



Risk factors associated with drug resistant focal epilepsy in adults: A case control study

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ARTICLE INFO

Keywords:

Complex partial seizure
Focal seizure
Intractable epilepsy
Refractory epilepsy
Risk factor
Temporal lobe epilepsy

ABSTRACT

Purpose: Using an adult cohort of patients with focal epilepsy, we aimed to identify risk factors for development of drug-resistant epilepsy, which if identifiable would allow patients to receive appropriate counsel and earlier surgical treatment.

Methods: This is a case-control study nested within a cohort, 146 adult patients with focal epilepsy were included. Definitions were used in accordance with ILAE criteria. The odds ratio and its confidence interval were calculated. We performed a logistic regression analysis.

Results: Seventy-one [48.6%] patients met the criteria for drug-resistant epilepsy [cases] and 75 [51.4%] patients were controls. The mean age of patients was 44.5 ± 16.4 years. The most significant variables associated with developing drug-resistant epilepsy include younger age at diagnosis [18.75 vs. 32.2, $p < 0.001$], years of evolution of epilepsy [22.54 vs. 16.05, $p < 0.001$], number of AED [4.8 vs. 2.87, $p < 0.001$], complex partial seizures [51 vs. 35 OR 2.9, $p = 0.002$], having more than one seizure per month [51 vs. 38, $p = 0.009$], bi-temporal focus [14 vs. 4 $p = 0.008$] and mesial temporal sclerosis [23 vs. 11 $p = 0.01$]. Good response to first AED [7 vs. 29 OR 0.2, $p = 0.001$] and epilepsy secondary to encephalomalacia [8 vs. 20 OR 0.35, $p = 0.018$] might be protective factors against drug resistant epilepsy.

Conclusions: Longer time of epilepsy evolution, high frequency of seizures, complex partial seizure presentation, higher number of antiepileptic drugs, mesial temporal sclerosis and bitemporal epilepsy are predictive factors of subsequent pharmacoresistance.

1. Background

Epilepsy is the third most common neurological disorder [1]. It is one of the most common disabling diseases affecting about three million Americans and 50 million people around the world. The point prevalence of epilepsy in Canada is 5.2 per 1000 [2]. About 60% of patients with epilepsy [PWE] become seizure-free with anti-epileptic drugs [AED], and between 30–40% of patients continue to have seizures despite pharmacological treatment [3–5].

Drug-resistant epilepsy [DRE] is defined as a failure to adequate trials of two tolerated and appropriately chosen and used AED scheduled as a monotherapy or in combination to achieve sustained seizure freedom [4]. Pharmacoresistance establishes a significant burden on patients from medical, social and financial aspect. The annual cost for 2.3 prevalent cases is estimated at 12.5 billion [6,7]. A significant proportion of this is due to DRE. Additionally, patients with DRE have

some compromise in their quality of life. The majority of patients feel stigma, shame or disgrace associated with having the disease, and the stress of living with a chronic unpredictable illness [8].

Due to the significant burden of DRE, identifying risk factors that may lead to DRE can help physicians provide more aggressive medical or surgical management early in the course of the disease [9]. It can also help physicians recognize risk factors, which may be controlled, as well as provide needed data of seizure outcome to help counsel patients [9]. There is a substantial amount of literature in the pediatric population regarding risk factors for DRE in patients with focal and generalized epilepsy. However, there is a lack of knowledge regarding factors associated with drug-resistant focal epilepsy in adult population [10]. Therefore, we present a case-control study to determine the risk factors in adult patients associated with the development of drug-resistant focal epilepsy.

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<https://doi.org/10.1016/j.seizure.2019.10.020>

Received 3 June 2019; Received in revised form 22 October 2019; Accepted 31 October 2019

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2. Methods

2.1. Population and type of study

This is a case-control study nested within a cohort. We included patients older than 18 years of age who were diagnosed with focal epilepsy. These patients were recruited from a single center where two treating epileptologists have collected a database of 1200 PWE from a catchment area of 1.2 million people. The center has a single epilepsy program that serves the entire 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.

