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Multivariable prediction model of drug resistance in adult patients with generalized epilepsy from Colombia: A case–control study

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ABSTRACT

Introduction: Patients with drug-resistant epilepsy (DRE) account for most of the burden of epilepsy, and they have poor prognosis in seizure control, higher morbidity, and mortality.
Objectives: The objective of the study was to develop a prognostic model of drug resistance in adult patients with generalized epilepsy from Colombia.
Methods: In this case–control study of patients with generalized epilepsy, patients were separated into two groups: one group with DRE (cases) according to the new International League Against Epilepsy (ILAE) definition after a complete evaluation performed by an epileptologist and the other group without DRE (control). Variables were analyzed to identify statistical differences between groups and were then selected to construct a prognostic model from a logistic regression.
Results: One hundred thirty-three patients with generalized epilepsy were studied. Thirty-eight (28.5%) patients had DRE, and 95 (71.5%) did not have DRE. History of status epilepticus, abnormal findings from neurological examination, aura, any degree of cognitive impairment, epileptic seizures at any moment of the day, and any comorbidity were risk factors. The presence of seizures only in the waking state and idiopathic etiology were protective factors. A prognostic model was constructed with previously reported risk factors for DRE and other variables available in the population of this study. In the multivariable analysis, the history of status epilepticus (odds ratio (OR): 5.6, confidence interval (CI): 1.1–20.0, $p = 0.031$), abnormal findings from neurological examination (OR: 5.7, CI: 2.3–13.9, $p = 0.000$), and aura (OR: 6.1, CI: 1.8–20.8, $p = 0.003$) were strongly associated with DRE.
Conclusions: In adult patients with generalized epilepsy, aura, abnormal findings from neurological examination, and history of status epilepticus were predictive factors for DRE.

1. Introduction

Epilepsy is one of the most common neurological conditions. More than 50 million people around the world have an epilepsy diagnosis, with nearly 80% from developing countries [1–4]. About five million people have epilepsy in Latin America and the Caribbean [5]. In Colombia, there is a prevalence of 11.3 per 1000 persons [6], with an incidence of 81.7 per 100,000 person-years [7]. A burden of disease study estimated 5.25 disability-adjusted life year (DALYs) lost per thousand person-years in Colombia [7].

Medical treatment of epilepsy is able to control seizures in up to 80% of patients [8–10], but there is a group of patients whose seizures do not respond adequately to these therapies and who are classified as having drug-resistant epilepsy (DRE). The International League Against Epilepsy (ILAE) in 2010 [11] defined DRE as "failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom". This group of patients account for most of the burden of epilepsy in the population, because of the substantial frequencies of comorbid illnesses, psychological dysfunction, social stigmatization, reduced quality of life, increased risk of mortality, and decreased life expectancy [12]. Persistent seizures and drug adverse effects have risk and consequences that often outweigh the risk of epilepsy surgery. Several clinical trials report low perioperative mortality (0.1–0.5%) and high efficacy of up to 73% seizure freedom [13,14], but despite good outcomes, surgery remains underutilized or is performed late in the course of the disease [15].

There are some predictors of DRE identified in previous studies. The majority of research studies on drug-resistant epilepsy have been made in pediatric populations, but there are few studies in adult patients [16]. The most frequently reported predictive factor in the literature is the response to the first AED [9,16–18]. Other predictors identified are as follows: high frequency of seizure previous to diagnosis [19–21], symptomatic and cryptogenic epilepsies [16,22,23], occurrence of status

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epilepticus [17,19,24,25], a longer duration of epilepsy [26], a family history of epilepsy [22], a history of febrile seizures [16,22,23], abnormal findings from neurological examination and/or developmental delay [16,20,24], and abnormal electroencephalography (EEG) findings [19,20].

In Colombia, the prevalence of DRE is estimated between 15 and 37% [27,28]. This is the first study in our country that specifically addressed the predictive factors of DRE in adult patients with generalized epilepsy. We conduct this study considering that predictors of drug resistance in low-income countries may be different from that in developed countries by many factors and considering that the early identification of this group of patients could allow them to receive an earlier aggressive treatment or potential invasive therapies (vagal nerve stimulation or epilepsy surgery). The aim of this study was to develop a prognostic model of drug resistance in adult patients with generalized epilepsy from Colombia.

2. Materials and methods

2.1. Patients and sample

This case–control study was composed of patients diagnosed with generalized epilepsy who attended the epilepsy center Neurocentro in the period from 2013 to 2016. We included patients between the ages of 18 and 80 years with a diagnosis of generalized epilepsy based on the ILAE diagnostic criteria [29], with a complete clinical history, including those who came for the first time as those with a previous diagnosis and attended a follow-up visit by an epileptologist. The center receives and follows complex cases but also assesses patients with new onset epilepsy. We excluded patients with pseudocrisis without epilepsy documented by video-EEG telemetry. All the patients were studied by a clinical ground of neurologists, an epileptologist, and in the indicated cases by psychiatrists, neuropsychologists and neurosurgeons.

