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Predicting drug resistance in adult patients with generalized epilepsy: A case–control study

Alexandra Voll [b], Lizbeth Hernández-Ronquillo [a,b], Samantha Buckley [b], Jose F. Téllez-Zenteno [b,*]

[a] Community Health and Epidemiology, University of Saskatchewan, Canada
[b] Saskatchewan Epilepsy Program, Department of Medicine, Division of Neurology, University of Saskatchewan, Canada

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ABSTRACT

Objectives: Using an adult cohort of patients with generalized epilepsy, we aimed to identify risk factors for development of drug-resistant epilepsy (DRE), which if identifiable would allow patients to receive earlier treatment and more specifically individualized treatment plans.
Methods: For the case–control study, 118 patients with generalized epilepsy (GE) between the ages of 18 and 75 were included after selection from a database of 800 patients referred from throughout the Saskatchewan Epilepsy Program. Definitions were used in accordance with ILAE criteria. The odds ratio and its confidence interval were calculated. We performed a logistic regression analysis.
Results: Forty-four (37%) patients fulfilled the definition of DRE (cases), and seizures in 74 (63%) patients were not intractable (controls). Patients with DRE were significantly younger than the controls at the onset of epilepsy (6.6 vs. 18.8 years, $p = <0.001$). Significant variables on univariate analysis were the following: epilepsy diagnosed prior to 12 years (OR: 12.1, CI: 4.8–29.9, $p < 0.001$), previous history of status epilepticus (OR: 15.1, CI: 3.2–70.9, $p < 0.001$), developmental delay (OR: 12.6, CI: 4.9–32, $p < 0.001$), and cryptogenic epilepsy (OR: 10.5, CI: 3.9–27.8, $p < 0.001$). Our study showed some protective factors for DRE such as a good response to first AED, idiopathic etiology, and history of febrile seizures. In the logistic regression analysis, two variables remained statistically significant: developmental delay and more than one seizure type.
Conclusion: Our study has identified a set of variables that predict DRE in patients with generalized epilepsy. Risk factors identified in our study are similar to those previously identified in pediatric studies, however, our study is specifically tailored to adult patients with generalized epilepsy.

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1. Background

It is estimated that seizures in 6% to 69% of patients fail to respond to standard medical and surgical therapies and therefore these patients to experience debilitating refractory seizures [1,2]. They are classified as having drug-resistant epilepsy (DRE), a diagnosis with poor prognostic implications such as higher rates of premature death, injuries, psychosocial dysfunction, and reduced quality of life [3]. The early identification of patients with DRE would enable clinicians to more effectively strategize treatment plans for these often complex cases.

The 2010 International League Against Epilepsy (ILAE) task force defined DRE as "failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drugs (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" [3]. Seizure freedom is defined as at least three times the duration of the longest interseizure interval prior to starting a new intervention. Patients must be observed for at least 12 months to determine this period. If no interseizure interval has been previously identified, seizure freedom should be defined as at least 12 months.

In this study, we explored risk factors for medically intractable generalized epilepsy in an adult population. The majority of the literature surrounding medical intractability in patients with generalized and focal epilepsy is based on pediatric populations [4]. However, a few studies were identified as being aimed at an adult population. Mohanraj [5] found that a history of febrile seizures was the only factor contributing to treatment failure. Nicolson et al. [6] studied a population of both pediatric and adult patients with idiopathic generalized epilepsy and found that atypical presentation (defined as onset younger than 3 years or older than 20 years or with an atypical seizure type [absence or myoclonic]) had a significantly worse prognosis than those who did not. Fernando-Dongas et al. [7] found that patients with valproic acid (VPA)-refractory JME were more likely to have EEG asymmetry, atypical seizure characteristics, and intellectual difficulty. Cutting and Gelisse [8] reported a positive relation between psychological complications and DRE. Benjamin et al. [9] found that drug resistance was a feature of patients with a higher frequency of spike–wave discharges on their EEGs.

Our objective was the identification of risk factors associated with DRE in adult patients with generalized epilepsy in the setting of a

* Corresponding author at: Department of Medicine, Division of Neurology, Royal University Hospital, Saskatoon, SK S7N 0W8, Canada.
E-mail addresses: jftellez@yahoo.com, jose.tellez@usask.ca (J.F. Téllez-Zenteno).

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standard epilepsy clinic where patients with childhood and adult onset seizures are assessed.

2. Methods

2.1. Population and type of study

We included patients between the ages of 18 and 75 who had been previously diagnosed with generalized epilepsy and followed up by the treating epileptologist. These patients were recruited from a single center where two treating epileptologists have collected a database of 800 patients with epilepsy from a catchment area of 1.1 million people. The center has an epilepsy program that serves the whole province of Saskatchewan, and it is the only center that provides epilepsy surgery. The center receives and follows complex cases but also assesses patients with new onset epilepsy. We used a case–control study methodology. Diagnoses and definitions were used in accordance with the 1985 ILAE criteria [10], and we used the current definition of DRE by the ILAE [3]. Patients who met the criteria for DRE according to the ILAE classification were classified as cases. The control group was formed with patients who did not fulfill the new definition of DRE. The diagnosis of generalized epilepsy was determined on clinical grounds with EEG confirmation in all cases and followed the criteria of the ILAE. We calculated a sample size using the variable developmental delay with the following parameters (case proportion = 49%, control proportion = 4, power 0.80, alpha 0.05), and we needed at least 53 cases and 53 controls [11]. We included all the available cases and controls in our database in order to have at least one case and two controls. We believe that being the sole center in the province is an advantage for this study, having the opportunity to have a adequate number of cases in addition to having controls from the same geographical area. The project was reviewed and approved by the Research Ethics Board (REB) of the University of Saskatchewan.