Diagnoses and definitions were used in accordance with the 2014 ILAE criteria [11]. The diagnosis of focal epilepsy was determined on clinical grounds with the use of other available test such as MRI and EEG in all cases. We used the current definition of DRE by the ILAE [4]. 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 definition of DRE. We included all the available cases and controls in our database to match at least of one case and one control [1:1]. The project was reviewed and approved by the Research Ethics Board of the University of Saskatchewan.

2.2. Variables and definitions

We gathered the following information from the charts: socio-demographic characteristics, semiology of epilepsy, diagnostic tests, risk factors for DRE, and treatment. We created a collection sheet that was used to review the entire database. We collected from each patient information about the individual's demographics [age, gender, education level, occupation, marital status, number of children] and 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, family history of epilepsy and neurological abnormalities on examination]. Specific seizure semiologic profile was documented and cataloged according to the ILAE coding [12].

Information regarding the etiology of epilepsy was also collected [sustained perinatal insults, asphyxia during birth, pregnancy complication, and intrauterine viral infections], history of cranial trauma, cerebral neoplasm [malignant or benign], metabolic disorders, cerebrovascular disease, cerebral infection, presence of cortical dysplasia and hippocampal sclerosis [HS]. Epileptic syndromes were defined according to the ILAE definition as idiopathic [genetic], symptomatic [structural or metabolic] and cryptogenic [unknown][11, 12]. After defining each patient's syndrome and seizure profile, specific epileptic syndromes were documented, including West syndrome, Lennox–Gastaut syndrome, mitochondrial disease, Rasmussen encephalitis, and mesial temporal sclerosis [MTS].

Comorbid psychiatric conditions were also documented [depression, psychosis, behavioral problems, and anxiety and/or panic attacks]. Developmental delay was classified using the DSM-IV criteria as follows: Mild DD [IQ: 50–75, 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].

All relevant investigations were included in the database, including routine and ambulatory EEG, video EEG telemetry data, imaging results including CT scan, MRI and PET scan, and any neuropathology findings from epilepsy surgery. Finally, a detailed history of AED use was taken, including the following: first AED used, response to first AED [good or bad], dose, frequency, reasons for discontinuation [adverse effect, unsatisfactory control, long-term seizure freedom, pregnancy, financial issues, and patient/caretaker preference]. Other therapies were also

documented, including epilepsy surgery, ketogenic diet, and vagal nerve stimulation.

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. A *p* value < 0.05 was considered statistically significant. All analyses were performed using SPSS software [IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp]. For the model unconditional [unadjusted] associations were evaluated between each of the potential risk factors of interest and the diagnosis of DRE using all of the available observations for each risk factor. Risk factor with a *p*-value of ≤ 0.20 were initially retained. A manual backward stepwise selection strategy was then used to build the main effects model, retaining factors with *p*-values ≤ 0.05 . A type 3 likelihood ratio test was used to assess variables with more than two categories. Factors with *p*-values > 0.05 in final model were further evaluated as potential confounding variables, based on a $\geq 20\%$ change in the coefficients for the other risk factors. All possible interactions were explored between factors retained in the final model. The fit and adequacy of the final model were evaluated by plotting residuals and calculating the area under the receiver operator characteristic [ROC] curve for the final model.

3. Results

3.1. General description

As shown in Table 1, 146 adult patients with focal epilepsy were included. Seventy-eight patients [53.4%] were male. The mean age of PWE was 44.5 ± 16.4 year, and the average of evolution of epilepsy was 19.21 ± 15.38 years. The most common epileptic syndrome was

Table 1
General characteristics of patients with focal epilepsy.

