PREDICTIVE FACTORS FOR EARLY IDENTIFICATION OF PHARMACORESISTANT EPILEPSY

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SUMMARY – Epilepsy is one of the most common neurologic diseases. Despite improved diagnostic and therapeutic possibilities seizures remain refractory in more than 30% of patients with epilepsy. The aim of this study was to analyze the possible predictive factors for the development of pharmacoresistance in cryptogenic partial complex epilepsy. Patients were divided into two groups based on the number of seizures, clinical response to antiepileptic drugs and duration of the disease. One group consisted of patients resistant to anticonvulsant drugs and the other group of patients with well controlled seizures. Disease onset, electroencephalographic (EEG) findings and frequency of secondary generalization of partial complex seizures were analyzed in both groups. The results obtained showed a statistically significantly earlier occurrence of first epileptic seizure in the group of patients with pharmacoresistant epilepsy. The group of pharmacoresistant patients also had a statistically significantly higher proportion of secondary generalization of complex partial seizures as well as a higher proportion of patients with focal changes in EEG. These findings suggest that the onset of the disease at an earlier age, focal changes in EEG and secondary generalization of partial seizures may be early predictive factors for the development of pharmacoresistance in patients with cryptogenic partial complex epilepsy.

Key words: *Complex partial epilepsy; Pharmacoresistant epilepsy; Refractory epilepsy; Seizure; Predictive factors*

Introduction

Epilepsy is one of the most common neurologic diseases, its prevalence in the general population being 1%-2%[1,2]. Seizures are classified as partial or generalized[3]. Although studies have shown that the majority of people with epilepsy will enter long-term remission, seizures remain refractory in more than 30% of patients with epilepsy[4]. Diverse criteria have been used to define pharmacoresistant epilepsy. The International League Against Epilepsy has proposed a consensus definition of drug-resistant epilepsy by which drug resistant epilepsy is defined as a failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (either as monotherapy or in combination) to achieve sustained seizure freedom[5]. Pharmacoresistant epilepsy remains a considerable clinical problem. A number of studies have shown an association between intractable epilepsy and several clinical predictors including age at onset, neurologic deficit, high seizure frequency at onset, electroencephalographic (EEG) changes, and abnormal brain imaging[6-9]. The aim of this study was to identify the possible predictive factors for the development of pharmacoresistance in partial complex epilepsy. Study factors were age at onset of disease, development of secondary generalization of partial complex epilepsy, and EEG changes.

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Patients and Methods

This retrospective study was conducted during three years (2009-2011) at Department of Neurology, Dubrava University Hospital. The criteria for inclusion in the study were age between 16 and 66, diagnosis of cryptogenic partial complex epilepsy with or without secondary generalization, and magnetic resonance imaging findings within the normal ranges (non-lesional). Exclusion criteria were history of inflammatory brain disease, brain trauma, cerebrovascular disease, brain tumors, psychiatric disorders, neurodegenerative and metabolic disease, presence of nonepileptic seizures, as well as other possible causes of symptomatic epilepsy.

Patients were selected based on the number of seizures, antiepileptic drugs received within the last year of treatment, and at least three-year duration of the disease. The diagnosis of complex partial epilepsy with or without secondary generalization was based on medical history and heterohistory data, clinical manifestation of seizures, and multiple EEG recording, all in accordance with the international classification of epilepsy[10]. Based on these criteria, patients were divided into two groups. One group consisted of patients resistant to anticonvulsant drugs and the other group of patients with well controlled seizures. Patients in the pharmacoresistant group had two or more complex partial epileptic seizures *per* month in the previous one-year period, despite the use of at least two antiepileptic drugs. Patients with well controlled seizures were without epileptic seizures in the same period. All patients were tested for the regularity of taking medications by controlling serum concentrations of antiepileptic drugs. Lamotrigine concentration was determined by specific high-performance liquid chromatography, whereas concentrations of all other drugs were determined by fluoroimmuno-polarization[11,12].

Regarding efficacy of antiepileptic drugs, we analyzed age at disease onset, frequency of secondary generalization of partial seizures, and interictal EEG findings in patients with cryptogenic partial complex epilepsy. The study included 107 patients, 59 female and 48 male, average age 42 years. The average duration of illness was 25 years and the average age at first seizure occurrence 17 years. The majority of patients were treated with two (34.6%) or three (41.1%) antiepileptic drugs, while 19.6% of patients were treated with one antiepileptic drug. The mean number of antiepileptic drugs *per* patient was 2.32 (±0.86), 2.9 in pharmacoresistant patients and 1.7 in non-resistant patients. Thirty-seven (34.9%) patients had a diagnosis of complex partial epilepsy and 70 (65.4%) patients had a diagnosis of complex partial epilepsy with secondary generalization. Fifty-nine (55.1%) of 107 patients were in medication resistant group and 48 (44.9%) patients were in the group with good response to antiepileptic drugs.

Statistical analysis

Descriptive data (arithmetic mean, standard deviation, minimum and maximum score) are shown for continuous variables (such as age, sex, disease duration, age at first seizure, clinical phenotype), while the number and percentage of patients in every category are shown for categorical (nominal) variables. Conclusions were made at the level of 5% significance.

