Research Article

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Early Predictors of Refractory Epilepsy in Oran, Algeria: A Case-Control Study

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Abstract

Purpose: The goal of this retrospective study is to identify early predictors of intractable epilepsy.

Methods: This case-control study conducted from January 2007 to December 2012 included 106 patients with drug-resistant epilepsy and 212 controls with well-controlled epilepsy.Univariate and multivariate analysis of predictive factors of refractoriness were performed using logistic regression.

Results: In the final model, four factors significantly associated with intractable epilepsy were identified: aetiology ($p = 0.001$), high initial seizure frequency ($p < 10^{-4}$), status epilepticus ($p = 0.002$), and initial myoclonic seizures ($p < 10^{-4}$).

Conclusion: Our findings suggest that the risk of developing drug resistant epilepsy could be predicted at an early stage of the disease by some clinical features. This could help the clinicians to make the best therapy decisions and improve patient's quality of life.

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Introduction

Epilepsy is a common neurological disease characterized by recurrent and unprovoked seizures. According to data from WHO, there is more than 50 million people with epilepsy worldwide[1]. In 2/3 of cases, seizures can be well controlled by antiepileptic drugs (AEDs), but in the remaining third, seizures still un-controlled[2,3]. Patients in this latter group are defined as having intractable epilepsy and are at increased risk of injury and death due to poorly controlled seizures. They also are subject to multiple trials of AEDs, often at high doses that result in adverse effects. Furthermore, they have higher rates of cognitive, physical and psychiatric comorbidities; tend to be socially isolated; face social stigma; and have poorer quality of life than those with non-intractable epilepsy[4,5]. Early identification of drug resistant epilepsy (DRE) is essential to avoid further futile therapies that could be harmful, to optimize long-term outcomes, and to decrease the burden of care.

Although several studies have investigated the predictors of medical intractability, the results were highly variable. Differences in sampling methods, inclusion criteria and particularly in DRE definitions might explain the discrepant results[6-10].
In Algeria, the magnitude of drug resistant epilepsy (DRE) is unknown. Indeed, very few epidemiological studies on epilepsy have been published[11] and there is no data available on predictors of refractory epilepsy. Early identification of these patients would be essential in a developing country such as Algeria, where neurologists are facing challenges in both medical and surgical management of DRE.

Materials and Methods

This retrospective case–control study was carried-out at the Department of Neurology in Oran, Algeria from January 2007 to December 2012, in consecutive age matched patients who attended our epilepsy unit. The study included patients from 3 to 75 years of age. All were diagnosed with epilepsy by the same epileptologist (AC).
We excluded patients whose seizures were uncontrolled due to poor treatment adherence or subtherapeutic serum drug levels.
Cases with intractable epilepsy were consecutively recruited. Controls consisted of consecutive age matched patients

attending our epilepsy unit, who had no seizures during the last six months. Both cases and controls were evaluated regularly every three months.

Definitions

Epilepsy was defined as a predisposition to unprovoked seizures. For each patient, epileptic syndrome and seizures were defined according to the International League against Epilepsy (ILAE) Commission on Classification and Terminology 2005–2009 Report[12].

DRE was defined as the failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug (AED) schedules (whether as mono-therapies or in combination) to achieve sustained seizure freedom[13]. An AED trial was considered a failure if seizures persisted at the maximally tolerated dose. We defined controlled epilepsy as the absence of seizures for at least six months.

Status epilepticus was defined according to ILAE as any seizure lasting at least 30 minutes or repeated seizures over a period of 30 minutes or more, without recovery of consciousness[14]. A family history of epilepsy was defined as unprovoked seizures occurring in first-degree relatives. Neurodevelopmental delay was diagnosed based on clinical assessment completed by a neuropsychological evaluation. Neuroimaging was classified as normal or abnormal.

Data collection

Both of the epileptic groups were questioned on their medical history, and the clinical features of seizures were noted. These included: gender, perinatal history, history of febrile/neonatal seizures, age at onset of seizures, initial seizure type, and initial seizure frequency before treatment, outcome of the first AED trial, history of inaugural status epilepticus, neuro developmental status, severe head trauma and family history of seizure disorders. According to patient's history, clinical features, electroencephalography (EEG) records and brain imaging findings, the aetiology was classified as genetic, structural/metabolic, or unknown. The appropriate antiepileptic drug was prescribed taking into account seizures type, side effects, and interaction profiles of the available drugs.

All patients enrolled in this study provided their written informed consent.

Statistical analysis

Demographic details, clinical characteristics and other relevant data were analysed using statistical package SPSS (version 21.0 for Mac OS X). The association of each factor to the dependent variable was calculated from 2×2 tables, using a X^2 test of association, and a p-value of < 0.05 was considered significant. A univariate comparison between controls and cases was done for each potential predictor to calculate Odds Ratio (OR) and 95% Confidence Interval (CI). Finally, variables significant at the 5% nominal level were considered for multivariate analysis by logistic regression stepwise.

