every day	27	0	27		
Once a week	6	0	6		
Once a month	24	0	24		
Once a year	6	0	6		
More than 1 year	0	20	20		
More than 2 years	0	39	39		
<b>Onset type of seizure</b>					.674
Tonic-clonic	39	33	72		
Myoclonic	6	3	9		
Clonic	4	4	8		
Tonic	10	10	20		
Absence	3	6	9		
Atonic	1	3	4		

Asterisks indicate statistically significant differences.

APGAR, appearance, pulse, grimace, activity, and respiration; CI, confidence interval; CNS, central nervous system; EEG, electroencephalography; RR, risk ratio; SD, standard deviation.

in a group with intractable epilepsy and 3.1% in a group with epilepsy. Chawla et al. (17) found that the rate of microcephaly occurrence was 58% in children with intractable epilepsy and 2% in those with epilepsy. In these studies, microcephaly was found to be a significant risk factor for intractable epilepsy. In this study,

microcephaly was detected in 10 of 122 patients (8.2%). Of these, 9 patients (14.29%) were in the group with intractable epilepsy and 1 was in the group with epilepsy; therefore, consistent with the literature, microcephaly was found to be a significant risk factor for intractable epilepsy. This shows the importance of physi-

cal examination and anthropometric measurements, particularly during infancy. In the literature, patients with intractable epilepsy and microcephaly also have abnormal neurological findings such as mental retardation. Therefore, it is considered that microcephaly is an important risk factor for intractable epilepsy.

Another parameter that constitutes a risk for intractable epilepsy is the type of epilepsy (16, 17, 21, 22). Ohtsuka et al. (16) reported that the type of epilepsy was a significant risk factor for intractable epilepsy and that there was a 52% rate of symptomatic epilepsy in a group of patients with intractable epilepsy. Chawla et al. (17) found the rate of symptomatic epilepsy to be 80% in a group of patients with intractable epilepsy. In this study, 67 of 122 patients (54.92%) had idiopathic epilepsy, 36 (29.51%) had cryptogenic epilepsy, and 19 (15.57%) had symptomatic epilepsy. A total of 27 of 67 children with idiopathic epilepsy (40.2%), 23 of 36 children with cryptogenic epilepsy (63.9%), and 13 of 19 children with symptomatic epilepsy (68.4%) were in the group with intractable epilepsy. However, those with idiopathic epilepsy were found to be the majority in both groups, and our findings did not agree with the literature in terms of patient distribution. The parameter assessed in this study that is consistent with the literature is symptomatic epilepsy, which was found to be a significant risk factor for intractable epilepsy (15–17). The common feature of both symptomatic and cryptogenic epilepsy is the pathology that causes the epilepsy. Idiopathic epilepsy is defined as epilepsy without pathology but with a genetic predisposition. From the definitions of types of epilepsy, the factors that may constitute risk factors for intractable epilepsy are included in symptomatic and cryptogenic epilepsy. Therefore, we considered it normal to identify these types of 2 epilepsy as risk factors in this study.

A study examining the relationship between EEG abnormality and the development of intractable epilepsy (16) found that EEG abnormality caused the development of resistance. In a study by Ko and Holmes (21) EEG abnormalities were found in 73.6% of patients in a group with intractable epilepsy and 41% of patients in a group with epilepsy. Gururaj et al (12) reported no significant difference in EEG abnormalities between a group of patients with intractable epilepsy and another of patients with epilepsy. In this study, 47 in 63 patients (74.6%) in the group with intractable epilepsy had EEG abnormalities, which—in agreement with the literature—were found to be significant risk factors for intractable epilepsy. One of the main reasons why EEG abnormalities appear to be a risk factor for intractable epilepsy is because pathologies in the CNS—including tumors, scars, Alzheimer's, and metabolic and infective pathologies—are more likely to produce abnormal signals than normal brain tissue.

The literature notes that the presence of pathology in CNS imaging studies has been a significant risk factor for intractable epilepsy (12, 17, 21). Gururaj et al. (12) reported an abnormality in CNS imaging as one of the risk factors for intractable epilepsy. Similarly, CNS pathologies were found to be risk factors in intractable epilepsy in 2 different studies (17, 21). In this study, 66 in 122 patients (54.1%) had a CNS pathology. A total of 47 of these 66 patients (71.21%) were in the group with intractable epilepsy,

and the rate of the presence of pathology in CNS imaging was 74.6%. As consistent with the literature, an abnormality in CNS imaging was found to be a significant risk factor for intractable epilepsy. Considering that symptomatic epilepsy and abnormal neurological findings are a risk factor for intractable epilepsy, the presence of pathology on CNS imaging is expected to be a risk factor for intractable epilepsy.

A total of 2 different studies in the literature (17, 23) reported that CNS infections are risk factors for intractable epilepsy. In this study, only 5 of 122 patients (4.1%) had a history of CNS infection, and 3 of these (66.67%) were in the group with intractable epilepsy. In contrast to the literature, it was found that history of CNS infection had no effect on intractable epilepsy. This is thought to be due to the relatively small number of patients in this study.

