

A relationship between drug-resistant epilepsy and structural abnormalities in neuroimaging

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Abstract

Background and objectives: The purpose of the study was to seek a relationship between drug-resistant epilepsy and structural alterations in neuroimaging to strengthen the link between the clinical and surgical management. A second objective was to determine an association between drug-resistant epilepsy and subject gender, the age of first seizure, and the type of seizure. **Materials and methods:** Over 632 medical records were scrutinized in search of those satisfying the inclusion criteria to end up with a sample of 108 subjects. Neuroimaging specialists reviewed each of the magnetic resonance imaging (MRI) studies looking for abnormalities to make the structural diagnosis and define it. **Results:** Of the 108 patients included in the study, 51 patients (Group A) were refractory to medical treatment and 57 patients (Group B) showed an improvement with medical treatment. We quantified the frequency of structural lesions confirmed by neuroimaging in both groups. The results showed a statistically significant difference of 84.31% of patients in Group A with a confirmed structural lesion in an MRI study versus 52.63% of patients in Group B ($p = 0.004$ [odds ratio = 4.85, 95% confidence interval: 2.01-11.66]). **Conclusion:** Our results support the association between structural lesions diagnosed with MRI and drug-resistant epilepsy. Thus, this finding gives a chance of an opportune and precise approach for the surgical treatment of these patients.

Key words: Epilepsy. Drug-resistant epilepsy. Epilepsy surgery. Epilepsy neuroimaging.

Una relación entre la epilepsia farmacorresistente y las anomalías estructurales en la neuroimagen

Resumen

Antecedentes y objetivos: Buscar una relación entre la epilepsia farmacorresistente y las alteraciones estructurales en la neuroimagen para fortalecer el vínculo entre el manejo clínico y quirúrgico. Un segundo objetivo fue determinar una asociación entre la epilepsia farmacorresistente y el sexo del sujeto, la edad de la primera convulsión y el tipo de crisis epiléptica. **Método:** Realizamos un escrutinio de más de 632 registros médicos en busca de aquellos que cumplieran con los criterios

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de inclusión para terminar con una muestra de 108 sujetos. Los especialistas en neuroimagen revisaron cada estudio de resonancia magnética (IRM) para diagnosticar si había una lesión estructural presente y determinar cuál. **Resultados:** De los 108 pacientes incluidos en el estudio, 51 pacientes (grupo A) fueron refractarios al tratamiento médico y 57 pacientes (grupo B) mostraron una mejora con el tratamiento médico. Cuantificamos la frecuencia de lesiones estructurales confirmadas por neuroimagen en ambos grupos. Los resultados mostraron una diferencia estadísticamente significativa de 84.31% de pacientes en el grupo A con una lesión estructural confirmada en un estudio de IRM versus 52.63% de pacientes en el grupo B ($p = 0.004$ [OR = 4.85, CI 95%: 2.01-11.66]). **Conclusión:** Nuestros resultados respaldan la asociación entre las lesiones estructurales diagnosticadas con IRM y la epilepsia farmacorresistente. Por lo tanto, este hallazgo brinda la posibilidad de un enfoque oportuno y preciso para el tratamiento quirúrgico de estos pacientes.

Palabras clave: Epilepsia. Epilepsia farmacorresistente. Cirugía de epilepsia. Neuroimagen en epilepsia.

Introduction

Epilepsy is the neurological disorder with the highest prevalence in our service and a considerable percentage of our patients are resistant to drug treatment. There are plenty of original articles and reviews which state that these groups of individuals could obtain a benefit from surgical treatment. The neuroimaging studies have aided in localizing potentially resectable zones improving the surgical approach.

In 2008, the International League Against Epilepsy (ILAE) defined drug-resistant epilepsy as the epileptic condition with “a failure of adequate trials of two tolerated, appropriately chosen and used anticonvulsant drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.”¹ To fit inside this definition, four criteria should be considered: (1) the antiepileptic treatment should be selected depending on the type of seizure, (2) an adequate dose should be used for a significant period of time before discontinuing the drug trial, (3) the drugs should be well tolerated and free of adverse reactions, and (4) the lack of attachment to the treatment should not be the cause of drug failure.