Results

Patient profiles

A total of 303 individuals including 106 cases (with DRE epilepsy) and 212 controls (with well controlled epilepsy) participated in the study. The mean age was $33,8 \pm 14$ years, ranging from 3 to 75 years. In both case and control patients, there was a slight male predominance.

Clinical features

A comparison between cases and controls regarding clinical characteristics revealed several statistically significant differences (Table 1). Most controls (90.1%) began their seizures after age two years, while 21% of cases had a seizure onset before the age of two years. Generalized seizures were more frequent in controls than in cases ($p < 10^{-4}$). Epileptic syndromes were classified as structural/metabolic in more than third of cases, whereas in controls, there was a clear predominance of genetic epilepsies. 85% of controls were on monotherapy and around 90% of cases were on more than one AED.

Table 1: Comparison of clinical features between cases and controls.

Clinical features	Cases (n = 106)	Controls (n = 212)	P-Value
Age at onset			
< 2 years	24 (20.8%)	21 (9.9%)	0.008
> 2 years	84 (79.2%)	191(90.1%)	
Gender			
Male	61(57.5%)	111(52.4%)	0.380
Female	45(42.5%)	101(47.6%)	
Initial seizure type			
Generalized	42(42.9%)	145(70%)	0.000
Focal	49(50%)	60(29%)	
Generalized and focal	7(7.1%)	2(1%)	
Aetiology			
Genetic	34(32.1%)	97(45.8%)	0.000
Structural/ Metabolic	40(37.7%)	46(21.7%)	
Unknown	32(30.2%)	69(32.5%)	
Current number of antiepileptic drug			
0	0(0%)	9(4.2%)	0.000
Monotherapy	12(11.3%)	179(84.4%)	
Bitherapy	79(74.5%)	24(11.3%)	
polytherapy	15(14.2%)	0(0%)	
Current seizure frequency			
1- 4/month	43(40.6%)		
1- 6/week	49(46.2%)		
>1/ day	14(13.2%)		

Univariate analysis

In univariate analysis, age at onset, initial myoclonic seizures, seizure frequency before treatment, aetiology, history of neonatal seizures, history of status epilepticus, neuro-developmental delay and neurological abnormalities, were found to be significantly associated with DRE (Table 2). Those factors were entered into multiple logistic regression models, with probability for entry of the variables fixed at 0.05 and that for removal at 0.10.

Table 2: Univariate analysis

Variables with p <20%	OR	CI95%	P-Value
Gender			
Female	1	-	NS
Male	0.81	[0.51-1.30]	
Age at onset			
> 2 years	1	-	0.009
< 2 years	2,38	[1.24-4.57]	
Seizure frequency before treatment			
<1/month	1	-	0.000
>1/month	2.73	[1.83-3.63]	
Initial myoclonic seizures			
No	1	-	0.000
Yes	3.78	[1.81-7.90]	
Aetiology			
Genetic	1	-	0.017
Unknown	1.36	[0.76-2.45]	
Structural/Metabolic	2.29	[1.29-4.05]	
Initial status epilepticus			
No	1	-	0.000
Yes	5.42	[2.61-11.26]	
Family history of epilepsy			
No	1	-	NS
Yes	1,02	[0.58-1.80]	
History of febrile seizures			
No	1	-	NS
Yes	1.91	[0.99-3.66]	
Neonatal seizures			
No	1	-	0.048
Yes	5.30	[1.01-9.59]	
Neurologic impairment			
No	1	-	0.000
Yes	4.99	[2.25-11.05]	
Neurodevelopmental delay			
No	1	-	0.004
Yes	2.66	[1.37-5.17]	
Failure of first AED			
No	1	-	0.000
Yes	21.89	[11.99-39.97]	

Multiple regression analysis

As failure of adequate AED trials is incorporated in the definition of intractability, this variable is inextricably linked to intractable epilepsy and can no longer be considered as a prognostic factor. Furthermore, we found multi-collinearity between several variables such as aetiology, focal seizures, neurologic impairment and brain imaging abnormalities; so we decided not to enter the last three variables in the initial model. We also examined interactions between variables, such as age at onset and aetiology.

In the final multivariate model by stepwise logistic regression, high initial seizure frequency ($p < 10^{-4}$), initial myoclonic seizures ($p < 10^{-4}$), a previous history of status epilepticus ($p = 0.002$), and aetiology ($p = 0.001$) emerged as strong

independent prognostic factors of intractability in patients with epilepsy (Table 3).

Table 3: Multivariate analysis

Variables with p < 5%	OR a	CI 95%	P-Value
Initial seizure frequency			
< 1/month	1	-	0.000
> 1 /month	2.58	[1.68-3.48]	
Initial status epilepticus			
No	1	-	0.002
Yes	3.94	[1.66-9.36]	
Aetiology			
Genetic	1	-	0.001
Unknown	2.91	[1.38-6.16]	
Structural/Metabolic	3.75	[1.80-7.85]	
Initial myoclonic seizures			
No	1	-	0.000
Yes	8.33	[3.27-21.21]	

Discussion

Determining the prognosis of patients with epilepsy is a challenging task. The risk assessment of a patient can be useful in adapting the therapeutic strategy.