Results

Duration and onset of the disease

In the group of pharmacoresistant patients, the mean age at first epileptic seizure was 11.8 (SD 6.37) years with the mean disease duration of 30.4 (SD 11.97) years. In the group of patients with good response to antiepileptic drugs, the mean age at seizure onset was 23.4 (SD 11:57) years with the mean disease duration of 19.9 (SD 11:59) years (Fig. 1). The significance of differences was tested by t-test for independent samples, which showed the first seizure to occur significantly earlier in the pharmacoresistant group of patients (t=8.448; ss=105; p<0.001). The same group had a significantly longer disease duration com-

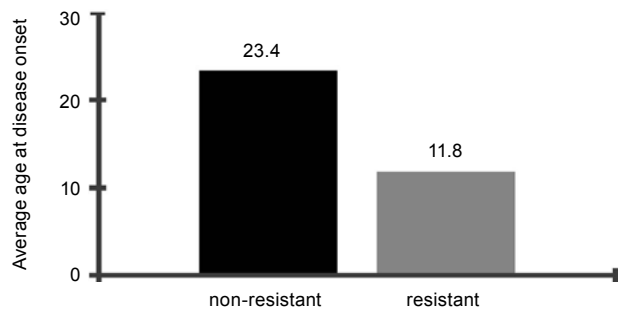

Fig. 1. Mean age (years) at disease onset according to pharmacoresistance.

pared to the group of non-resistant patients (t=4.495; ss=105; p<0.001).

Seizure type

A significantly higher proportion of pharmacoresistant patients had complex partial epilepsy with secondary generalization (79%), while the number of patients without secondary generalization was significantly lower (21%). In the group of non-resistant patients, no differences were found regarding seizure type (partial seizure with or without secondary generalization) and the proportion of each phenotype was 50%. The significance of differences in seizure type was tested by χ^2-test, which showed the difference to be statistically significant (χ^2=9.86; ss=1; p<0.01). Among pharmacoresistant patients, there were a significantly higher percentage of those with secondary generalization of complex partial seizures compared to those with complex partial seizures without secondary generalization (Fig. 2).

Electroencephalographic findings

The EEG changes in our study were described as epileptic paroxysmal discharges, diffuse dysrhythmia, asymmetry and focal discharges (slow waves, sharp waves, spike-wave complex). Epileptic paroxysmal discharges were present in an extremely small percentage of resistant (4%) and non-resistant (2%) patients, while there was an equal proportion (46%-44%) of resistant and non-resistant patients with asymmetric EEG changes. Focal discharges were found in a higher percentage of pharmacoresistant patients (39%), while among non-resistant patients there were a higher percentage of diffuse dysrhythmic EEG findings (44%).

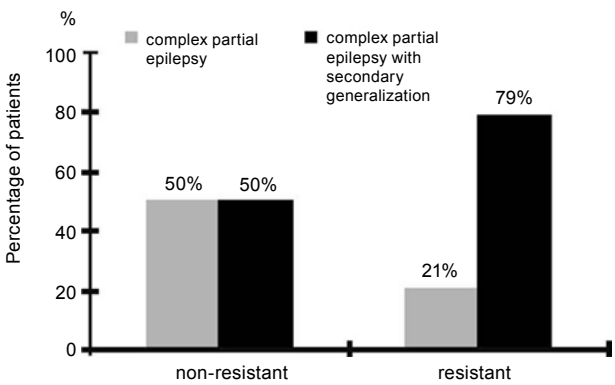

Fig. 2. Seizure type according to pharmacoresistance.

The significance of differences was tested with a series of χ^2-test. A significantly lower percentage of patients with diffuse dysrhythmia were found among pharmacoresistant patients (χ^2=13.564; ss=1; p<0.001) compared to the group of non-resistant patients. There was no statistically significant difference in the presence of epileptic paroxysmal discharges between resistant and non-resistant patients (χ^2=0.222; ss=1; p>0.05). There was no statistically significant difference in the presence of asymmetry either (χ^2=0.028; ss=1; p>0.05). The percentage of patients with focal discharges was significantly higher in the group of pharmacoresistant patients (χ^2=11.545; ss=1; p<0.001) compared to the group of non-resistant patients (Fig. 3).

Discussion

During years of research, some clinical factors have been found to be associated with drug resistant epilepsy. It has been proven that the occurrence of epileptic seizures at an early age, high frequency of seizures before medication initiation, a history of febrile convulsions, some phenotypic types of seizures, structural brain damage and malformations of cortical development are associated with poor response to therapy[13,14]. It is important to identify the high-risk group of patients and to detect pharmacoresistance early because these patients could be included in non-medication forms of treatment such as epilepsy surgery.