N = 146	
Gender N [%]	
Male	78 (53.4)
Female	68 (46.6)
Age \pm SD, [range]	44.5 ± 16.4 , (18–87)
Age at diagnosis \pm SD, [range]	25.6 ± 19.3 , (3 months–80 years)
Years of evolution of epilepsy \pm SD, [range]	19.2 ± 15.3 , (1–61)
Type of seizures N [%]	
SPS	40 (27.4)
CPS	86 (59)
SG	71 (48.5)
Syndrome N [%]	
Symptomatic	113 (77)
Cryptogenic	33 (22.6)
Etiology N [%]	
Unknown	33 (22.6)
MTS	34 (23.3)
Encephalomalacia	25 (17.1)
Cortical dysplasia	15(10.30)
Benign cerebral tumor	12(8.20)
Malignant tumor	5(3.4)
Other	22(15.1)
Focus N [%]	
One focus	105 (72)
Two foci	31(21.2)
Multiple foci	9 (6)
Hemisphere	1(0.7)

Abbreviations: SPS: simple partial seizure, CPS: complex partial seizure, SG: secondary generalization, MTS: mesial temporal sclerosis, SD: standard deviation.

Table 2

Risk factors for DRE in patients with focal epilepsy [N = 146].

	DRE n = 71	No DRE n = 75	OR	p
Age (± SD) years	38.5 ± 14.7	47 ± 17.3	NA	0.008
Gender (%)				
Male	38(%)	40(%)		0.98
Female	33(%)	35(%)		
Age at diagnosis of epilepsy (± SD)	18.7 ± 15.2	32.2 ± 20.6	NA	0.001
Diagnosis of epilepsy less than 12 years (# patients)	18	12	2.57(1.16,5.7)	0.02
Years of evolution of epilepsy mean (± SD)	22.5 ± 15.4	16.0 ± 14.7	NA	0.01
History of brain surgery as the cause of the epilepsy	6	14	0.40 (0.14-1.1)	0.07
History of febrile seizures	4	4	1.06 (0.25-4.4)	0.93
History of developmental delay	5	4	1.3 (0.35-5.22)	0.74
Any psychiatric comorbidity	12	9	1.2 (0.5-2.8)	0.63
Etiology				
Unknown	17	15	1.3 (0.6-2.2)	0.56
Cortical dysplasia	9	5	2.0 (0.65-6.4)	0.22
MTS	23	11	2.8 (1.2-6.3)	0.01
Encephalomalacia	8	20	0.35 (0.14-0.85)	0.01
Any tumor	3	9	0.32 (0.08-1.25)	0.08
One epileptic focus	46	59	0.5 (0.2-1.2)	0.62
Bi-temporal	14	4	4.36 (1.36-13.9)	0.008

symptomatic with 113 patients [77%], and the most common etiology was MTS with 34 patients [23.3%]. Furthermore, the most common localization of epilepsy was one focus, with 105 patients in total [72%].

3.2. Comparison of variables between case and control

Seventy-one [48.6%] patients met the criteria for DRE [cases] and 75 [51.4%] patients were non-DRE [control group]. Tables 2 and 3 outlines the variables found to be associated with drug-resistant focal epilepsy in adults. The most significant variables associated with developing DRE in adults include age at diagnosis of epilepsy [18.7 vs. 32.2 years, $p < 0.001$], years of evolution of epilepsy [22.5 vs. 16.0, $p < 0.001$] and number of used AED [4.8 vs. 2.87, $p < 0.001$].

3.3. Predictors of drug resistant focal epilepsy in adults

Several other variables were found to be significantly associated with developing drug-resistant focal epilepsy in adults. These include, Complex partial seizures [CPS] [51 vs. 35, OR 2.9 CI: 1.5–5.8, $p = 0.002$], more than one seizure per month [51 vs. 38, $p = 0.009$], bi-temporal focus [14 vs. 4 $p = 0.008$], MTS [23 vs. 11 $p = 0.01$] and diagnosis of epilepsy for more than 12 years [22 vs. 12, OR 2.35 CI: 1.06–5.2, $p = 0.032$].

3.4. Variables reducing the occurrence of DRE in adults

As outlined in Tables 2 and 3, two factors may reduce the risk of drug-resistant focal epilepsy in adults. These include encephalomalacia [OR:0.35; 95%CI: 0.14–0.85, $p = 0.018$], and good response to the first AED [OR: 0.2; 95%CI: 0.08–0.5, $p = 0.001$].