In the United States, there are 750,000 patients with drug-resistant epilepsy. Only 7,500 surgical procedures per year are done for these patients resulting in a low number of patients treated with a potential ameliorative procedure².

The neuroimaging techniques can provide information about the structural abnormalities and, therefore, data about the probable etiology of the seizures which in return will suggest a potential focus. The advantages of these studies are the non-invasiveness, the possibility of patient selection for surgery, and the ability to predict a prognosis posterior to surgery³.

Both in adults and children, the main etiologies of imaging provable epilepsy are hippocampal sclerosis, cortical development malformations, and brain tumors. In patients with drug-resistant focal epilepsy that is

candidates to surgical treatment, there is an identifiable relevant abnormality in 85% of the cases on a magnetic resonance imaging (MRI). In the remaining percentage, there is a possibility that the underlying cause is a subtle cortical development malformation or gliosis. By spectroscopy, it is feasible to find a reduction in the NAA/(Cho + Cr) ratio, which is a feature reported for brain regions that shelter an epileptic focus⁴.

The most successful drug combination for seizure management consists in drugs with different mechanisms of action⁵. It must not be forgotten that the adverse effects can be a consequence of AED combination rather than the effects of an AED alone⁶. Therefore, a personalized treatment plan must be formulated for each case and information for the patient and their family must be issued in any given possibility that seizure control state would not be easily achieved. Furthermore, patients with drug-resistant epilepsy must be informed of the risk of developing sudden death related to epilepsy and take appropriate cautions^{7,8}.

Kwan and Brodie reported in 2000 a study of 525 subjects on a period of 13 years where 27% of the cases were classified as idiopathic epilepsy (without a recognizable but possibly genetic etiology), 29% secondary to a structural lesion, and 45% as cryptogenic (with an undetermined but probably structural etiology). Seizure control was accomplished in 63% of the cases. About 43% with epilepsy secondary to a structural lesion persisted with seizures after drug treatment in comparison with 26% with idiopathic epilepsy⁹.

It has been described that the prognosis and the success of the drug treatment depend on the cause of epileptic seizures. The patients without an identifiable structural lesion have a better prognosis to remain free of seizures (50%). Instead, the patients with cortical development malformation have a chance of 25% and with unilateral hippocampal sclerosis of 11%^{10,11}.

In 2005, Cochrane realized a meta-analysis, in which 177 studies (16,253 patients) were identified searching

for the outcome of the candidates who underwent epilepsy surgery. The majority were retrospective studies and four were clinical trials. Of all the 16,253 candidates, 65% (10,518) had a satisfying outcome¹².

Two ECA studies reported by JAMA on 2015 with a total of 118 patients with temporal lobe epilepsy found a higher percentage of seizure free on patients who underwent an epilepsy surgery compared to those who underwent a continuous pharmacologic therapy (58% vs. 8% [n = 80] and 73% vs. 0% [n = 38], p ≤ 0.001). The epilepsy surgery was less effective when the lesions were extratemporal when the etiology was not related to a structural abnormality or both. Hippocampal sclerosis and benign brain tumors were associated with better results compared to other pathologies¹³.

As a result of the failure to control seizures in drug-resistant epilepsy, the risk of premature death increases, quality of life decreases, and it is highly likely that patients with this problem may have an identifiable lesion through an MRI study. Our objective is to determine a relationship between drug-resistant epilepsy and lesions discovery through neuroimaging with the purpose to consider a surgical approach and offer an improved treatment. To prove said relationship, we will analyze the brain MRI studies of a sample of patients with and without the diagnosis of drug-resistant epilepsy with the hope of obtaining and comparing the frequency, in which the structural lesions are present in both types of epilepsies.

