Review Article
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Prognostic factors for the development of drug-resistant epilepsy

Abstract

Drug-resistant epilepsy is a top-priority social health problem which requires early individual treatment due to its dramatic repercussions for the patient and society. As a consequence of the crises, these patients present a worse quality of life, so their diagnosis is essential to establish possible therapeutic alternatives. The identification of the factors associated with drug resistance can predict in a certain way whether a patient will have epilepsy resistant to drugs in the short and long term. A number of factors contributing to a poorer prognosis has been identified and described. For patients with newly diagnosed epilepsy, the principal factors were the time interval between index seizure and AED start that only influences the short-term outcome. Also a number of seizures in the first year after AED start is associated with both short- and long-term outcomes. In conclusion the long-term prognosis of newly diagnosed epilepsy patients is in keeping with published reports. But it is necessary investigate more specifically each factors independent and future studies should be developed.

Keywords: drug-resistant epilepsy, prognostic factors, antiepileptic drug

Volume 1 Issue 4 - 2018

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Received: July 11, 2018 | **Published:** July 17, 2018

Abbreviations: AED, antiepileptic drug; DRE, drug-resistant epilepsy; ES, epileptic seizures; ILAE, International League Against Epilepsy; MRI, magnetic resonance imaging; CT, computed tomography; adjHR, adjusted hazards ratio; OE, oxidative stress OE; TLE, temporal lobe epilepsy; LE, level of evidence, EEG, electroencephalogram

Introduction

Epilepsy is one of the most frequent neurological diseases, representing a significant burden for the patient and the society.[1] As one of the most prevalent chronic neurological disease characterized by the recurrence of unprovoked seizures, epilepsy is afflicting seventy million people worldwide, with 50.4 per 100,000 people newly diagnosed every year, with a prevalence of 5—8 cases per 1000 habitants depending on the age group.[2,3] It is characterized by recurrent spontaneous seizures due to an imbalance between cerebral excitability and inhibition.[3] Conventional treatment for epilepsy is based on long-term, continuous administration of antiepileptic drugs (AEDs). The purpose of these drugs is to achieve total control over epileptic seizures without provoking side effects in order to improve the patient's quality of life.[4] It has been shown that 47% of patients with new-onset epilepsy can achieve complete seizure-freedom with the first AED, 13% of the remaining 53% may become seizure-free using a second agent, and only 4% with a third agent and/or polytherapy.[5] Even when provided with optimal AED treatment, approximately 25% of patients with epilepsy continue to experience seizures.[6] These patients have what is known as intractable, refractory, or drug-resistant epilepsy (DRE). It has been demonstrated in many population groups than the 20-40% of the patients with epilepsy are resistant to AED. Brodie et al demonstrated in a Scottish population that close to 25 % of the patients were resistant to AED and 16 % oscillate between free periods of seizure that last more of a year and relapses. Picot et al.,[7] carried out an experiment in a French population where close to 22.5 % of the patients with epilepsy also suffer from drug-resistant epilepsy (DRE) and documented a prevalence of 1.36 for 1,000 (interval of confidence interval to the 95 %: 1,07-1,66).[8]

