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Predictors of outcome in newly diagnosed epilepsy: Clinical, EEG and MRI

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Abstract

Many clinical features in epilepsy have been assessed for their association with long-term epilepsy outcome. These factors include gender, age of seizure onset, type and duration of epilepsy, IQ, neurological examination finding, seizure frequency, duration between epilepsy onset and treatment initiation, duration between treatment initiation and response, failure vs. response to the first antiepileptic drug (AED), and number of AED tried or needed for seizure control. The most consistent factor associated with long-term epilepsy outcome is the ease of controlling seizures. This factor could be in terms of how soon seizures are controlled by AED, how frequent seizures recur despite treatment initiation, or how many AED had to be used to control seizures. Other than the EEG patterns of catastrophic epilepsies, EEG findings in general have a limited role in predicting epilepsy treatment outcome.

Clinical predictors are presently needed to guide research studies for discovering reliable laboratory-based biomarkers. Moreover, currently known clinical, EEG and MRI predictors of epilepsy outcome should be used to counsel patients and their families about the prognosis and the appropriate treatment options of their epilepsy.

INTRODUCTION

We are at the beginning of an era of identifying chemical and genetic biomarkers that are relevant to seizure disorders. An example is the discovery that HLA-B*1502 allele confers high risk for carbamazepine induced Stevens-Johnson and toxic epidermal necrolysis syndromes in Han Chinese and many Southeast Asian populations.[1]

Studies have shown that two to four years following epilepsy diagnosis and treatment, approximately 75% achieve seizure control for at least one year.[2-4] Moreover, about 75% gain a five-year period of seizure remission during 20 years following diagnosis and treatment. Predictors of seizure or epilepsy remission are not necessarily the converse of predictors of intractable epilepsy. Moreover, the outcome of seizure or epilepsy remission could be separated into that seizure control while on antiepileptic drug therapy and that while off the therapy. Unfortunately, only a few studies in the literature specifically focused on epilepsy remission after antiepileptic drugs have been discontinued. This article concentrates on the clinical, EEG and MRI predictors of newly-diagnosed seizure disorder.

CLINICAL PREDICTIVE FACTORS

Many clinical features in epilepsy have been assessed for their association with long-term epilepsy outcome. These factors include gender, age of seizure onset, type and duration of epilepsy, IQ, neurological examination finding, seizure frequency, duration between epilepsy onset and treatment initiation, duration between treatment initiation and response, failure vs. response to the first antiepileptic drug (AED), and number of AED tried or needed for seizure control. The most consistent factor associated with long-term epilepsy outcome is the ease of controlling seizures. This factor could be in terms of how soon seizures are controlled by AED, how frequent seizures recur despite treatment initiation, or how many AED had to be used to control seizures. Of the patients who became seizure-free, majority (about 75%) became seizure free within the first year of AED treatment. Moreover, the number of seizures in the first 6 months following the presenting seizure (index seizure) is associated with long-term outcome. Seventy-five percent of those who had only the index seizure, and had no subsequent seizure, gained a period of at least five-year seizure freedom when followed long-term. The rate is progressively lower with greater number of seizures in the six-month period following the index seizure occurrence - about 60% for those with two seizures, approximately 50% for those with five seizures, and about 35%

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for those with 10 seizures.[5] Another study shows that the number of seizures in the three months before AED initiation is also associated with the rate of post-treatment seizure control.[6] About 70% of the patients who had only one seizure in the three-month pre-treatment period subsequently had no seizures; approximately 50% for those with 6 to 10 seizures; and only about 35% for those who had more than 20 seizures before treatment.

Surprisingly, the same study showed that the duration of epilepsy before AED treatment initiation is not predictive of long term seizure control. Seizure control was achieved in about 60% of all groups of patients: those with one to two years, those with three to five years, those with six to ten years, and those with more than ten years of epilepsy duration before treatment. The finding is supported by a study that demonstrated no difference in long-term outcome between patients who were immediately treated with AED after first seizure occurrence or recent epilepsy diagnosis and patients whose treatment was delayed.[7] Five years after eventual AED initiation, a minimum of two-year remission was achieved in 91% of patients immediately treated vs. 87% of patients whose treatment was delayed.

