Factors associated with seizure remission in intractable epilepsy
Les facteurs associés à la rémission des crises dans l'épilepsie réfractaire

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Abstract

Introduction: Patients with intractable epilepsy show variable course of the disease. They may show remissions followed by relapses. Little is known about factors associated with remissions in patients with intractable epilepsy

Participants and methods: This is a retrospective study of 200 patients diagnosed with intractable epilepsy who entered into a remission. We probed their clinical, electrophysiological and neuroimaging data. The cohort was followed for two outcomes, 1-complete seizure remission for ↗ 12 months and 2, age at which the patient entered into remission. The study outcomes were estimated using Kaplan-Meier analysis.

Results: female gender, mental subnormality, early onset seizure, localization related epilepsies (especially temporal lobe epilepsy), presence of abnormal neurological examination and high seizure frequency were associated with older age and shorter duration of remission respectively.

Conclusion: remissions during the course of intractable epilepsy can happen. Factors such as gender, onset of seizure and associated brain lesions could predict the occurrence of these remissions.

Key words: Intractable epilepsy- Remission-Gender-Onset.

Résumé

Introduction: Les patients atteints d'épilepsie réfractaire montrent des évolutions variables de la maladie. Ils peuvent présenter des rémissions suivies de rechutes. On connaît peu les facteurs associés aux rémissions chez les patients atteints d'épilepsie réfractaire.

Participants et méthodes: Il s'agit d'une étude rétrospective portant sur 200 patients ayant une épilepsie réfractaire avec rémission. Nous avons colligé leurs données cliniques, électrophysiologiques et de la neuro-imagerie. La cohorte a été suivie de deux résultats, remises de saisie 1 -complet pour ↗ 12 mois et 2 ans au cours de laquelle le patient est en rémission. Les résultats de l'étude ont été estimés en utilisant une analyse de Kaplan- Meier.

Résultats: le sexe féminin, détérioration intellectuelle, épilepsies liées à la localisation (épilepsie du lobe temporal notamment), examen neurologique anormal et nombre important de crises épileptiques ont été associés à un âge avancé et à une durée plus courte de la rémission respectivement.

Conclusion : La rémission au cours de l'épilepsie réfractaire peut se produire. Des facteurs tels que le sexe, l'apparition de la crise épileptique et des lésions cérébrales associées pourraient prédire la survenue de ces rémissions.

Mots clés: Epilepsie réfractaire – Rémission- Genre- Début.

Introduction

Up to two-third of people with epilepsy achieve long-term seizure freedom or terminal remission and the majority do so early in the course of the condition [1]. Seizures continue in up to one third of people with epilepsy despite appropriate treatment. It has also been suggested that in minority of people the course of epilepsy may alternate between periods of relapse and remission [2]. Among patients who fail to respond to the first AED only 11% subsequently became seizure free [3]. These results have implied that once a patient is identified as refractory, the likelihood of eventual seizure freedom is small. However, seizure remission in medically intractable epilepsy is a frequently seen condition. Until recently, there have been limited data regarding seizure prognosis in adults with medically treated intractable epilepsy. Several studies have provided data on the probability of attaining seizure freedom among this seriously affected group [4-5-6]. Prognostic information about who will develop pharmcoresistance is quite limited. In adult-onset epilepsy, there are no adequate studies based on well-defined cohorts and utilizing a meaningful definition of pharmacoresistance [7]. Little is written about the occurrence of remission and relapses during the course of intractable epilepsy. Here we report our analysis of a cohort of patients with intractable epilepsy who entered in a remission for at least 6 months.

Participants and methods

This is a retrospective study where we reviewed the clinical data of patients diagnosed with intractable epilepsy who entered in a remission of seizure frequency during their course of the disease. The time scale for patients was from 2000 till 2010. Mean follow up period was 8.57 years. The diagnosis of intractability were based on The new International League Against Epilepsy (ILAE) consensus definition of drug resistant epilepsy that requires "failure of two tolerated, appropriately chosen and used antiepileptic drug schedules to achieve sustained seizure freedom" (i.e., either 12 months or three times the longest interseizure interval) [8]. Remission was defined as being free of any

interval) [8]. Remission was defined as being free of any seizures by self-report for at least 6 months.

Two hundred patients with all seizure types and with different medical regimen were included. The clinical data we probed were age, age of onset, age at entering 1st remission, associated mental subnormality, gender, history of febrile seizures, family history of epilepsy, seizure type according to the 1981 seizure classification [9], epilepsy syndrome[according to the 1989 classification [10], seizure frequency in the past year, aetiology, history of status epilepticus (SE),the results of neurological examination (normal or abnormal), EEG findings done at first visit [normal EEG or abnormal EEG (focal ,multifocal or generalized epilpetiform discharges)] and the findings of neuroimaging [MRI brain]. Thorough analysis was done to exclude patients with false refractoriness due to non epileptic seizures, inadequate treatment and non compliance.

The cohort was followed for two outcomes 1-complete seizure remission for ↗ 12 months and age at which the patient entered into remission. The study outcomes were estimated using Kaplan-Meier analysis.

Statistical analysis: parametric, non parametric and correlation tests were used to analyze the data. All tests have been performed using SPSS11.

Results

Two hundred patients [96 males and 104 females] fulfilling the criteria of intractability who also entered in a remission of seizure frequency for at least 6 months were enrolled in the study. Table I shows demographic data of the 200 patients included in the study.