Espinoza-Jovel et al.,[9] provided evidence, in a population of low financial resources in Bogotá, in which close to 15.4 % of the patients were resistant to AED and 14.4 % has an indeterminate response.[9] On the basis of the mentioned data, and considering that epilepsy is a frequent disease, with a prevalence of 10.3 per 1,000 (for countries of low financial resources), we can assume that the number of patient resistant to AED is high.[10] As a consequence of poor control over their epileptic seizures, they present an increased risk of early death, trauma, and psychosocial alterations, while their quality of life is diminished.[11] The International League Against Epilepsy (ILAE) defines drug-resistant epilepsy as ''failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom''. However, it should be emphasized that the AEDs must be treated adequately. An "adequate trial" includes, choosing an appropriate AED for the type of seizure being treated (e.g., failure of carbamazepine in treating idiopathic generalized epilepsy would not be considered a true failure), and titrating up the dose to the maximum tolerated dose. An AED that triggers allergic reaction or causes significant adverse effects that requires switching to another AED, may not be counted as failure either. It is also critical to define "seizure-freedom" when assessing the success or failure of an AED. The recommended definition is sustained seizure freedom for a period 3 times the longest inter-seizure interval, or 1 year, whichever that is longer.[12] It would take many years to treat an epileptic patient with the entire range of AEDs available today in both monotherapy and combination therapy. This would confirm the patient's epilepsy as completely untreatable, but would also consume crucial time during which the patient could suffer irreparable damage. Patients with DRE generally have a poor quality of life, various comorbidities, and a high mortality rate. For this reason, DRE should be treated as an entity requiring personalized treatment as early as possible to provide

the precise diagnosis, propose the best possible pharmacological treatment or consider alternative treatment, and recommend lifestyle changes that are important for the patient's social adaptation. Identifying patients with drug-resistant epilepsy is essential in order to optimize drug treatment, start the evaluation process to determine if they are candidates for surgery, and opt for surgery or other non-pharmacological alternatives on a case-by-case basis.[13] The knowledge of the probability of remission and recurrence of the epileptic seizure facilitates as much the clinical handling like the continued information to the patient and to his family about evolution and expectations of future of the disease.

After beginning a treatment with one AED, the persistence of the seizure requires modifications in the therapeutic boarding. The change of one AED for another one can provoke in some cases as much as worsening of the seizure and the appearing of new side effects. It is important to know the successful odds of the successive therapeutic regimens in order to optimize the available resources. On the other hand, the issue with the probability of response to the successive therapeutic regimens has a clear relation to the definition of the drug-resistant epilepsy.

Discussion

The analysis of many patients with drug resistant epilepsy has led to the identification of factors related with a poor prognosis in the treatment response. Knowledge and the identification in each patient of individual way of the clinical factors related with the development of resistance to medical treatments would support the decision of early surgical treatment, hence avoiding the reduction of quality of life secondary to the evolution of disease and the utilization of treatments with side effects as well as the mortality with the reiteration of seizure. It is important to enhance that all these factors work together like independent predictors, so the risk of developing a DRE increases when it shows up more than one.

Neonatal hypoxia and psychomotor growth

The association between neonatal hypoxia and DRE is a known factor. Investigations developed in child with focal DRE shown this factor as well as determinate factor on therapeutic failure.[14] The underlying mechanism in experimental studies base on glycoprotein P over expression in endothelial cerebral cells mature in vitro in rats with hypoxia and drugs resistance.[15] According to the latest investigations, abnormal psychomotor growth is a factor with statistic relevance and clearly association with the develop of DRE. In the research conducted by Martínez et al in Mexico the presence of prenatal hypoxia it occurred in 27% (n=24) of patients refractory to treatment (p=0.06). Thirty-one patients with drug resistance (27%) had a history of abnormal psychomotor development (p=0.02).[16] This agrees with previous studies, in which it was observed that only Five patients (6.7%) from a sample of 69 with epilepsy and mental retardation fulfilled the term 'freedom from crisis' after six months of follow-up.[17]

Family history of seizure

The family history of epilepsy as risk factor for resistance to treatment was recently described in a study accomplished in the Spanish population, where 1st and 2nd degree relatives of patient with DRE have been found with a relative prevalence of epilepsy of 34,9% compare to (0,5% a 1%) general prevalence.[18] A study realized in Mexico in the National Institute of Neurology and Neurosurgery by Martínez et al.,[16] this factor had an evident association with the incidence of DRE. The family history of epilepsy seems to be a determining factor for drug resistance and was present in 34% (n=39) of patients refractory to treatment and in 18% (n=10) of the patients who met criteria for freedom of crisis (p=0.025).[16] The above data matchesbwith that obtained by Brodie et al.,[7] in 2007 and other studies, where this factor is highlighted as one of the main predictors of drug resistance in epilepsy. The presence of epileptic seizures in several generations of the same family makes us suspect in a possible genetic cause of epilepsy. Then, it would be possible to state that genetic epilepsies have a worse prognosis than the other types of epilepsy? Would it even be possible to state that there are genes linked directly or indirectly with resistance to antiepileptic drugs?

