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Brief report

Risk factors for drug-resistant epilepsy in adult patients

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ABSTRACT

Introduction: Drug-resistant epilepsy occurs in about 30% of epilepsy patients. It has been suggested that etiology or seizure type would increase the risk of pharmacoresistance. This study aims to compare the characteristics of patients with drug-sensitive epilepsy with patients with drug-resistant epilepsy to identify risk factors.
Patient and methods: A multicentric cohort study was conducted between 2019 and 2022. We included patients >18 years-old with epilepsy but excluded psychogenic non-epileptic seizures and less than 2 years of follow-up.
Results: We included 128 patients, of whom 46 had drug-resistance epilepsy, and 82 responding to medication. Both groups showed similar characteristics. Febrile seizures (OR: 7.25), focal epilepsy (OR: 2.4), focal seizures with loss of consciousness (OR: 2.36), structural etiology (OR: 2.2) and abnormal MRI (OR: 4.6) were significant risk factors for drug-resistance epilepsy.
Conclusion: Following other studies, we observed that factors such as epilepsy type, seizure type, structural etiology, abnormal MRI, and febrile seizure increased the risk for drug-resistance epilepsy, in our population.

Factores de riesgo de epilepsia farmacorresistente en pacientes adultos

Palabras clave:
Epilepsia farmacorresistente
Anticonvulsivos
Epilepsia refractaria
Epilepsia sensible a fármacos
Farmacorresistencia

RESUMEN

Introducción: La epilepsia farmacorresistente se presenta en aproximadamente 30% de los pacientes que padecen epilepsia. Se ha sugerido que la etiología o el tipo de crisis aumentarían el riesgo de farmacorresistencia. El objetivo de este estudio es comparar las características de los pacientes con epilepsia fármacosensible con las de los pacientes con epilepsia farmacorresistente para identificar los factores de riesgo.
Pacientes y métodos: Se realizó un estudio de cohorte multicéntrico entre 2019 y 2022. Se incluyeron pacientes >18 años con epilepsia pero se excluyeron las crisis psicógenas no epilépticas y menos de dos años de seguimiento.
Resultados: Se incluyeron 128 pacientes, de los cuales 46 tenían epilepsia farmacorresistente y 82 respondían a la medicación. Ambos grupos mostraron características similares. Las crisis febriles (OR: 7,25), la epilepsia focal (OR: 2,4), las crisis focales con pérdida de conciencia (OR: 2,36), la etiología estructural (OR: 2,2) y la resonancia magnética anormal (OR: 4,6) fueron factores de riesgo significativos de epilepsia farmacorresistente.

Abbreviations: ASM, anti-seizure medications; DRE, drug-resistant epilepsy; DSE, drug-sensitive epilepsy; SUDEP, sudden unexpected death in epileptic patients; RF, risk factor.

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Conclusión: Siguiendo otros estudios, observamos que factores como el tipo de epilepsia, el tipo de crisis, la etiología estructural, la RM anormal y las crisis febriles aumentaban el riesgo de epilepsia farmacorresistente, en nuestra población.

Introduction

Epilepsy is a neurological disease characterized by an excessive neurological discharge predisposing to seizure, affecting 1% of the world's population.[1] Despite existing several anti-seizure medications (ASM), approximately 30% of patients with epilepsy continue to have seizures even under medication, called drug-resistant epilepsy (DRE).[2] According to the ILAE (international league against epilepsy), DRE is the failure of adequate trials of two tolerated and appropriately chosen and used ASM schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.[3] Pharmacoresistant epilepsy has been associated with poor quality of life and an increased risk of sudden unexpected death in epileptic patients (SUDEP) (incidence between 1.1 and 5.9 per 1000 person-years in DRE vs. 0.54–1.3 per 1000 patient-years in drug-sensitive epilepsy [DSE]).[4,5]

A systematic review of risk factors (RF) in childhood found that RF for DRE were abnormal EEG, status epilepticus, symptomatic etiology, multiple seizure types, and febrile seizures.[6] Voll et al. have described that, characteristics such as etiology, response to 1 ASM and febrile seizure increase RF of DRE.[7] Although studies in the child population are abundant, publications in the adult population are limited. For this reason, our study aimed to compare the characteristics of adult patients with DSE versus DRE to identify risk factors in our population.

Methods

Design

A multicenter cohort study was conducted in two general hospitals in Buenos Aires, Argentina. The participating hospitals were Hospital General de Agudos Dr. Teodoro Alvarez and Hospital Británico de Buenos Aires between March 2019 and April 2022.