Table I: shows demographic data of the 200 patients included in the study.

Factor	Range	[Mean [SD
Age in years	20.42	12.238
Age of onset of epilepsy	12.62	10.87
Age at 1st remission	24.10	12.094
Duration between onset and remission	11.26	6.247

Twenty percent of the remissions occurred within the first years after diagnosis. One hundred seventy patients had localization related epilepsies while the remaining thirty had generalized epilepsies. Table II shows description of the clinical and neuroimaging findings in the cohort.

Table II: Description of the clinical and neuroimaging findings in this study.

	Number of the patients (%)
Family history of epilepsy	14 patients (7%)
History of febrile seizure	24 patients (12%)
Presence of mental subnormality*	29 patients (14.5%)
Presence of hemiplegic cerebral palsy	32 patients (16%)
Abnormal MRI findings	
mesial temporal sclerosis	28 patients (14%)
encehalomalacia	22 patients (11%)
cortical dysplasia	10 patients (5%)

low IQ, delayed mental developmental milestones or poor scholastic achievement.

We used both the duration of remission and the age at which remission occurred as an indicator of remission susceptibility to define the relation between different factors and remission susceptibility.

One hundred thirty six [68 %] patients entered in remission for less than 1 year while 64 patients [32 %] entered in remission for more than 1 year .Male patients entered in remission at a statistically significant younger age. Normal mental developmental milestones were associated with younger age at remission. Patients with pediatric onset epilepsy [younger than 10 years] have entered remission in older age. The group of patients with localization related epilepsies entered in remission at the same age as patients with generalized seizures yet they had a significantly shorter duration of remission.

The presence of motor deficit in epileptic patients was associated significantly with later onset of remission. The presence of this deficit did not affect the longevity of the remission duration. Patients with average more than 5 seizures per month had a statistically significant shorter duration of remission. Patients with mesial temporal sclerosis had the shortest duration of remission. The presence of family history of epilepsy or past history of febrile seizures did not influence the age at remission. The longevity of duration from onset did not affect remission duration or age at remission. The presence of EEG abnormality in epileptic patients did not affect remission duration or age at remission.

Discussion

Although about one third of epileptic patients are labeled as having intractable epilepsy many people enter remission after several years of continuous seizure activity and after trials of more than two drugs [11-12]. Research on prognosis has largely focused on early predictors of subsequent intractability and identified factors have included: failure to respond to the first two appropriate AEDs tried [3], high seizure density prior to commencing treatments [13], epilepsy syndrome and seizure type and aetiology [14].

In this study we analyzed the clinical, electroencephalographic and radiological data of a cohort of patients with intractable epilepsy who entered in a remission for at least 6 months among a cohort of patients with intractable epilepsy. We found that female gender, mental subnormality, early onset seizure, localization related epilepsies (especially temporal lobe epilepsy), presence of abnormal neurological examination and high seizure frequency were associated with older age or shorter duration of remission.

Structural brain pathology may appear as neurodeficits (cerebral palsy or mental retardation/learning disability) or MRI lesions and can predispose patients to early onset of epi¬lepsy. In this study, patients with evidence of structural brain pathology were associated with older age at remission. Berg in 2009 proposed that the effects of epileptic activity may be more severe and less reversible

when they disrupt neurodevelopmental processes during critical times in development. This also could be explained by the role of other brain areas in controlling seizure development [7].

Patients with neuroimaging findings were having shorter remission duration. Sillanpää in 1993 reported that an underly¬ing congenital cause or early childhood brain damage causing neurodeficits are a strong predictor for a poor long-term seizure outcome [15]. This finding does not coincide with those reported by Neligan et al. who found that neuroimaging findings did not influence the entrance in intermittent seizure pattern in their patients [16]. Low in 2007 demonstrated that early destructive lesions in the developing brain have poor correlation with clinical and eletrencephalographic outcome. However, there is a correlation between the frequency of epileptic discharges and the presence of atrophy [17].

The proportion of patients entering 5 years terminal remission was highly dependent on the length of time to first year remission after starting adequate treatment. Not entering remission within 5 years of starting treatment predicts failure to achieve long-term seizure freedom in the future for the vast majority of patients [18]. In our cohort of patients with intractable epilepsy the duration from onset did not affect remission duration or age at remission.

Temporal lobe epilepsy with mesial temporal sclerosis seems to be the most refractory to medical treatment. Different explanations have been proposed to explain this observation such as impairment of drug penetration into the brain by efflux transporters, role of initial precipitating injury, the loss of antiepileptic drug sensitivity at certain target sites in the brain and other theories [19]. In this study patients with partial epilepsies had shorter duration of remission compared to those with generalized epilepsy. Moreover those with mesial temporal sclerosis had the shortest remission.

Patients with pediatric onset epilepsy [younger than 10 years] have entered remission in older age. It is known that epileptic activities can disrupt neurodevelopmental processes leading to neuronal damage especially if happened during critical times of development as during childhood. This could explain why the pediatric onset of seizure was associated delayed age of remission.

In conclusion; female gender, mental subnormality, early onset seizure, localization related epilepsies (especially temporal lobe epilepsy with mesial temporal sclerosis), presence of abnormal neurological examination and high seizure frequency could predict less possibility of remission in patients with intractable epilepsy.

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