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The Relationship of Familial EEG Characteristics with Age and Gender in Primary Generalized Epilepsy

Primer Jeneralize Epilepside Ailesel EEG Özelliklerinin Yaş ve Cinsiyet ile İlişkisi

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Abstract

Objective: Epilepsy is basically a group of electrical brain dysfunctions, in which many factors play a role in its etiology. Less is known about primary generalized epilepsies than focal epilepsies. Most forms of them are thought to have a genetic basis. In recent years, interest in genetics has also increased in epilepsy, and family studies and epidemiological studies have shown that some forms of epilepsy are inherited. Electroencephalography (EEG) is one of the most important examinations that show the cerebral bioelectric activity and the changes therein. The aim of this study is to examine the EEGs of primary generalized epilepsy patients with typical EEG findings and the EEGs of their first-degree relatives, and to show the genetic effect here.

Method: Patients diagnosed with primary generalized epilepsy according to the International Classification of Epilepsy and Epileptic Syndromes (ILAE-1998) criteria were selected among epilepsy patients who were admitted to neurology outpatient clinic. EEG examination was performed in the first-degree relatives of these patients who could also be reached.

Results: One hundred patients (59 females, 41 males) were included in the study. The seizures of these patients were primary generalized type (PGE), which presented as a generalized tonic-clonic seizure, myoclonic seizure, absence seizure, or combinations of these. Two hundred-nineteen first-degree relatives of 100 patients with PGE, who could be reached, were examined with EEGs. Ten of them had seizures and 48 of them had EEG pathology.

Conclusion: As a result of this study, it was understood that the cerebral bioelectrical activity characteristics of patients with PGE showed a significant difference according to age and gender, although this was

Öz

Amaç: Epilepsi temel olarak etiyolojisinde birçok faktörün rol oynadığı, elektriksel olan bir grup beyin fonksiyonu bozukluğudur. Primer jeneralize epilepsiler hakkında ise fokal epilepsilere göre daha az şey bilinmektedir. Bunların çoğu formunun genetik temellere dayandığı düşünülmektedir. Son yıllarda epilepside de genetiğe olan ilgi artmıştır, aile çalışmaları ve epidemiyolojik çalışmalar ile epilepsinin bazı formlarının kalıtsal olduğu gösterilmiştir. Elektroansefalografi (EEG) ise serebral biyoelektrik aktiviteyi ve buradaki değişiklikleri gösteren en önemli tetkiklerdendir. Bu çalışmanın amacı tipik EEG bulgusu gösteren primer jeneralize epilepsi hastalarının EEG'leri ile bu hastaların 1. derece yakınlarının EEG'leri incelenerek, buradaki genetik etkinin gösterilmesidir.

Yöntem: Nöroloji polikliniğine başvuran epilepsi hastaları arasından International Classification of Epilepsy and Epileptic Syndromes (ILAE -1998) kriterlerine göre primer jeneralize epilepsi tanısı almış hastalar seçildi. Bu hastaların arasından ulaşılabilen 1. derece yakınlarında da EEG incelemesi yapıldı.

Bulgular: Çalışmaya 100 hasta (59 kadın, 41 erkek) alındı. Bu hastaların nöbetleri primer jeneralize tipte olup, jeneralize tonik klonik nöbet, miyoklonik nöbet, absans nöbet veya bunların kombinasyonları şeklinde prezente olmaktaydı. Yüz primer jeneralize epilepsili hastanın ulaşılabilen 219 birinci derece yakınının EEG'leri incelendi. Bunların 10'unda nöbet, 48'inde ise EEG patolojisi saptandı.

Sonuç: Bu çalışmanın sonucunda primer jeneralize epilepsili hastaların serebral bioelektrik aktivite özelliklerinin istatistiksel olarak desteklenmemekle birlikte yaşa ve cinsiyete göre önemli bir farklılık gösterdiği anlaşılmıştır. Bu da epileptogenez üzerindeki etkisi ve

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not supported statistically. This shows the necessity of more detailed genetic studies in order to understand its effect on epileptogenesis and the differences in cerebral sensitivity.

Keywords: Electroencephalography, epilepsy, genetic

serebral duyarlılıktaki farklılıkların anlaşılması için daha ayrıntılı genetik incelemelerin gerekliliğini göstermektedir.

Anahtar kelimeler: Elektroansefalografi, epilepsi, genetik

Introduction

Idiopathic generalized epilepsies (IGEs) constitute a large portion (39-59%) of all epilepsies. Now also known as genetic generalized epilepsies, they are diagnosed on the basis of specific electroencephalographic findings as well as clinical features. Bilateral synchronous, symmetrical, and generalized spike-wave discharges are diagnostic electrophysiological features (1). Other common features include polyspike and polyspike wave discharges. Although less common, other EEG abnormalities in IGE include occipital intermittent rhythmic delta activity and photoparoxysmal response (PPR) (2,3).