It is necessary to carry out analytical studies intended only to demonstrate the association between family history of epilepsy and resistance to antiepileptic drugs.

Catamenial epilepsy

The seizures increase in direct relation to menstruation, this event has been confirmed by scientific evidence.[19,20] The hypotheses accomplished in animal models show that the progesterone decreases the neuronal firing and therefore the epileptiform spontaneous activity and induced. It also delays the kindling and decreases the recurrence of crises. On the other hand, the role of estrogens as exciters of the neuronal membrane is known through the increase of NMDA receptors (N-methyl-D-aspirate) and the decrease of inhibitory neurotransmission mediated by γ-amino butyric acid. It is estimated that approximately one third of women with drug resistance experience catamenial epilepsy.[21] In Martínez et al.,[16] 10 out of all patients presented catamenial epilepsy, which represent the 9 % of the cases; all of which suffer from DRE.(p=0.02).[16]

Onset seizure and etiology

All the available studies show some influence of the etiology and the focal onset of seizure in the prognosis of epilepsy. The frequency of drug resistance in patients with focal seizure onset was more significant than observed in generalized seizure. This results are consistent with the other found in 246 patients with DRE where the major percent of DRE was related with de epilepsy focal onset (80,5%) in comparison with generalized indeterminate epilepsy patients.[22] In Martinez et al the focal onset of seizures was found in 88 patients (72%) with drug-resistant epilepsy, in contrast with 34 (28%) crisis-free patients in this group. Fifty patients had onset of generalized seizures, of which 27 (54%) were drug-resistant. A statistically signifcant difference was found for greater refractoriness in focal onset epileptic seizures (p=0.02).[16] According to Brodie MJ et al.,[7] of 118 patients with genetic generalized epilepsies, 64% achieved remission. Interestingly, a history of febrile convulsions was associated with a reduced likelihood of remission (p=0.032) in this analysis. Nocturnal seizures have been found to predict a lower chance of sustained remission. Patients with a first nocturnal seizure are at increased risk of relapse. This may reflect an increased susceptibility to experience recurrent seizures. A poor compliance with treatment in patients with nocturnal seizures, that by definition have a lower impact on daily life activities, is another possible explanation.[23]

In investigation by Ashmawi et al.,[24] 104 patients (36.2%) had nocturnal seizure. Within 9 months, 25% of patients had started a sustained remission. Sustained remission was affected by many factors

Citation: Castellano SYC, Baños LP. Prognostic factors for the development of drug-resistant epilepsy. *MOJ Curr Res & Rev.* 2018;1(4):164–168. DOI: 10.15406/mojcrr.2018.01.00026

but only poor treatment response and presence of nocturnal seizures were independent predictors of lower chance of sustained remission.[24] This association between etiology and poor prognosis is clear in relation to the crisis secondary to neurological deficits presumably present at birth but it is not both when other causes of symptomatic ES are considered. Studies that include children and adults found a worse prognosis in patients with neurological abnormalities present at birth but not in patients with acquired brain damage later. In contrast, all the studies that refer to childhood epilepsy (in which as mentioned, many of the symptomatic cases suffer neurological deficits presumably present at birth) find association between the symptomatic etiology and a worse prognosis.[25] Demographic studies show that acquire causes or symptomatic (cerebrovascular disease, neoplasia or vascular malformations) involve to a better prognosis than genetic or congenital causes like cortical dysplasia, mesial-temporal sclerosis or dual pathology.[26]