In our group of patients with cryptogenic pharmacoresistant complex partial epilepsy, the mean age at disease onset was significantly earlier than in the

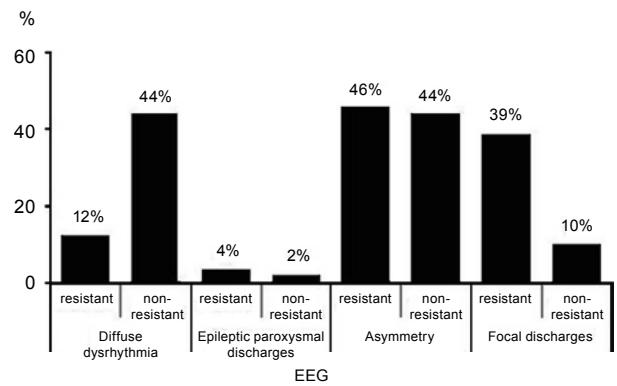

Fig. 3. Differences in electroencephalographic (EEG) findings according to pharmacoresistance.

group of patients with well-controlled seizures (11.8 years *vs*. 23.4years). Our results are consistent with the results reported by Aiki *et al*.[15], who define the six possible risk factors for the development of pharmacoresistance, i.e. younger age at the time of diagnosis, presence of focal changes in EEG, symptomatic etiology of epilepsy, partial seizures or several phenotypically different types of seizures, and cognitive impairment. Camfield *et al*.[16] found that the age at onset of first seizure could be a predictive factor for refractory epilepsy, which was confirmed in studies by other authors[17-21]. Our study also showed a higher frequency of secondary generalization of partial seizures in the group of pharmacoresistant patients compared to the control group, suggesting that a larger number of phenotypically different epileptic seizures could be a possible predictive factor of drug resistance. Furthermore, our findings showed that the duration of disease was significantly longer in the group of patients with intractable epilepsy than in the group of patients with well-controlled seizures. Patients in the former group were treated with a significantly higher number of antiepileptic drugs. These differences are most likely to have significant effects on reducing the quality of life in patients with a resistant form of the disease. The percentage of focal EEG changes was significantly higher in the group of patients with pharmacoresistant epilepsy than in the group of patients with well-controlled seizures. A significantly lower percentage of diffuse dysrhythmic EEG findings were found among patients with pharmacoresistant epilepsy. Milder asymmetries in EEG, as well as paroxysmal changes are found equally in both groups. There have been a lot of doubts in the significance of focal epileptiform activity as a possible predictor of pharmacoresistance. Some earlier studies did not confirm its prognostic significance in newly diagnosed epilepsy[22,23], but our results confirm conclusions of Schreiner *et al*.[2] and Aiki *et al*.[15] that focal epileptiform activity is one of the possible predictors of pharmacoresistance. It is possible that focal EEG changes may be a predictive factor for pharmacoresistance in patients with longer disease duration, since in our study the average duration of the disease was 25 years.

In conclusion, earlier age at disease onset, focal changes in EEG, and secondary generalization of partial seizures may be early predictive factors for the development of drug resistance in patients with cryptogenic partial complex epilepsy.

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Sažetak

PREDIKTIVNI ČIMBENICI ZA RANO PREPOZNAVANJE FARMAKOREZISTENTNE EPILEPSIJE

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Epilepsija je jedna od najučestalijih neuroloških bolesti. Usprkos napretku dijagnostičkih i terapijskih mogućnosti epileptični napadaji ostaju refraktorni u više od 30% bolesnika s epilepsijom. Cilj ovoga istraživanja bio je analizirati moguće prediktivne čimbenike za razvoj farmakorezistencije kod bolesnika s kriptogenom parcijalnom kompleksnom epilepsijom. Na temelju broja napadaja, učinkovitosti antiepileptične terapije te duljine trajanja bolesti bolesnike s parcijalnom kompleksnom epilepsijom podijelili smo u dvije skupine. Jednu skupinu su činili bolesnici s medikamentno rezistentnim oblikom bolesti, dok su drugu skupinu činili bolesnici s dobrim odgovorom na antiepileptičnu terapiju. U obje skupine se ispitivala dob početka bolesti, analizirao se nalaz elektroencefalograma (EEG) te učestalost sekundarne generalizacije parcijalnih kompleksnih napadaja. Dobiveni rezultati su pokazali da je u skupini bolesnika s farmakorezistentnim oblikom bolesti statistički značajna ranija dob pojave prvog napadaja. Također je utvrđeno da je u skupini farmakorezistentnih bolesnika statistički značajno veći udio bolesnika kod kojih dolazi do sekundarne generalizacije parcijalnih kompleksnih napadaja, kao i veći udio bolesnika sa žarišnim promjenama u EEG-u. Dobiveni rezultati ukazuju na to da ranija dob početka bolesti, žarišne promjene u EEG-u i sekundarna generalizacija parcijalnih epileptičnih napadaja mogu biti rani prediktivni čimbenici za razvoj medikamentne rezistencije u bolesnika s kriptogenom parcijalnom kompleksnom epilepsijom.

Ključne riječi: *Kompleksna parcijalna epilepsija; Farmakorezistentna epilepsija; Refraktorna epilepsija; Epileptični napadaj; Prediktivni čimbenici*