IGEs have different subgroups, such as juvenile myoclonic epilepsy, childhood absence epilepsy, and juvenile absence epilepsy. This group of epilepsies has the most genetic characteristics among all types of epilepsy. Chromosomal localization of some epileptic syndromes has been achieved. Changes have been detected in 6p11-12, 15q14, and 5q34 in juvenile myoclonic epilepsy; 22q in benign familial neonatal convulsion; and chromosome 8q (and 16p12, according to some studies) in childhood absence epilepsies (4-7).

Among epilepsy examinations, electroencephalography (EEG) gives us information and allows us to record the bioelectric activity of the brain. Whether there is a genetic influence on EEG findings has been a remarkable issue in terms of the importance of genetics in both epilepsy and the electrical activity of the brain. Studies have shown the genetic characteristics of some basal activity variants and epileptiform discharges in EEG (2).

This study aimed to investigate whether there were genetic features in terms of both clinical presentation and EEG by examining first-degree relatives of IGE patients.

Materials and Methods

Patients who were diagnosed with primary generalized epilepsy with anamnesis, clinical and electroencephalographic features according to the International Classification of Epilepsy and Epileptic Syndromes (ILAE-1998) criteria were selected among the patients who were admitted to the neurology outpatient clinic. This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital (25.3.2019/61-13).

Inclusion criteria: Patients with diffuse bilateral synchronous and symmetrical spike-wave discharges, which are characteristic of primary generalized epilepsy, on their EEG were examined.

The exclusion criteria from the study included; 1) A trauma or an operation that might be a risk for epilepsy, 2) A pathology that might pose a risk for epileptic seizure in routine hemogram or biochemistry screenings, 3) Having another neurological disease other than epilepsy, and 4) Pathology in cranial magnetic resonance imaging determination.

EEGs of patients' relatives with and without a history of seizures were examined. They were divided into two groups as those with normal and abnormal EEG. These were grouped as those with spontaneous multiple spike waves, those with spike-wave discharge complex, those with sharp waves, those with 4-7 Hz/min theta rhythm, and those with photosensitivity.

Statistical Analysis

SPSS 26.0 program was used in the analysis (Statistical Package for the Social Sciences, version 26.0 for Windows, SPSS Inc., Chicago, IL). Descriptive data for categorical variables were expressed as numbers and percentages. Relationships between categorical variables were evaluated with the chi-square test. The statistical significance level in the analyses was accepted as $p<0.05$.

Results

One hundred patients (59 females, 41 males) aged between 12 and 37 years were included in the study. Generalized tonic-clonic seizure (GTCS) was observed in 87 patients, myoclonic seizures in 6, absence seizures in 1, both GTCS and myoclonic seizures in 16, and combinations of both GTCS and absence seizures in 12 patients (Table 1).

Two hundred-nineteen first-degree relatives of 100 IGE patients who could be reached were examined with EEGs. History of seizure was detected in 10 relatives of 100 patients

before or during the study. One of 10 relatives who had this seizure was the mother of the patient and the other 9 were siblings. Eight of them had GTCS and 3 of them had myoclonic seizures. Both GTCS and myoclonic seizures were detected in 1 patient's relative. EEG disorder was found in 9 of these relatives with seizures, and the EEG of 1 patient's relative was found to be normal (Table 2).

EEG pathology without seizures was detected in first-degree relatives of 48 patients. The relatives of the patients who had no seizures but had EEG disorder were 10 fathers, 7 mothers, 28 siblings, and 3 children. In EEG disorders, 10 bilateral synchronous spike waves, 32 sharp waves, 13 theta activity, and 7 both sharp and theta wave paroxysms were observed. Most of EEG disorders were observed in siblings (Table 3). When these people were evaluated according to their age groups, 27 of them were found to gather in the 2nd and 3rd decades. (Graph 1, Table 4). When 48 first-degree relatives of patients with EEG disorders were evaluated according to gender, it was observed that 31 were female and 17 were male, which was not found to be statistically significant (Table 5).

PPR were examined as another parameter in the EEG. PPR was found to be positive in 23 (23%) of the patients and in 16 relatives of these 23 patients.