Nonetheless at investigations of Martínez et al.,[16] obtained an elevated drug resistance in patient with suffer of indeterminate generalized epilepsy (32%). Cryptogenic and symptomatic epilepsy present major resistance than idiopathic. Also a bad prognostic in control of secondary epilepsy to hypoxia, cranial trauma, cerebrovascular disease and dysplasia were found. According to Ashmawi et al.,[24] in a retrospective cohort study from an epilepsy center in Greater Cairo, the presence of a structural lesion and other markers of disease severity, which were found by univariate analysis to be associated with a reduced chance of remission. In Scotland, in a prospective study, Brodie MJ et al.,[27] shown the prognosis was marginally better in patients with genetic epilepsy (n=222, 66% seizure free) than indeterminate (n=314, 57% seizure free) or structural (n=244, 56% seizure free). Outcomes in the 558 patients with newly diagnosed focal epilepsies varied according to the underlying pathology. Many patients in each category, including some with mesial temporal lobe epilepsy, had no further seizures after starting AED therapy. Patients with post-traumatic epilepsy had the worst outcomes (35% seizure free), while those with underlying cerebral atrophy (71% seizure free) or cerebrovascular disease (70% seizure free) did best. Remission rates in patients with cortical dysplasia (60%), hippocampus atrophy (50%) and primary brain tumors (52%) appeared little different from those with other focal epilepsies.[27] Although, symptomatic etiology was indicated to be an independent predictor of remission in other studies, no adequate evidence was shown in study realized by Jiang et al to confirm it. It maybe because that the etiology of the common epilepsy usually is a biological combination genetic with acquired factors.[28]

Psychiatric comorbidities

Psychiatric diseases are often associate with epilepsy in comparison with general population with a prevalence of 35% to 50% been depression and anxiety the most frequent.[29] The relation between this disease is complicated and bidirectional. This comorbidities has been associated with endurance reduction to the AED, which could interfere in the treatment adhesion and increase the risk of epileptic seizure. Has been identify a relation between the diagnosis of depression before the beginning of the disease and a high risk of DRE.[4] The drug resistant epilepsy was found in a 30% of patient with previous psychiatric disease.[16] Previous studies already evidence a causal association between the psychiatric diseases, the suicidal attempt and epilepsy. Also, has been indicated the bidirectional relation between epilepsy and psychiatric disease. Specifically, the frequency of depression was approximately in 20 % in the patients with epilepsy and it is a condition not diagnosed in neurological reference centers, as well as one of the more direct indicators of poor quality of life, in addition to that it is a possible predictor of drug resistance.[30] In a cohort investigation develop in 2007 with 780 patient by Hitiris et al.,[31] demonstrated interrelation between psychiatric comorbidities and therapeutic failed with AED, and they indicated like an alternative that the neurobiological process implicated on depression, anxiety and psychosis could interfere in the process of epileptic seizures due an increasing cerebral dysfunction and the probability of suffer an DRE.[31] The most interesting of this investigation was the observation that studies the presence of psychiatric comorbidities increasing the likelihood of subsequent refractoriness of the epilepsy (odds ratio 2.17, 95% confidence intervals 1.33–3.55; p=0.002). The previous shows the need a multidisciplinary approach to epileptic patient where psychiatric and neurological evaluations are capable to determinate psychiatric disease associated.