Another important predictor of seizure control or remission is the number of AED needed to control seizures soon after treatment initiation. It is well-known from the study of Kwan and Brodie that seizures could be controlled by the first AED used in 47% of the patients.[8] Only 13% of those who failed the first AED will have seizure control with the use of the second AED. The rate of seizure control is disappointingly at only 1% with the use of the third and the subsequent AEDs tried. Therefore, it can be suspected from these observations that whether or not a person's epilepsy will be controlled is dependent on biological factors inherent in the person, and that the outcome could be predicted in the first year or two following seizure onset or AED treatment. Indeed, rapid response to AED treatment, defined as 75% to 100% seizure reduction in the first three post-treatment months, is associated with 10 times greater chance of gaining five-year remission than the lack of rapid treatment response.[9] In childhood-onset epilepsy, the etiology of epilepsy is also associated with seizure-freedom while no longer taking AED. The long-term cumulative probability of experiencing five-year remission without AED is nearly 90% with idiopathic epilepsy, approximately 60% with cryptogenic epilepsy, and only about 25% with remote symptomatic epilepsy.

The importance of the predictive factors discussed above is emphasized by the finding in childhood-onset epilepsy that if no unfavorable factors are present, virtually all children will experience a prolonged period (at least five years) of seizure remission.[10] However, none will enter remission if all three of the following factors are present: high initial seizure frequency, poor short-term outcome, and remote symptomatic etiology. Also, review of the literature by Camfield and Camfield revealed the following Class I evidence of predictors of epilepsy remission: normal neurologic/intellectual abilities, seizure-onset age of <12 years, infrequent or easily controlled seizures.[11] The remission rate is 80% if all three factors are present, but only 20% if none is present.

More recently, Petrovski and colleagues identified three independent predictors of seizure control: lower score in the A-B Neuropsychological Assessment Scale, absence of MRI lesion, and genomic classifier.[12] The Scale is a 24-item questionnaire that inventoried for the burden of neuropsychiatric symptoms, including those of mood disorders. The finding raises the possibility that high score on the Scale is a reflection of underlying neurobiological and neurochemical dysfunctions that are co-morbid with severe epilepsy. It has been observed in other studies that a history of psychiatric disorder is associated with poor response to medical or surgical treatment of epilepsy.

EEG AND MRI FINDINGS AS POTENTIAL PREDICTIVE FACTORS

Only a few EEG findings have some predictive value. These are the EEG patterns that are observed with the catastrophic epilepsies, such as hypsarrhythmia, multifocal spikes and sharp waves with marked background slowing, and continuous spike and wave during slow wave sleep. Yet, the underlying etiology or syndrome may be an equally or more important determinant of epilepsy outcome.

As mentioned above, presence of MRI lesion is associated with greater likelihood of seizure recurrence following single seizure presentation or new-onset epilepsy. Interestingly, functional imaging using magnetic resonance spectroscopy (MRS) has also detected an abnormality associated with AED failure when no gross lesion could be detected by structural MRI imaging.[13] The N-acetyl aspartate/Creatine (NAA/Cr) is lower

in AED failure patients than in AED responders and normal subjects.

COMMENT

A few predictors of seizure remission is currently known, foremost of which is the ease with which seizures can initially controlled, idiopathic etiology of the seizure disorder, and normal neurological or intellectual status. These predictive factors have been consistently observed across studies, especially of childhood-onset epilepsy. Further application of diagnostic technology to the prognostic assessment of seizure disorders is likely to yield additional prognostic information. Transcranial magnetic stimulation of the brain has shown that response to AED treatment is associated with increase in motor threshold of the stimulation, whereas there is no change in the threshold when AED failed.[14]

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