Table 3

Risk factors for DRE in patients with focal epilepsy [n = 146].

	DRE n = 71	No DRE n = 75	OR	p
Temporal (location)	52	46	1.72 (0.8-3.4)	0.13
More than one seizure per month	51	38	2.5 (1.2-4.9)	0.009
Good response to the first AED (%)	7	29	0.2 (0.08-0.5)	0.001
Frequency of seizures per month	8.5(20.2)	6.0 (12.43)	NA	0.38
Complex partial seizures	51	35	2.9 (1.5-5.8)	0.002
Partial secondary generalized	40	31	1.8 (0.95-3.5)	0.070
MRI lesion	48	58	0.61(0.29-1.27)	0.19

3.5. Multivariate analysis

Using a logistic model, a good response to the first AED decreased the risk to develop DRE, OR 0.2, [95%CI 0.000000018-0.45, $p = 0.029$].

4. Discussion

Focal epilepsy is the most common seizure disorder, and approximately 30% of patients will experience physically and socially disabling seizures despite taking AED [4,5]. The underlying mechanisms of drug resistance remain largely unclear. Overall seizure outcomes in adults with focal epilepsy have changed little over the past 30 years despite the introduction of several AED with a range of different mechanisms of action [13]. Published epidemiological data over the last years have identified several risk factors that correlate with a poor prognosis in children. In this study, we assessed factors, available at the time of diagnosis, predictive of subsequent pharmacoresistance in adult patients with focal epilepsy. In our study the most significant factors associated with developing DRE in the univariate analysis included younger age at the diagnosis and longer time of evolution of epilepsy, the presence of CPS, high frequency of seizures, MTS on MRI, and bi-temporal epilepsy. Good response to first AED and epilepsy secondary to encephalomalacia were protective factors to drug resistance. Finally, the more AEDs the patient has received, the more risk of progressing to DRE.

The underlying cause of epilepsy is a major prognostic factor for recurrence. Focal epilepsies relating to structural brain abnormalities are less likely to enter remission compared that occurring in patients with structurally normal brains, even if they have newly diagnosed epilepsy [14]. This study supports the observation of worse outcomes in patients with temporal lobe epilepsy [TLE] and HS [15]. A complex study reviewing patterns of seizures of children and adult patients with

incident DRE showed that TLE patients were significantly more likely to experience worst outcome trajectory patterns in comparison with all the other focal and generalized epilepsy patients despite of age [16]. Similarly, several studies identifying early predictors of DRE in children [$p = 0.023$] [17] and adults [18] have demonstrated that HS is highly correlated with drug resistance [$p = 0.02$] [17]. However, an important proportion [46%] of patients with TLE could have remission, suggesting, as in other populations, that some temporal cases have a more benign form [18,19].

Apart from the etiology, there is a known impact of duration of epilepsy in years on severity of disease. In average, in our cohort, patients with DRE had 6 years more of evolution compared with controls without DRE. Similar findings were reported by a study of lesional partial epilepsies in Korea [178 vs. 102 months] [20], and in a study carried on in Macedonia where DRE patients suffered the disease during 22 years and seizure-free patients suffered the illness during 14 years [21]. Recurrent limbic seizures have been shown to produce neuronal loss and mossy fibers sprouting in the hippocampus, which in turn can facilitate the emergence of further seizures [22]. By contrast, patients with a mild course of TLE are more likely to be older [$p = 0.002$], have late-onset epilepsy [$p < 0.001$], and shorter evolution [$p < 0.001$] [23]. The longer the duration of epilepsy the higher the number of tried AED. In general, higher number of previously tried AED is associated with drug resistance [21].