Subjects

Patients over 18 years of age with an epilepsy diagnosis according to the ILAE definition with at least 2 years of follow-up were included. Patients suffering of psychogenic non-epileptic seizures and patients who had less than 2 years of follow-up at the time of recruitment, were excluded. This study was approved by the ethics committees of both hospitals. All the patients signed an informed consent.

We used the ILAE definition for the diagnosis of epilepsy and for drug-resistant epilepsy diagnosis. We also used the ILAE classification for seizure type and epilepsy.[3]

Variables

Demographic variables, family and personal history, age at epilepsy diagnosis, and seizure type were collected. Complementary studies (neuroimaging, electroencephalogram) results were used to determine the etiology, and type of epilepsy.

Statistical analysis

Continuous variables were described as median and interquartile range (25–75% percentiles). Qualitative variables were described as mean and percentage. To compare the difference between DRE and DSE variables, the Mann–Whitney test was used for continuous variables and the Fisher's test for qualitative variables. A multivariate analysis was performed to evaluate the predictive value of RF and they were expressed as OR and 95% CI. The software used were Graphpad Prism 8.02 and Medcalc 12.2.1.

Results

Population characteristics

In the period studied, 128 patients were included with a mean age of 39 (30–50); 44.5% (*n*: 57) were male. They were grouped into DRE patients (*n*: 46, 35.93%) and DSE patients (*n*: 82, 64.07%).

Demographic characteristics and personal history of drug-resistant and drug-sensitive epilepsy groups

Demographic characteristics of both groups were similar; however, febrile seizures and evolution time had a significant increase in patients with DRE compared with DSE population (Table 1).

Epilepsy characteristics of the drug-resistant and drug-sensitive groups

Seventy patients (54.68%) had generalized epilepsy, while 41.40% (53 patients) had focal epilepsy, the latter being more frequent in patients with DRE. There was a significant increase in the proportion of patients with focal seizures with loss of consciousness in the drug-resistant group compared to the drug-sensitive group (*p*: 0.02) (Table 1).

Complementary studies and etiology

One hundred and thirty-four neuroimaging studies were evaluated (101 magnetic resonance images and 33 computer tomography). According to the ILAE, epilepsy protocol was used for magnetic resonance images (MRIs). Comparative analysis between MRIs demonstrated a significant increase in pathological findings in patients with DRE, while computer tomography findings were similar in both groups (Table 2).

Prolonged electroencephalograms (EEG) were studied from 106 patients, of which 75 reported epileptic abnormalities. Although the finding of epileptic discharges was more frequent in patients with DSE, no significant difference was found between the two groups (*p*: 0.37). Moreover, in the location of the epileptogenic zone, no difference was observed between both groups. The main region involve was the temporal lobe followed by the frontal lobe in both groups (DRE and DSE).

Finally, the main etiology of epilepsy was structural. Malformations, brain tumors, and vascular disease predominated in both groups. In patients with DRE, the most frequent finding was mesial temporal sclerosis (11 of 28 patients), while dysplasia was the

Table 1
Characteristics of patients.

	Drug-resistant epilepsy	Drug-sensitive epilepsy	*p*-Value
No. of patients (%)	46	82	
Age	39 (30.5–47.5)	39 (29.7–50)	0.8
Time of evolution (years)	20.5 (13.7–35.2)	16 (7–24)	**0.03**
Male (n, %)	23 (50%)	34 (41.46%)	0.36
Age at first seizure (years)	17.5 (12.7–26.2)	22 (13.7–34.2)	0.13
Personal history (n = 89)	44	45	
TBI	6 (13.63%)	10 (22.22%)	0.9
Febrile seizure	8 (18.18%)	2 (4.44%)	**0.04**
Drugs	1 (2.27%)	0 (0%)	0.9
Family history	6 (13.63)	19 (42.22%)	0.24
Others	13 (29.54)	20 (44.44)	0.67
Epilepsy type (n = 128)	46	82	
Generalize	21 (45.65)	49 (62.82)	0.14
Focal	25 (54.34)	28 (35.89)	**0.03**
Unknown	0 (0)	5 (6.41)	0.15
Seizure type (n = 128)	46	82	
Generalized	21 (45.65)	50 (60.97)	0.1
Focal impaired awareness seizures	23 (50)	24 (29.26)	**0.02**
Focal aware	2 (4.34)	4 (4.87)	0.9
Unknown	0 (0)	4 (4.87)	0.3

TBI: traumatic brain injury; others: pregnant complication/birth complication, malformations, central nervous system infection.

Table 2
Complementary studies and epileptogenic zone.