The relationship between the history of febrile seizure and intractable epilepsy was investigated in several studies, and 2 of these (20, 21) reported that the former was a risk factor for the latter. However, others studies have found that a history of febrile seizures has no significant effect on intractable epilepsy (10, 12, 16, 18, 24, 25). The results of this study, in which the history of febrile seizures was not a risk factor for intractable epilepsy, are more in agreement with the latter.

Some studies have also investigated head trauma as a risk factor for intractable epilepsy (14, 26). Malik et al. (14) reported that prior head trauma is a risk factor for intractable epilepsy while Saygi et al. (26) obtained contrasting results. In this study, head trauma was not seen as a possible risk factor for intractable epilepsy. The difference between these results was thought to be a result of clinical findings on head trauma not being separated by clear limits. An investigation into the relationship between intractable epilepsy and head trauma, in another study that examines these variables in detail, is recommended.

In a study by Gururaj et al. (12) no significant relationship was found between consanguineous marriage and intractable epilepsy; our findings are similar.

Huang et al. (18) found that a family history of seizures was not a significant risk factor for intractable epilepsy; our findings are similar on this issue as well.

Two different studies (27, 28) reported that perinatal risk factors significantly increased the likelihood of intractable epilepsy. However, Russo et al. (29) reported that perinatal risk factors were not a significant risk factor for intractable epilepsy while Sidenvall et al. (30) reported that although perinatal risk factors were not risk factors for intractable epilepsy, a low APGAR score was significant. A study by Cansu et al. (23) found that both perinatal risk factors and an APGAR score  $\leq 6$  were significant risk factors for intractable epilepsy. In this study, APGAR scoring was performed, in addition to the other factors measured, to evaluate the perinatal risk factors; this was done by examining patient medical records. Our results showed that an APGAR score  $\leq 6$  was not a significant risk factor for intractable epilepsy but that it

was significant in borderline cases.

In terms of prenatal, perinatal, and postnatal characteristics, Sidenvall et al. (30) reported that problems during pregnancy—such as pre-eclampsia, maternal infection, and exposure to smoking—are risk factors for intractable epilepsy. Cansu et al. (23), however, did not identify a history of maternal infection as a risk factor; however, they found that perinatal problems such as hypertension to be risk factors for intractable epilepsy. Daoud et al. (31) identified the abnormal perinatal history criterion as a risk factor but did not identify subtitles for intractable epilepsy; however, they did state that this finding was debatable due to its subjective nature. In this study, gestational diabetes mellitus; pre-eclampsia; infections or drug use during pregnancy; exposure to smoking (an actively/passively smoking mother); and jaundice were hypothesized as prenatal, perinatal, and postnatal causes of intractable epilepsy. These hypothesized factors were not significant risk factors for the same; the low number of patients with prenatal, perinatal, and postnatal abnormalities in this study could be one way it is different from others in the literature.

There was no relationship between the type of seizure and the development of intractable epilepsy in 3 different studies; (26, 32, 33) however, there are studies in which focal-onset seizures were more common in patients with intractable epilepsy (15, 34). This study found no significant relationship between type of seizure and intractable epilepsy. The literature shows that the impact of seizure type on intractable epilepsy is not clear.

Some studies have reported seizure frequency as a risk factor for intractable epilepsy (10, 15, 18). Berg et al. (10) reported that more than half of patients with intractable epilepsy had seizures every day, and Chawla et al. (17) found that the rate of intractable epilepsy was higher in patients who had frequent seizures. In this study, 42.9% of patients with intractable epilepsy had seizures every day, 9.5% had seizures once a week, 38.1% had seizures once a month, and 9.5% had them once a year. Thus, 90.5% of patients with intractable epilepsy included in the study had seizures at least once a month. However, the frequency of seizures was not taken as a risk factor for intractable epilepsy; it was instead used to identify patients with intractable epilepsy. This was because the seizures that occurred in patients with intractable epilepsy could not be controlled with appropriate drug treatments; therefore, the number of seizures was taken as a criterion when determining which patients presented with intractable epilepsy.

There are also studies showing that the presence of a specific epileptic syndrome is a significant risk factor for intractable epilepsy; (10, 19) for example, Berg et al. (10) reported that West syndrome is a risk factor for intractable epilepsy although Ko and Holmes (21) reported that West syndrome alone did not increase the risk of intractable epilepsy. Yılmaz et al. (19) found that specific epileptic syndromes were a risk factor for intractable epilepsy. Similarly, this study found that the presence of a specific epileptic syndrome was a significant risk factor for intractable epilepsy.

#### Limitations

The low number of patients included in this study is one of its

limitations. Future studies should involve more patient groups.

#### Conclusion

The lack of a clear definition of intractable epilepsy in the literature and its limits have led to studies on the topic presenting differing findings. Future studies to determine the exact criteria with which to evaluate the risk of patients developing intractable epilepsy and patient follow-ups on the same will play a role in guiding the diagnosis, treatment, and prognosis of patients with intractable epilepsy.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Gaziantep University (Approval date: 18.01.2018 No: 2018/23).

**Informed Consent:** Informed consent was obtained from the families of the patients.

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