Early Identification of Refractory Epilepsy

NEJM 2000 February 3; 342: 314 – 319

At the time of this trial, up to 30% of patients with epilepsy failed to enter remission despite appropriate anti-epileptic drug (AED) therapy, and such patients, understandably, had a significantly reduced quality of life. Unfavorable prognostic factors for refractory epilepsy had been identified (i.e., early-onset epilepsy, symptomatic or cryptogenic epilepsy, several seizure types, etc.), though the overarching goal of this study was to further identify any additional factors that were associated with a poor response to AED therapy and that could be used to identify patients at risk for refractory epilepsy.

Experimental design and statistics: This study was a prospective observational trial conducted at an epilepsy unit in Scotland (1984 – 1997), which evaluated consecutive, unselected children, adolescents, and adults diagnosed with epilepsy and started on AED therapy (and without a prior h/o AED use). On initial visits, general history in terms of each patient's epilepsy history was obtained; on subsequent visits, EEG monitoring and MRI brain imaging were performed to help aid in the epilepsy diagnosis and classification when appropriate. Seizure and epilepsy types were classified according to the ILAE criteria[1]. For patients diagnosed with epilepsy, appropriate AED therapy was started based on each patient's seizure and epilepsy type and taking into consideration drug ASE profiles. After initial visits, follow up visits occurred q4-6wks for the first 6 months, then q4 months after, during which AED response and compliance were recorded (median f/u of 5yrs).[2] Patients were treated with a single AED where possible, and one AED was changed to another if patients continued to have seizures or if they had intolerable ASEs with the first drug. A combination of AEDs was used in patients who continued to have poor seizure control despite trials of 2 or 3 AEDs. If appropriate, patients could be referred for surgery. Seizure freedom was defined as no seizures for a minimum of 1yr while on the same dose of an AED, or while off AED therapy. If patients continued to have seizures, they were considered as refractory. From the data set, two groups of patients were identified: those with and those without seizure freedom during follow up. Statistically, Chi-square tests and Mann-Whitney tests were used to compare different prognostic variables between the 2 groups.

Results: A total of 525 patients referred to the treatment clinic eventually constituted the study group; a total of 470 from this group had never received an AED in their past. Sex, age, age at referral, % with a FMH of epilepsy, and % with a h/o febrile convulsions were similar between those patients who did and did not obtain seizure-freedom by the end of the study period (**Table 1**). At the last clinic visit, 63% of the original 525 patients were seizure-free, though significant risk factors for a lack of seizure freedom included epilepsy type (symptomatic or cryptogenic > idiopathic, 40% vs. 26%, RR of 1.5) and # of seizures prior to AED initiation (>20 seizures higher risk than <20 seizures pre-AED initiation, 51% vs. 29%, RR: 1.8, **Fig 2**). In terms of AED therapy, 68% of the 423 pts on 1 AED at the last follow up were seizure free, 23% of the 53 pts on 2 AEDs were seizure-free, and none of the 5 pts on 3 AEDs were seizure-free (**Fig 1**)[3]. Finally, of those patients who had never received an AED (n = 470), 64% became seizure free during treatment: 47% (n = 222) became seizure free after use of their 1st AED, but only 13% obtained seizure freedom when switched to a 2nd drug, and only 4% when again switched to a 3rd drug (**Table 2**). In the remainder w/o initial seizure freedom (n = 248), 113 failed the 1st AED due to

[1] Seizures: convulsive, non-convulsive, or partial; Epilepsy: idiopathic (JME, CAE), symptomatic (+ structural lesion), or cryptogenic (no identifiable lesion)

[2] Patients who consistently showed high rates of non-compliance were excluded from the final study analysis.

[3] No differences existed in terms of seizure-freedom relative to which AED was started.

ineffectiveness of the drug, and only 11% of this patient group obtained seizure freedom later; better rates of seizure freedom occurred in those who failed the first AED due to ASEs, drug reactions, or other reasons (**Fig 3**).

Conclusions: Overall, the results from this study identified major, patient-specific variables that predict later risk for refractory epilepsy. Given that such variables were present early in the course of each patient's epilepsy (i.e., symptomatic epilepsy, high #seizures pre-treatment), this data suggests that the refractory nature of epilepsy is likely present at disease onset, rather than a feature that evolves over time. In addition, while this study confirmed a high likelihood of seizure freedom with 1 AED in most patients with epilepsy (with no clear differences based on which AED is started), data here also showed that response to a first AED was also a clear prognostic factor for later seizure freedom. Specifically, if a 1st AED fails to yield seizure freedom, the chance of seizure freedom after trialing a 2^{nd} or 3^{rd} AED is also quite low. As such, the data here collectively showed the importance of identifying refractory epilepsy early, especially in the patient populations with the variables highly associated with uncontrolled epilepsy, to optimize both medical and surgical treatment options.

Summary created by Elaine Sinclair, D.O.