	Drug-resistant epilepsy *N* (%)	Drug-sensitive epilepsy *N* (%)	*p*-Value
MRI (*n* = 101)	41	60	
Abnormal	28 (68.29%)	20 (33.33%)	**<0.0006**
Normal	13 (31.70%)	40 (66.66%)	
CT (*n* = 34)	11	23	
Abnormal	3 (27.27)	6 (26.08)	0.9
Normal	8 (72.72)	17 (73.91)	
EEG (*n* = 106)	39	67	
Abnormal	30 (76.92)	45 (67.16)	0.37
Focal	14 (46.66)	21 (46.66)	0.48
Generalized	16 (53.33)	24 (53.33)	0.48
Normal	9 (23.07)	22 (32.83)	0.18
Etiology (*n* = 128)	46	82	
Symptomatic (structural)	28 (60.89)	31 (37.80)	**0.01**
Idiopathic/undetermined	18 (39.13)	51 (62.19)	

MRI: magnetic resonance image; CT: computer tomography; EEG: electroencephalography.

most frequent malformation (8 of 31 patients) in patients with DSE (Table 2).

Medication

Second and third-generation ASM were the most indicated. Valproate and carbamazepine (second-generation drugs) and levetiracetam (third-generation drugs) were the most common ASM used. In the case of DSE, carbamazepine, and levetiracetam (19 patients for each drug) were the most frequently indicated while, in patients with DRE, levetiracetam, lamotrigine, and topiramate (taken by 33, 15, and 13 patients) were the more common ASM that were combined.

Risk factors of drug-resistant epilepsy

A logistic regression analysis showed factors with significantly increased risk of DRE, even after adjusting by years of evolution were: focal epilepsy (OR: 2.4; 95% CI: 1.0–5.5); focal seizures with loss of consciousness (OR: 2.4; 95% CI 1.0–5.5); abnormal MRI (OR: 4.6; 95% CI: 1.8–12), structural etiology (OR: 2.2; 95% CI: 1.0–5.0) and febrile seizure in childhood (OR: 7.25; 95% CI: 1.4–38.0) (data not shown).

Discussion

It has been previously described that epilepsy affects the quality of life, with a higher impact on those patients who cannot control seizures.[5] The prevalence of drug-resistant epilepsy varies between 15% and 33% in the literature. A meta-analysis, which included more than 13,000 patients, mainly children, determined a prevalence of 30%,[8] in agreement with Tellezo–Zenteno reporting a 33% prevalence.[2] In our study, the prevalence of DRE was higher than previously described (35.93%).

Etiology is another RF associated with DRE. Structural etiology (brain tumors, trauma, malformations) increases the risk 2-fold, agreeing with other studies.[2]

Concerning personal history, we found that febrile seizures increase the risk of DRE, in agreement with the results of studies realized by Tripathi and Voll.[7,9] However, we did not find that suffering a traumatic brain injury increased the risk of pharmacoresistance, in contrast to Hintiris et al.[10]

Neuroimaging studies allow for finding structural causes. As other studies reported, we found that abnormal MRI was a RF. Regarding the usefulness of EEG, some studies established a relationship between epileptic findings and the risk of DRE. However, this was not the case in our study.

Regarding clinical characteristics, focal epilepsy was more frequent RF in patients with DRE (OR 2.81; 95% CI: 1.11–7.11). We even found that the prevalence of focal impaired awareness seizures was higher in patients with DRE, being also a RF (OR: 2.06, 95% CI: 0.93–4.6) in concordance with the results of Tripathi et al.[9] This result could be related to etiology, as the main etiology in focal epilepsies was structural. In the case of DSE, juvenile myoclonic epilepsy (idiopathic epilepsy) was more frequent, explaining the high incidence of generalized epilepsy.

Finally, the most prescribed ASM were second and third-generation drugs, being related to their metabolism and, in the case of patients who received more than two drugs, to their mechanism of action, as they must be different to attempt to generate a synergistic effect. Furthermore, it should be considered that as the number of drugs and their doses increase, so does the risk of secondary pharmacological complications and adverse effects, which are less frequent in the case of third-generation ASMs. Another reason for the increased use of levetiracetam and lamotrigine is the lower risk of congenital malformations compared to second-generation ASM.

In the present study, we found a higher prevalence of drug-resistant epilepsy than previously reported. Multiple factors, including epilepsy, seizure type, and personal history, increase the risk of drug resistance. Therefore, these factors should be considered when assessing patients, in addition to a close follow-up, to take action earlier, either by initiating a combination of ASM prematurely or by considering advanced therapy to control seizures.

Ethical considerations

All the patients signed an informed consent.

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Conflict of interest

The authors have no conflicts of interest to declare.

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