Patients were separated into two groups: the case group composed of patients with DRE according to the recent ILAE definition, and the control group composed of patients who do not met criteria for DRE. The study was approved by the Bioethics Committee of Neurocentro and Universidad Tecnológica de Pereira under the category of research without risk. The principles of confidentiality of information established by the Declaration of Helsinki were followed.

2.2. Case source

We obtained information from clinical records available in eOficlinic® digital database, in which the diagnostic filter was used to find the patients diagnosed with epilepsy, and then chose those with generalized epilepsy according to ILAE classification [29]. Each clinical record was analyzed individually by the research team and cataloged with the use of a data collection sheet. The following variables were obtained:

- *2.2.1 Sociodemographic*: age, gender, marital status, address, sex, place of residence (urban or rural), education, and occupation.
- *2.2.2 Clinical and surgical*: triggers, family history of epilepsy, history of status epilepticus, etiology grouped according to the origin (vascular, tumoral, infectious, traumatic, neuronal migration disorder, mesial temporal sclerosis, idiopathic, metabolic, autoimmune, perinatal hypoxia, mixed, and others), aura (symptoms previous to seizures), seizures with pain, seizure schedule (during sleep, awake, or both), longer seizure-free time, age at onset, association with moon phases, cognitive impairment, seizure-related injuries, neurological physical examination (normal or altered), neuroimaging, neuropsychological assessment, epilepsy surgery (lobectomy, callosotomy, hemispherectomy, lesionectomy, and deep brain stimulation), and comorbidities.
- *2.2.3 Pharmacological*: current and previous AEDs, adverse reactions to AEDs, and drug resistance, according to ILAE criteria [11].

2.3. Variable definitions

Drug-resistant epilepsy was defined by the 2010 ILAE task force as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" and was measured clinically by an epileptologist when the patient met the criteria. Abnormal finding from neurological examination was defined as any alteration in the components of the neurological examination. Aura was defined according to the definition of the ILAE as "a sensation being experienced at seizure onset, without objective clinical signs of a seizure evident to the observer". Abnormal findings from neurological examination and aura were clinically measured by an epileptologist before DRE diagnosis. Status epilepticus was defined according to the latest definition of the ILAE as "a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after 5 min)" [30].

2.4. Statistical analysis

Continuous variables were summarized through the calculation of mean, standard deviation, median, and interquartile range (IQR), depending on whether the variable followed a normal distribution. Categorical variables were calculated in absolute terms and through proportions. Comparisons between the means of continuous variables were carried out using Student's *t*-test if they followed a normal distribution according to the Shapiro–Wilk test. Continuous variables with nonnormal distribution were compared using the median test. The comparison of proportions was made with the chi-square test or Fisher's exact test. All comparisons were made at the 5% significance level.

This study included patients with generalized epilepsy who were part of a cross-sectional study of 354 adult patients with epilepsy [28]. At the time we conducted the first study, we suspected that there could be some predictors of DRE in our patients with generalized epilepsy, but because of the lack of studies in Colombia or Latin America, it was not possible to say that predictors were the same as those reported in other populations. For this reason, we included in the univariable analysis other variables available in our patients, taking into account the Bradford Hill criteria for causation. We also included in the univariable analysis the previously reported predictors of DRE in the literature and those that were available in our patients (occurrence of status epilepticus, cryptogenic epilepsy, a longer duration of epilepsy, family history of epilepsy, and abnormal findings from neurological examination).

Multivariable analysis using logistic regression was conducted in order to find a prognostic model; it was constructed using previously reported risk factors for DRE and other variables available in the population of this study that we suspect could be associated with DRE. Internal validation of the multivariable model was evaluated by measuring the number of those correctly classified by the model and the area under the receiver operating characteristic (ROC) curve (AUC) to assess the discrimination, and we performed Hosmer–Lemeshow test for calibration.

Table 1
Analysis of continuous variables in patients with generalized epilepsy (comparison of patient characteristics).

	Cases (n = 38), median (IQR)	Control (n = 95), median (IQR)	p value*
Age (years)	34 (26–42)	33 (21–55)	0.82
Age at onset (years)	2 (1–11)	13 (7–21)	<0.001
Years of evolution	25 (21–36)	17 (9–33)	<0.001
Seizure-free time (days)	30 (6–150)	420 (60–1095)	<0.001
Number of AEDs	3 (2–3)	1 (1–2)	<0.001
Number of previously used AEDs	2 (0–3)	1 (0–2)	0.025

AED: antiepileptic drug, IQR: interquartile range.
* Median test.