Table 1. demographic features of patients

Number of cases	277
Number of cases excluded	177
Number of cases included	100
Gender	
Male	41
Female	59
Age	
0-9	0
10-19	64
20-29	26
30-39	10
40-49	0
50-59	0
Seizure type	
GTCS	87
MS	6
AS	1
GTCS+MS	16
GTCS+AS	12

GTCS: Generalized tonic clonic seizure, MS: Myoclonic seizure, AS: Absence seizure

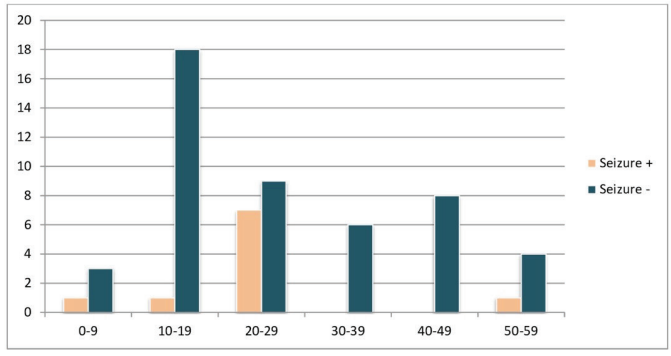
Table 2. Distribution of first-degree relatives of patients with EEG disorders and seizure

n	10
Relatives	
Mother	1
Sibling	9
Seizure type	
GTCS	8
MS	2
GTCS + MS	1
EEG pathologies	
(+)	9
(-)	1

GTCS: Generalized tonic clonic seizure, MS: Myoclonic seizure, EEG: Electroencephalography

Discussion

EEG shows the bioelectrical activity of the brain and is the most important epilepsy examination technique. It allows for the diagnosis of IGEs with specific findings, such as bilateral synchronous spike-wave discharges. Whether there is a genetic effect on EEG is an important issue, both



Graph 1. Distribution of first-degree relatives of patients with EEG disorders by age

EEG: Electroencephalography

Table 3. Distribution of EEG disorders among family members

	Mother	Father	Sibling	Child
n	7	10	28	3
EEG pathologies				
Sharp wave	5	8	18	1
Spike wave	1	0	7	2
Slow wave	2	5	6	0
Sharp + slow wave	1	3	3	0
Spike + slow wave	0	0	0	0

EEG: Electroencephalography

Table 4. Chi-square test findings on the distribution of family members with impaired EEG by age

Age	EEG pathologies	
	+ (%)	(-) (%)
0-9	14 (82.4)	3 (17.6)
10-19	35 (67.3)	17 (32.7)
20-29	38 (79.2)	10 (20.8)
30-39	29 (82.9)	6 (17.1)
40-49	30 (78.9)	8 (21.1)
50-59	15 (78.9)	4 (21.1)
Total	161 (77.0)	48 (23.0)
	X^2=3.965 p=0.555	

EEG: Electroencephalography

Table 5. Distribution of relatives with impaired EEG by gender

		EEG abnormality		Total
Gender		(-)	(+)	
Woman	n	80	31	111
	%	72.1	27.9	100
Man	n	81	17	98
	%	82.7	17.3	100
Total	n	161	48	209
	%	77	23	100
	X^2=2.723 p=0.099			

EEG: Electroencephalography

in terms of epilepsy and the role of genetics in the electrical activity of the brain (8-10). When the patients with IGE included in our study were evaluated, the majority were gathered in childhood, adolescence, and young adulthood. In the literature, childhood absence epilepsy is seen in 13-17% of children, and JME has been reported in 11% of adults and 3% of children. GTCSs are seen at a rate of 27-31% in adults (11). Our patient group was predominantly composed of young adult and adolescent patients, and, as in the literature, GTCSs were more common than absence or myoclonic seizures (4,8).

In our study, the first-degree relatives of patients with IGE were examined. The extent to which genetic characteristics were reflected in EEG in this type of epilepsy and the features of this reflection were investigated.

The majority of all epilepsies are IGEs. In monozygous twin studies conducted in these patient groups, it was found that epilepsy had a transmission rate of 90% (12). Metrakos and Metrakos (13) showed that among 211 patients with centrencephalic epilepsy, 13% of the patients' siblings also had seizures, and 37% had EEG pathology without seizures. In our study, 10% of the patients' relatives had seizures, and 48% had EEG pathology without seizures. This finding suggests that pathological cerebral neural activity may be common among patients' relatives despite the lack of seizure activity. On the other hand, in a study by Jayalakshmi et al. (14), EEG examinations were performed on 132 first-degree relatives of 31 JME patients in India; 12% of those had seizures, and EEG pathology was found in 12.9% of those without seizures. Although fewer EEG disorders were found in the relatives of asymptomatic patients, there was another remarkable feature: While the average age of cases with seizure-free EEG disorders was 19.6 years, the average age of those with normal EEGs was 32.4 years (14). This raises the question of whether the younger age group may be more sensitive to EEG disorders.