2.2. Variables and definitions

We gathered the following information from the charts: sociodemographic characteristics, characteristics of epilepsy, treatment, diagnostic tests, and risk factors for DRE. The entire patient database was analyzed and catalogued with the use of a collection sheet. Each patient database collected information about the individual's general demographics (age, gender, education level, occupation, marital status, number of children, substance history), seizure history (initial seizure frequency, age at diagnosis and years of evolution, presence of neonatal seizures, febrile seizures or status epilepticus, frequency of seizures at the time of evaluation, first AED used, response to first AED [good or bad], family history of epilepsy, comorbid conditions, neurological abnormalities on examination, presence of developmental delay (DD) (mild, severe, profound) or autism, and comorbid psychiatric conditions, i.e., depression, psychosis, behavioral problems, and anxiety and/or panic attacks). Specific information regarding the etiology of epilepsy was also collected: whether epilepsy was idiopathic, genetic, or cryptogenic; if perinatal insults were sustained (i.e., asphyxia during birth, pregnancy complication, or intrauterine viral infections were documented); history of cranial trauma, cerebral neoplasm (malignant or benign), metabolic disorders, cerebrovascular accidents, cerebral infection, presence of cortical dysplasia or mesial temporal sclerosis, etc. Specific seizure profiles were documented and catalogued according to the ILAE coding (IIA–F, III, IV). Profiles included absence, myoclonic, clonic, tonic, tonic–clonic, and atonic seizures. Unclassifiable seizures were classified as III, and seizures too frequent to distinguish individual seizures were classified as IV.

Epileptic syndromes were identified according to the ILAE definition [10]. Idiopathic syndromes are generally thought to arise from genetic abnormalities that lead to alteration of basic neuronal regulation. Symptomatic epilepsy is defined as epilepsy that arises from the effects of an epileptic lesion, whether that lesion is focal (i.e., tumor), or a defect in metabolism causing widespread injury to the brain. Cryptogenic syndromes involve a presumptive lesion that is otherwise difficult or impossible to uncover during evaluation. After defining each patient's syndrome and seizure profile, specific epileptic syndromes were documented, including West syndrome, Lennox–Gastout syndrome, childhood absence epilepsy (CAE), juvenile myoclonic epilepsy (JME), mitochondrial disease, Rasmussen encephalitis, mesial temporal sclerosis (MTS), or others. All relevant investigations were included in the database collection sheets, including routine and ambulatory EEG and results, video EEG telemetry data, imaging results, including CT, MRI, and PET scans, history of epilepsy surgeries and outcome, and any neuropathology findings. Finally, a detailed history of AED use was taken, including the following: dose, frequency, reasons for discontinuation (adverse effect, unsatisfactory control, long-term seizure freedom, psychosocial concerns, i.e., pregnancy, administrative reasons, i.e., lost to follow-up, financial issues, patient/caretaker preference, others), and outcome dimension. Other therapies were documented, including ketogenic diet and vagal nerve stimulation. Developmental delay was classified using the DSM-IV criteria as follows: Mild DD (IQ: 50–75, often academic skills up to the 6th level, self-sufficient), moderate DD (IQ: 35–55, carry out work and self-care task with moderate supervision, live within a community), severe DD (IQ: 20–40, master very basic self-care skills and some communication, live in group home), and profound DD (IQ < 20–25, may develop basic self-care and communication skills).

2.3. Statistical analysis

We used descriptive statistics to assess frequencies and distributions. As appropriate, numerical and categorical data were compared with either *T*-test or Chi-squared test. We calculated odds ratios and corresponding confidence intervals. We also performed a logistic regression analysis of the most significant risk factors.

3. Results

3.1. General description

One hundred eighteen patients with generalized epilepsy were included. Seventy-one (60%) were males, and 47 (40%) were females. The mean age at onset of epilepsy was 14.2 ± 11.4 (range: 0–55). The mean age of patients was 32.5 ± 13.1 (range: 18–75). The mean number of years of evolution of the epilepsy was 18.2 ± 13.9 (range: 0–70). Overall, forty-four (37%) patients fulfilled the definition of DRE (cases) and seventy-four (63%) patients did not have DRE (controls). Sixty-two percent of patients in our study started having seizures in childhood (younger than 16 years).

3.2. Comparison of numerical variables between cases and controls

Patients with DRE were significantly younger than the controls at the onset of epilepsy (6.6 vs. 18.8, $p < 0.001$), had more years of evolution (24.1 vs. 14.7, $p < 0.001$), and had used more AEDs (5.9 vs.2.6, $p < 0.001$). See Table 1.

Table 1
Analysis of continuous variables.

	No DRE n=74 (mean, SD)	DRE n=44 (mean, SD)	p value
Age (years)	33.6 ± 12.7	30.5 ± 13.7	0.21
Age at onset (years)	18.8 ± 11.1	6.6 ± 6.9	<0.001
Years of evolution	14.7 ± 13.1	24.1 ± 13.5	<0.001
Number of status epilepticus events	1 ± 0	3.4 ± 3.7	0.39
Number of AEDs	2.6 ± 1.8	5.9 ± 2.2	<0.001
Number of seizures per month	2.6 ± 9.5	28.1 ± 93.6	0.09