Poor control of seizures, despite the introduction of the first anti-epileptic treatment, is a very important factor in the subsequent evolution [10,24]. Resistance to the first drug seems to have a significant influence on the appearance of a pharmacoresistance in children [17], and adults [19,25]. Kwan and Brodie reported that overall, 50% of patients respond to first AED, 10% respond to the second AED, and only 3% respond to a third drug or multiple drugs. Furthermore, only 10% of patients who fail initial monotherapy due to lack of efficacy subsequently became seizure-free, compared to 40–50% of those who fail due to side effects [9]. The ILAE recommends that 12 months of remission, or three times the longest pretreatment inter-seizure interval, should be used as the minimum period to evaluate the effectiveness of AEDs [26]. Some longitudinal studies have demonstrated that patients who are seizure-free for the initial six months of the first drug initiation have a 90% chance of being seizure-free at 12 months [27], and a 72% chance of being seizure-free at 36 months [28]. Our study confirms that the good response to the first AEDs is a protective variable to develop DRE. This variable has been identified extensively in previous cohorts of patients with focal and generalized epilepsy [29].

Interestingly in our study, patients with epilepsy-related to areas of encephalomalacia had a better prognosis. There are very few reports about epilepsy-related to areas of encephalomalacia, and it is unclear if they have a high tendency to develop intractable epilepsy [30,31]. In general, surgical series from epilepsy centers report few cases of patients with DRE associated with areas of encephalomalacia compared with other more frequent etiologies such as MTS and cortical dysplasia, suggesting less tendency for intractability [31].

Although the effect of seizure types seems to be less critical than other mentioned factors, some studies have suggested a significant effect on prognosis [14]. In the classic longitudinal study of patients with epilepsy in Rochester, Minnesota, prognosis was less favorable for those with CPS and adult-onset epilepsy, in comparison to patients with generalized-onset seizures diagnosed before ten years of age [32]. In general, outcomes tend to be poorer in patients with localization-related epilepsies in comparison with patients classified as having idiopathic generalized epilepsies [13,14]. However, it is not clear if patients with CPS have a worst outcome than patients with simple partial seizures.

Historically pharmacoresistance has been associated with several other factors such as family history of epilepsy, febrile seizures in infancy, traumatic brain injury as the cause of the epilepsy [13], intellectual disability [18], and psychiatric comorbidity, particularly

depression [25]. Our study did not identify a significant association between DRE and these factors.

4.1. Strength and limitations

There are several limitations to this study; in particular the fact that this is a retrospective study based on medical charts review. Consequently this may not allow accurate estimates of some clinical variables. Second, the sample size of our cohort is relatively small. It is possible that some prognosis factors may be missed due to the reduced sample size. Further studies with a larger sample cohort are required. Third, a convenience sample from a single specialized epilepsy center setting was used for this study, limiting the generalization of our results to other patient cohorts. Outcomes in our cohort are invariably different from those in cohorts of patients with chronic epilepsy followed in a community hospital setting. However, we believe that being the sole center in the province is an advantage, having the opportunity to have a acceptable number of cases in addition to having controls from the same geographical area. Finally, we did not measure the number of seizures before initiation of treatment in our population, and recently high pretreatment seizure density has been identified as an important predictor factor of drug resistance.

5. Conclusion

We demonstrated a number of factors predictive of subsequent pharmacoresistance in adult patients with focal epilepsy. Longer time of epilepsy evolution, high frequency of seizures, CPS presentation, high number of AEDs, MTS and bitemporal epilepsy are the most important. These results can help adult epileptologists and neurologists to identify patients with focal epilepsy that are at risk for DRE. This will allow identified patients to receive earlier treatment and more specifically individualized treatment plans. Epileptologists could be more aggressive, earlier on, with potentially invasive therapies, such as epilepsy surgery for suitable candidates. Early referral and treatment may improve the patients' quality of life and help them to avoid mortality and morbidity from a variety of factors, including adverse effects resulting from multiple AEDs, which are not providing additional benefits.

Conflict of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Dr. Tellez-Zenteno receives grants from the University of Saskatchewan, Saskatchewan Health Research Foundation, and the Royal University Hospital Foundation, Saskatoon, Saskatchewan. Pragma Laboni Roy, Lizbeth Hernandez-Ronquillo, and Lady Diana Ladino have nothing to disclose.

We confirm that we have read the Journal's position on issues involved in ethical public.

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