Metrakos and Metrakos (13) also supported this finding. The genetic characteristics of paroxysmal bilateral synchronous 3 Hz spike and wave discharges were investigated in patients with petit mal and grand mal seizures. The study demonstrated that centrencephalic-type EEG pathology had autosomal dominant inheritance. However, it was also found that this transition might differ depending on age, and there was a transition characteristic almost completely specific to those aged 4.5-16.5 years (13). Although it was not statistically significant, a peak in the number of patients with EEG pathology in the second decade was observed in our study (Table 4). The ages of patients' relatives who did not show pathology on EEG were concentrated in the third and fourth decades. In a similar study by Degen and Degen (15), 83 siblings of 54 patients with epilepsy were scanned with EEG, and epileptiform activity was observed in 41%. The highest rate of epileptiform activity was also found in the age group of 6-14 years (15). Detecting EEG pathology is important in terms of increased risk of epilepsy.

Determining the risk of cerebral seizures in individuals with spike wave discharges is difficult. Baier and Doose (8) found that the risk of seizures was 33% in patients with spike wave discharges in the relatives of patients with IGE with minor seizures. There was no difference in patients with only PPR or 4-7 Hz slow-wave pathology compared to those with normal EEGs.

Another important feature in our study was gender affinity (Table 5). Among the relatives of patients who had pathological EEGs, 64.5% were women and 35.5% were men. Similarly, Degen and Degen (15) examined the siblings of patients with absence epilepsy; EEG pathology was found in 54.5% of the patients' sisters but in only 30% of

their brothers. In the study conducted by Baier and Doose (8) the brothers and sisters of patients with IGE with minor seizures were examined, pathological EEG was detected in 24% of sisters, while this rate was found to be 11% in men. A similar relationship was shown in another study conducted on patients with JME (8). This has shown us that, gender is also an important parameter in genetic transition as well as age, and the female gender is at higher risk in terms of EEG pathology among patient relatives.

Another remarkable result is the genetic transition feature observed in photo paroxysmal response. PPR was found to be positive in 23 patients and in 16 (59%) of the relatives of these 23 patients. PPR is an EEG finding that is observed at a rate of 15% to 40% in all IGEs, especially in JMEs. In different studies including twin groups, the genetic inheritance feature of PPR has been emphasized (14-16). For example, in the study conducted by Doose and Waltz (17), in 49% of patients with positive PPR, PPR was found to be positive in their siblings.

It is known that many EEG features and clinical features may have a genetic inheritance in epileptic patients. Resistance to epilepsy or hypersensitivity to epilepsy is under the control of many endogenous and exogenous factors, including genetic features. In addition to factors such as sleep, wakefulness, HPV, sound, or light, hereditary traits play an important role. However, heredity has an important place among the endogenous features. Genetic properties play a very important role in the development of pathological discharges as well as in the regulation of the bioelectrical ground activity of the brain. The presence of EEG pathologies such as bilateral synchronous spike-wave discharge and bilateral 4-7 Hz theta waves, which are specific to PGE, also highlights the role of the heredity in asymptomatic relatives. The results of our study have suggested that this situation may be related to age and gender, and the increase in the incidence of pathological discharges between the ages of 5 and 17 years was remarkable. The authors demonstrated changes in EEG background activity during some developmental periods. This may reflect a period correlated with an increase in cerebral sensitivity to convulsions and may explain the tendency to EEG pathology that occurs in an age-dependent manner.

An important question is the type of genetic inheritance. Variables such as the type of seizure, the age at the onset of the seizure, and the activation methods used in the relatives of the patient affect the cerebral activity. This suggests a polygenic mode of heredity.

Conclusion

Our findings showed the importance of the effect of genetics on EEG in IGE. Pathologies detected in the EEG in the relatives of patients with IGE may reflect the hereditary feature in cerebral sensitivity and indicate that there are genetic determinants of cerebral excitability. Especially in women, susceptibility to genetic effects may be more pronounced in childhood and adolescence.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital (25.3.2019/61-13).

Informed Consent: The consent of the patients was obtained for the study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Ö.B.M., M.F.Ö., Design: Ö.B.M., M.F.Ö., Data Collection or Processing: Ö.B.M., Analysis or Interpretation: Ö.B.M., M.F.Ö., Critical Revision of Manuscript: M.F.Ö., Writing: Ö.B.M., M.F.Ö.

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