Seizure before treatment and treatment response

A follow-up of 321 patients with refractory epilepsy for 20 years by Hitiris et al.,[31] showed that the number of seizures prior to the treatment of epilepsy (more than 10) was associated with a twice-increased risk of developing drug resistance.[32] A higher pre-treatment seizure frequency, is here a predictor of remission when not adjusting for treatment response, has been repeatedly associated with a more severe outcome and a lower chance of remission and can be again explained by the intrinsic severity of the disease. A focused approach to patients with newly diagnosed epilepsy was developed in Glasgow, Scotland by Brodie MJ.[7] From the outset patient data were collected prospectively since 1982 and a series of 4 analyses have been undertaken over the intervening years, with results from the latest still being written for publication. The first set of analysis was undertaken in 1999 focusing on 470 previously untreated patients with newly diagnosed epilepsy (median age 29 years, range 9–93 years). There was a significant linear trend in the proportion of patients with uncontrolled epilepsy relative to an increasing number of pretreatment seizures ($p<0.001$). The second set of analysis involving 780 patients was undertaken in 2003. This relationship was also observed with seizure frecuency 6 and 12 months before the diagnosis of epilepsy was made and treatment started. Interestingly, total seizure numbers prior to treatment initiation did not predict outcome.[27] Jong-li et al.[28] in a study with the purpose to explore predictors for short- and long-term prognosis of newly diagnosed epilepsy indicated that the chance of attaining 2-year and 5-year remission significantly decreased as the number of seizures in the first year after AED start and the time interval between index seizure and AED start increased.

Multivariate analysis confirmed the overall influence of the number of seizures in the first year after AED start on both short and long-term outcomes of newly diagnosed epilepsy. The time interval between index seizure and AED start>12 months is independently associated with only short-term outcome (OR=1.9, p=0.03), and as it lasted up to more than 60 months, the likelihood of unfavorable outcome got even greater (OR=2.8, p=0.02). However, to be noted, the study did not indicate that the time interval between index seizure and AED start will eventually influence the long-term outcome. In conclusion the time interval between index seizure and AED start was indicated to be the independent risk factor only for the short-term outcome, but it did not play a role in the long-term outcome, like which is also shown in prior studies.[28] This finding suggested that the time interval between

Citation: Castellano SYC, Baños LP. Prognostic factors for the development of drug-resistant epilepsy. *MOJ Curr Res & Rev.* 2018;1(4):164–168. DOI: 10.15406/mojcrr.2018.01.00026

index seizure and AED start might not be associated with the intrinsic nature of drug-resistant epilepsy. Besides, the time interval between index seizure and AED start in this study is quite long (median, 26.4 months; IQR, 3–15), partially due to the extensive presence of treatment gap in low-income countries.[33] As for the seizure frequency in the first year after AED start, the study identified its prominent role in both short and long-term outcomes. Patients with 2 seizures in the first year after AED start are significantly more likely to fail terminal remission (5- year).

What's more, as the number of seizures in the first year after AED start climbed up to 5, the possibility for unfavorable long-term outcome rose as well, this suggests that it's imperative to initiate adequate, tolerated and appropriately chosen AED schedules after the definitive diagnosis of epilepsy. Further auxiliary examinations, cautious reevaluation and differentiation are justified to guide more tailored therapy for patients with poor seizure control.[28] In general, when an antiepileptic treatment is started that is independent of the type of seizure, the possibility of being free of convulsions during the first year is around 60-70%. In the case of not obtaining total control of the disease, the addition of a new drug increases a 10% more probability of reaching a crisis-free state. If in spite of this the patient persists with epileptic seizures the percentage of improvement that adds the use of a third anticonvulsant does not go beyond 5%. This has allowed us to conclude that one of the predictive factors for developing refractory epilepsy is the inadequate initial response to drugs as well as the frequency of seizures before treatment. According to Ashmawia et al.,[16] remission was affected by neurological examination, MRI/CT findings, etiology, pre-treatment seizure frequency, number of drugs taken, and response to the first AED but multivariate analysis confirmed only treatment response as an independent predictor of remission. Compared to patients successfully treated, those with poor response to the first drug had an adjHR (adjusted hazards ratio) of 0.14 (95% CI 0.08–0.24). When response to the first AED was removed from the model, pre-treatment seizure frequency attained significance. Compared to patients diagnosed at the time of the first seizure, the adjHR was 0.91 (95% CI 0.60–1.37) in those seen after 2–5 seizures, and 0.64 (95% CI 0.43–0.96) in those seen after 6+ seizures. Treatment response can be considered a marker of a low disease severity rather than the effect of a timely therapeutic intervention, as the effects of treatment are independent from the number of seizures experienced prior to treatment start.[24]