Refractory patients have a higher risk of premature death, trauma, psychosocial difficulties, and reduced quality of life[15]. These patients are generally treated with multiple AEDs, which in combination can lead to cognitive and behavioural disorders. Knowledge of prognostic factors at an early therapeutic stage of epilepsy could facilitate patient management.

Previous studies have reported a slight predominance of epilepsy in males than in females[16]. The exact cause of this male predominance is not known. However, gender was not a predictor of drug resistance in the present study. This result is in agreement with the findings of Kwan and Brodie[17].

The first factor strongly correlated in the literature with the risk of developing refractoriness is the aetiology of epilepsy. Our study showed that the aetiology of epilepsy is an important predictor of treatment response. This is in agreement with findings by Berg et al who reported intractable seizures in 34.6% of children with symptomatic/cryptogenic and 2.7% with idiopathic generalized childhood epilepsy. In their prospective evaluation of 613 patients, a symptomatic aetiology was significantly frequent in the group with DRE[18]. Furthermore, several large cohort studies have been performed on the prediction of seizure remission, among which the UK National General Practice Study of Epilepsy[19] and the Dutch Study of Epilepsy in Childhood[20]. These identified prognostic factors such as idiopathic aetiology, related to long lasting seizure remission as the opposite of intractability. In a previous report aiming to document the clinical characteristics and inheritance pattern of genetic epilepsy in Algerian families, seizure control was achieved in 21 patients (52.5%) using mono or polytherapy. Twenty-eight (70%) were seizure-free for 3 months and two (5%) have been weaned for 10 years[21]. These results might suggest that genetic aetiology is predictive of better seizure control.

In the present study, the high seizures frequency before initiation of the first AED was shown to be a predictive factor

of refractory epilepsy. This is in line with the results of Chawla et al. Who observed that 76% of cases vs 22% of controls had one or more seizures per day (P < 0.001)[22]. In the sample of Tae-sung and Holmes, daily seizures were reported in 50.7% of cases and 25.6% of controls (p < 0.001)[23]. In their multivariate analysis, Huang et al. reported a high risk of refractoriness (OR: 6.54, CI: 3.13–13.7) in patients who have experienced more than ten seizures before treatment[24]. The high initial seizure frequency could cause brain injuries leading to intractability.

Previous studies have shown that myoclonic seizures were predictive of drug resistance[22,25] while others have found no relationship between DRE and seizure type[26]. In our study, initial myoclonic seizures were significantly associated with intractability ($p < 10^{-4}$). Indeed, most epilepsies with myoclonic seizures such as juvenile myoclonic epilepsy, progressive myoclonic epilepsy and severe myoclonic epilepsy in infancy are drug-resistant or drug dependent.

Initial status epilepticus was an important factor for predicting development of DRE, which was in agreement with several studies[23,27]. However, some studies did not confirm this association[28]. Nevertheless, we cannot conclude whether status epilepticus history is a predictor of drug resistance or the consequence of poor seizure control. Further prospective studies may provide answers to this question.

A significant proportion of available studies observed a higher risk of DRE in patients whose disease has appeared at a young age[18,29,30]. In our study, this association was observed in univariate analysis, however, without statistical significance in multivariate analysis.

History of neonatal seizures was also correlated with DRE but only in univariable analysis[6,8,22,31]. Similarly, in our sample, we observed a significant tendency towards a higher risk of refractory epilepsy in this situation, but the association was not significant in multivariable analysis.

Developmental delay was observed in 20.8% of cases vs. 9% of controls, but significant association was obtained only in univariate analysis. This is in line with results of several studies[3,9,22].

We have not found any predictive value for family history of epilepsy in first-degree relatives. Studies aiming to assess the association between family history and intractability failed to reach statistical significance of this association[3].

This could be explained by the fact that genetic epilepsies are probably of better prognosis than symptomatic epilepsies.

The incidence of febrile seizures (FS) in the general population is 3 to 4%. In our study, FS were found in 19% of cases vs. 10% of controls. Despite this result, FS were not predictive of unfavourable outcome.Some authors have even concluded that the history of FS was a protective factor against intractability[18].

The present study has several limitations: it was conducted in an epilepsy unit, where patients with refractory epilepsy are often referred for reassessment, so the study population was not representative of the population concerned. In addition, although we collected data prospectively, the study could be subject to recall bias. We believe that additional prospective population-based studies, considering also new predictors such as pharmacological, genetic, neurobiological, and immunological factors, are warranted. Such studies could facilitate patient management and stimulate the development of more effective therapeutic strategies, reducing the medico-social and economic burden of intractable epilepsy.

In conclusion, our findings suggest that some clinical features can predict intractability in patients with epilepsy. Early identification of these patients allows their transfer to specialized centres where a neurosurgical treatment should be considered.

Conflicts of interest
The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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