Materials and methods

Subject selection was carried out in the follow-up of patients of the Epilepsy Clinic of the Neurology Service at the Central Hospital “Dr. Ignacio Morones Prieto” by the review of the medical record of all patients with the diagnosis of epilepsy from January 2017 to September 2018 (632 patients). Afterward, we applied the inclusion and exclusion criteria to end up with our final sample (n = 108) (Table 1). We defined and selected a group of drug-resistant epilepsy patients in accordance with the ILAE criteria (51 subjects). The control group was confirmed by patients with the diagnosis of non-resistant epilepsy (57 subjects) and depending on the age and sex similarities with the group being studied (i.e. the drug-resistant epilepsy group). The diagnosis was supported by a least one electroencephalographic study in all patients. Due to the age group, patients with infantile epileptic syndromes that are resistant to antiepileptic drug treatment were not taken into consideration for this study.

Table 1. Inclusion and exclusion criteria for the study

Inclusion criteria
– Patients older than 15 years of age
– Having at least one brain MRI study
– Having at least one EEG confirming the epilepsy diagnosis (although the absence of abnormal EEG does not rule out epilepsy, this was an inclusion criterion).
– Meeting the ILAE criteria for drug-resistant epilepsy from Kwan et al., 2010 ¹⁴ .
Exclusion criteria
– Poor attachment to antiepileptic drug therapy
– Going through antiepileptic drug adjustment
– Not to having a wish to participate in the study
– Having undergone an epilepsy surgery

EEG: electroencephalogram.

All patients were classified according to the either acquired or congenital presence or absence of abnormalities in brain imaging. At the same time, the lesions or malformations were classified in groups: hippocampal sclerosis, cortical development malformation, tumor, neurocysticercosis (NCC)/calcification, stroke, and other causes of minor prevalence.

We used an HD2 G5 1.5 T with an eight-channel neurovascular exploration coil MRI equipment. All available brain imaging studies were included whether they were conducted inside our institution or outside. Analysis of the imaging studies was done by a group of neurologists trained for neuroimaging interpretation and corroborated by a neuroradiologist of the Central Hospital to determine the presence or not of a structural abnormality. Successively, if a lesion was present to clarify which structural lesion was it about. For the diagnosis of hippocampal sclerosis, the increase in T2 signal with changes in fluid-attenuated inversion recovery, the N-acetyl aspartate/(choline + creatinine) index below 0.71, and hippocampal atrophy by comparison between hemispheres in T1 was considered¹⁵⁻¹⁸. The most common cortical development malformation found was focal cortical dysplasia, which was diagnosed as cortical thickness changes, effacement of the gray matter-white matter union, and T1 cortical hyperintense signal regarding a normal cortex, while in T2 a radial white matter hyperintense signal beneath the area of the dysplasia¹⁹. Stroke lesions were diagnosed with the usual parameters for a chronic ischemic lesion seen as a cavitated cystic encephalomalacia in the area of the old ischemia. As NCC is a prevalent infectious disease on our medium, we decided to include the brain MRI studies displaying the nodular calcified state seen as hypointensities in T1- and T2-weighted image²⁰.

Statistical analysis

To capture the data, we used a Microsoft Office Excel® (2010) spreadsheet. The variables under study (frequency of drug resistance and neuroimaging confirmed structural lesions) were written down as absolute and relative frequencies. The quantitative variables were kept as means and for determining their dispersion, the standard deviation, the minimum, and maximum were used.

The analysis and realization of graphics were carried out in MegaStat and Microsoft Office Excel®. This analysis was made in parallel with the program SPSS v.18.0. The comparison of categorical variables was made through crosstabs using the Chi-square test or the hypergeometric distribution as appropriate to determine variable independence considering $p < 0.05$ as statistically significant. Similarly, a multivariate analysis and logistic regression were done to establish the attributable risk.

Protocol approval and ethical aspects

The realization of this investigation was approved by the Investigation and Ethics Committee of the Central Hospital “Dr. Ignacio Morones Prieto” previous to the start of the medical record selection. All patients gave their consent for the usage, manipulation, and publication of their record data and brain MRI study.