Oxidative stress

Inflammation, in turn, appears to play a central role among the various mechanisms that have been connected to epileptogenic process.[34] For example, proinflammatory molecules, reactive astrocytosis, activated microglia, and other indicators of inflammation have been found in the hippocampus of patients with TLE, in and around epileptic tubers in patients with tuberous sclerosis, and in some epileptic cases with cortical dysplastic lesions.[35]

Recently, accumulating evidence supports the association between OS and seizures, in the process of their generation, and in the mechanisms associated with its refractoriness to drug therapy. Alterations in the antioxidant enzymes[36] and increases in the indicators of oxidative damage to biomolecules, such as malondialdehyde (MDA), protein carbonyls and 8-hydroxy-2-deoxyguanosine and activation of the nicotinamide adenine dinucleotide phosphate Oxidase have been reported.[37] Clinical and preclinical data support the participation of OS and mitochondrial dysfunction in the epileptic process, suggesting that specific inflammatory pathways are chronically activated in the epileptogenic brain tissue. These results highlight the need for research that enables us to understand the role of the OS in the pathogenesis of drug-resistant epilepsy and particularly, to clarify the relationship between OS, inflammation and immunological deficit as physiopathological mechanism in TLE. OS and mitochondrial dysfunction occur as a consequence of prolonged epileptic seizures and influence seizure-induced brain injury. Conversely, OS can render the brain more susceptible to epileptic seizures. Therefore, OS and mitochondrial dysfunction may be both an important cause and a consequence of prolonged seizures. An Insight into the mechanisms by which seizures initiate OS and mitochondrial dysfunction and vice versa may provide novel therapeutic approaches for the treatment of epilepsies. Further investigations into the role of inflammation and the immune response in CNS, particularly in drug-resistant epilepsy may add important insights in the understanding of the epileptogenic mechanism and open new ways of neuromodulatory treatment of epilepsy.[38]

Other factors

In several descriptive investigations, several factors related to resistance to antiepileptic drugs have been identified. In children (prospective study):[39] age younger than one year, symptomatic epilepsy, mental retardation or overall developmental delay, pathological neuroimaging study, or a high seizure frequency prior to being diagnosed with drug-resistant epilepsy (level of evidence [LE] II). In adolescents:[8] focal epilepsy, mental retardation or psychiatric disturbances (LE II). In adults (prospective study):[39] symptomatic focal epilepsy, initial consciousness impairment during seizures, multiple seizure types, tonic-akinetic seizures, or anomalies on the electroencephalogram (EEG) (LE IV). But by analyzing many of these factors independently, a strong association has not been demonstrated and the levels of evidence are unreliable. To demonstrate the association between the factors mentioned above, it is necessary to carry out many future investigations that analyze each factor independently, in populations with diverse demographic characteristics, for long periods of time.

Conclusion

All the information mentioned previously shows that drug-resistant epilepsy is a frequent, expensive and disabling condition. Although multiple predictors of drug resistance have been designed. It is necessary to highlight the etiology of epilepsy, the number of seizures before starting treatment with ADE, as well as the responses to drugs after starting treatment as the main factors that influence the development of drug-resistant epilepsy. Future studies should aim to document modifiable risk factors and biological markers that allow an early identification of patients at high risk of developing this condition, and positively impact the neurobiological course of the disease.

Acknowledgements

None.

Conflict of interest

The author declares that there is no conflict of interest.

Citation: Castellano SYC, Baños LP. Prognostic factors for the development of drug-resistant epilepsy. *MOJ Curr Res & Rev.* 2018;1(4):164–168. DOI: 10.15406/mojcrr.2018.01.00026

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Citation: Castellano SYC, Baños LP. Prognostic factors for the development of drug-resistant epilepsy. *MOJ Curr Res & Rev.* 2018;1(4):164–168. DOI: 10.15406/mojcrr.2018.01.00026