Results

We examined 632 medical records with the diagnosis of epilepsy confirmed by electroencephalogram. Only 108 met the inclusion criteria. The main causes of exclusion were the lack of brain imaging, the poor attachment to drug therapy, or being through drug therapy adjustment. Of the 108 patients included in the study, 55 were female (50.92%) and 53 male (49.07%) with an age range from 16 to 72, a mean of 34 years, and a median 30 years.

All the selected candidates were classified in one of two groups. Group A of the drug-resistant epileptic was confirmed by 51 patients (47%) and Group B of the non-drug-resistant epileptic by 57 patients (53%) (Table 2). Four variables were contemplated (age, gender, age of first seizure onset, and type of seizure) for the secondary objective. Of those, only two showed a statistically significant difference between the control group and the drug-resistant group.

We calculated the frequency of structural lesions on neuroimaging depending on the presence or not of abnormalities on the brain. The results reported a

Table 2. Patient demographics Percentage of the frequency of drug-resistant and non-resistant epilepsy with a given variable

Variable	Group A (n = 51) Drug resistant	Group B (n = 57) Non-drug resistant	p
Mean age	31.8	36.6	0.70
Gender			
Female	27 = 52.9%	28 = 49.1%	0.692
Male	24 = 47.1%	29 = 50.9%	
Age of onset			
< 5	20 = 62.5%	12 = 37.5%	0.005
6 – 18	26 = 51%	25 = 29%	
> 18	5 = 20%	20 = 80%	
Type of seizure			
Focal onset	47 = 92.2%	36 = 63.2%	< 0.001
Generalized onset	4 = 7.8%	21 = 36.8%	

Table 3. The frequency of structural lesions on each group

	Positive for lesion	Negative for lesion	Total	Frequency (%)
Group A	43	8	51	84.31
Group B	30	27	57	52.63
Total	73	35	108	67.59

statistically significant difference indicating that 84.31% of the patients of Group A showed a structural lesion on MRI compared with the control Group B, in which 52.63% presented a lesion, with $p = 0.004$ (odds ratio = 4.85, 95% confidence interval: 2.01-11.66). This association explains that for every drug-resistant epileptic patient with no evidence of structural lesion, there are almost five patients that do have a lesion (Table 3).

The lesions observed were classified in both groups making a comparative analysis of the frequencies of each group. We noticed that the risk of drug resistance was different between the types of lesion being hippocampal sclerosis the most frequently associated to drug resistance (78.57%) followed by the cortical development malformations (60%) (Table 4).

Taking the age of onset into consideration, the subjects who had their first epileptic seizure between the 1st year of age and 5 years had a resistance frequency of 62.5%; in an inverse manner, when the first seizure presented after the 18 years of age, the percentage of resistance decreases 20%. In the in-between group (6-18

Table 4. The frequency of drug resistance in each type of studied lesion

Type of lesion	Yes	No	Total	Drug resistance (%)
0. Normal	8	27	35	22.86
1. Calcifications/NCC	5	4	9	55.56
2. Hippocampal sclerosis	22	6	28	78.57
3. Stroke	5	5	10	50
4. Tumor	0	2	2	0
5. Cortical developmental malformations	6	4	10	60
6. Others	5	9	14	35.71

years of age), the number of resistant and non-resistant was equivalent (49% vs. 51%, respectively). Hence, there is statistical evidence of an association between the beginning of the seizures at a young age and the probability to develop drug-resistant epilepsy ($p = 0.005$).

If the seizure onset was focal, then the probability to present drug resistance was higher compared to the generalized onset. In the drug-resistant Group A, there was a high prevalence of focal onset seizures (94%) with only three patients displaying a generalized onset (6%), whereas in the control Group B, 21 patients (36.84%) had a generalized onset and 36 (63.15%) a focal onset ($p = 0.0001$).

The more used antiepileptic drugs by the patients were carbamazepine (51%), levetiracetam (45%), and valproate (37%). With a minor usage was Lamotrigine (22%) and topiramate (17%), whereas oxcarbazepine, primidone, lacosamide, and phenytoin were the less frequent (<10%). There was not a significant difference in the usage between A and B groups.

Discussion

The data found supported the relationship between structural lesions observed on an MRI study and drug-resistant epilepsy. However, this affirmation does not mean that any type of lesion could be a risk factor for the development of drug resistance. For this reason, the lesions were classified resulting in hippocampal sclerosis and cortical development malformation occupying the higher percentage of found lesions in the drug-resistant patients.

In particular, the hippocampal sclerosis is the most studied pathology in the epileptic patients and with an excellent success rate after a surgical procedure,

having an absence of crisis to almost 70% of the cases and with a low frequency of neurological complications and mortality (< 1%)²¹.

The age of onset of epileptic seizures appears to be a risk factor for developing drug resistance. The results showed an association curve in which the lower the age of onset the higher the risk of developing drug resistance. This finding is similar to the one reported in a Chinese pediatric sample where it is described that the patients presenting the first seizure in their 1st year of age had a predisposition to develop drug resistance²².

Another fact that supports the final result is the difference found in the type of crisis, where the focal onset was present in 94% of the drug-resistant patients keeping an association with the higher percentage of structural lesions found in this patients compared with the non-drug-resistant ones (84% vs. 52%). This fact was described in a previous study realized in our country²³.

There were not effectiveness differences within the variety of AED used as described by the comparisons made by Cochrane studies between the effectiveness of AED in monotherapy²⁴. Even when valproate-lamotrigine combination is considered in those patients with drug resistance, as this therapy has demonstrated to be superior to others in some studies²⁴, in our medium, the patients do not always count with the economic support to acquire this specific AED combination, and in the majority of occasions, the most affordable AED therapy is used.

Stroke is frequently identified as an acute cause of epileptic seizures in adults of < 65 years and 25% of the patients could have drug-resistant epilepsy²⁵. The results we found tell us that 50% of our patients presenting with post-stroke epilepsy had AED resistance. However, we recommend to not consider this percentage due to the few cases we revised (only 10 subjects) and further research is advised.

A study from India indicates that a low proportion of subjects exhibit drug-resistant epilepsy while having an underlying NCC lesion or a cause-effect relationship between an NCC calcification and hippocampal sclerosis²⁶. Another study from Brazil states that NCC alone (or isolated) only counts in a low percentage (1.56%) of the etiologies of drug-resistant epilepsy and that NCC calcification associated lesions account for a higher percentage of the causes (27%). This calcification appears to be deeply correlated with hippocampal sclerosis ($p \leq 0.001$)²⁷. All things considered, as our study included a low number of subjects with NCC (nine individuals) and cysticercosis incidence varies depending on the endemicity of each country, we advise not

to take for granted our result on infectious etiologies of drug-resistant epilepsy.

In our study, there were included few patients with brain tumors due to not fulfilling the inclusion criteria and the management of the majority of them is in charge of the service of neurosurgery of this institution. For this reason, we could not obtain strong conclusions with respect to this population and recommend further research. Likewise, there were not included patients under the age of 16 that are treated by the service of neuropediatrics.

There is a relationship between the structural lesions seen in MRI study and the probability to develop drug-resistant epilepsy, and this is the reason that for every patient who does not have visible injuries, there are almost five patients who have it.

The risk of resistance is different within the distinct types of lesion, the variety of ages of seizure onset, and the type of onset of the seizure. Hippocampal sclerosis, the early onset of epilepsy and the focal onset seizures are more related to resistance.

Those results allow us to perform an MRI in this type of patient and analyze this study thoroughly and intensely, guided by clinical data in search of lesions, especially in those patients with drug-resistant focal epilepsy. We hope that this sort of study contributes with enough evidence to protocolize this variety of cases and perform a surgical management with a higher frequency and in an opportune and sooner manner on a patient that could potentially and finally benefit from this alternative therapeutic approach.

Conflicts of interest

None of the authors has any conflicts of interest to disclose.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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