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Clinical conditions of long-term cure in childhood-onset epilepsy: A 45-year follow-up study

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ABSTRACT

Clinical conditions of long-term cure in childhood-onset epilepsy, defined as sustained remission off antiepileptic drug (AED) treatment, are not well known. To address that clinically important question, we determined clinical factors predictive of long-term seizure cure in a population-based cohort of 133 patients followed up since their first seizure before the age of 16 years. At the end of the 45-year follow-up (mean = 39.8, median = 44, range = 11–47), 81 (61%) of the 133 patients had entered at least 5-year remission off AEDs, meeting our definition of cure. The 81 patients were seizure-free off AEDs for a mean of 34.4 (median = 38, range = 6–46) years and 59 (73%) of the 81 patients following the first standard medication until the end of follow-up (mean = 36.5, median = 39, range = 14–46 years). Four independent factors were found to be associated with cure compared with having seizures while on AEDs: seizure frequency less than weekly during the first 12 months of AED treatment ($p = 0.002$), pretreatment seizure frequency less than weekly ($p = 0.002$), higher IQ (>70; $p = 0.021$), and idiopathic or cryptogenic vs. symptomatic etiology ($p = 0.042$). Patients with seizure frequency of less than once a week during early treatment and idiopathic etiology had a ninefold chance to of being cured since the onset of the first adequate antiepileptic therapy until the end of follow-up compared with patients who a symptomatic etiology had at least weekly seizures while on AEDs (RR = 8.7, 95% CI = 2.0–37.0; $p < 0.001$). In conclusion, IQ, etiology, and seizure frequencies both in the first year of AED treatment and prior to medication appear to be clinical predictors of cure in childhood-onset epilepsy.

1. Introduction

During treatment with a variety of different antiepileptic drugs (AEDs), as many as 2 of 3 newly treated patients with epilepsy will enter remission for several years [1–4]. Well-known factors predicting sustained remission on AEDs include intelligence, etiology of the epilepsy, and early drug response [1,5–8]. However, there is little information on clinical factors predicting epilepsy cure in new-onset epilepsy. Long-term remission off AED treatment has recently been reported in all patients with rolandic epilepsy [9,10]; it was also reported in 81% with secondarily generalized tonic–clonic seizures only, in 57% with complex partial seizures [11], and in 26% with juvenile myoclonic epilepsy [12]. Nevertheless, an ILAE task force recently noted that no adequate data are available on seizure recurrence risk after being seizure-free and off medication for extended periods of time [13]. Cure is usually defined as sustained seizure remission following withdrawal of AEDs [13,14]. For the definition of cure used in this study, see the Methods section. Several studies have scrutinized factors associated with cure following surgery of chronic, drug-refractory epilepsy in children [15]. There is uncertainty, however, which early features, if any, predict cure in individuals with medically treated childhood-onset epilepsy followed from their first seizure. The purpose of the present study was to examine which clinical features available at presentation or in the first 12 months of AED treatment predict seizure cure in medically treated patients followed for several decades since the onset of their epilepsy in childhood.

2. Methods

2.1. Patients

The baseline study subjects included all children aged 15 years or less who were living in the catchment area of the Turku University Hospital, Turku, Finland between 1961 and 1964 who met the criteria for epilepsy (two or more unprovoked seizures) [16–18]. Subjects were identified on the basis of hospital, institution, and primary health-care records and a review of the National Health Service records, a registry of all patients residing in Finland. Altogether, 245 patients were identified, 223 (91%) of them were seen in the Turku University Hospital. The remaining 22 (9%) patients were seen in other hospitals, institutions, and public or private primary or outpatient care offices. In Finland in the 1960s, the rule

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was that children with epileptic seizures were referred for evaluation. Untraceable and subsequently beyond the study remained only three more patients who, in an ongoing surveillance, were identified and who met the inclusion criteria. Thus, the patient sample represents a population-based cohort of 0 through 15 year old children with epilepsy.

The 245 patients included 150 (61%) patients with incidence cases, i.e., they were first evaluated for epilepsy from 1st January 1961 to 31st December 1964. The remaining 95 (39%) patients had been seen for epilepsy both before and during the study period of 1961 to 1964. They had had at least one seizure in the preceding three years before the evaluation during the study period (prevalent cases). All 245 patients were examined and evaluated by one child neurologist [19] enrolled in a prospective follow-up of medical and social outcomes for an additional 40 years. For the ascertainment of the diagnosis of epilepsy prior to baseline in 1972, one or more conventional EEG recordings were made using a 16-channel EEG machine, the "10–20" international system of electrode placement, a minimum recording time of 30 min with both unipolar and bipolar derivations during both wakefulness and sleep, and both photic stimulation and hyperventilation as provocation methods. The EEG data were analyzed in detail but, after the first two decades of follow-up, the EEG observations were excluded from the prognostic analyses because no significant contribution to the outcome was found. The psychological examinations for determining intelligence level were performed on clinical grounds in the vast majority at onset of epilepsy or at school entry for the assessment of school class placement. Follow-up included ongoing review of the medical records and a comprehensive evaluation with five-year intervals. In 1992, in addition to the structured extensive questionnaires, the evaluation included clinical examination completed with appropriate tests for physical fitness and laboratory investigations. The study design and some earlier results have been reported in detail previously [4,20–23].

For the present study, patients were selected among those 150 incident patients who had been followed since the onset of epilepsy. The exclusion criteria were short follow-up (<10 years), inadequate medication (self-reported noncompliance or off AEDs in spite of seizures), and patients with 5-year terminal remission on AEDs for whom it is difficult to ascertain cure. The final cohort numbered 133 patients including two groups to be compared: those who had entered cure, i.e., in remission off AEDs (n = 81), and those who had not entered cure, i.e., on AEDs and having seizures during the last 5 years of follow-up (n = 52) (Fig. 1).

2.2. Definitions

Epileptic syndromes, epilepsies, epileptic seizures, and etiology of seizures were defined according to the guidelines for epidemiologic research of the International League Against Epilepsy [16–18]. Status epilepticus in this study is defined as seizures lasting more than 30 min or recurrent seizures lasting a total of more than 30 min without the patient fully regaining consciousness [16,18,22]. Remission of epilepsy ever was defined as a seizure-free period of 5 or more consecutive years any time during follow-up as suggested in the literature [1]. Terminal remission was the term used for 5-year or longer remission at the end of follow-up. Terminal remission could be uninterrupted from the start of treatment to the end of follow-up (remitting course) or be interrupted by relapse (remitting–relapsing course). Early uninterrupted terminal remission was defined as complete seizure freedom from the start of the first adequate therapy not interrupted by relapse until the end of the follow-up period. The definition of adequate medication included choice and dosage of AEDs or AEDs in accordance with contemporary practice parameters of good therapy and good compliance. Cure was defined in accordance with the literature as entering at least 5-year terminal remission following withdrawal of all AEDs during sustained remission [13,14]. Compliance was determined by questioning the patient. Compliance was termed good if the patient answered "Yes, according to the given instructions" to the question: "Have you taken your drugs regularly?". The other options were as follows: "Yes, regularly, but less than instructed"; "I have occasionally forgotten medication"; "I have taken the medication irregularly"; "There have been longer breaks in the medication"; and "I have spontaneously discontinued the medication". The methods of planned discontinuation have been described previously [4,7].

2.3. Statistical analysis

The chance of cure was assessed with univariate and multivariable modified Poisson regression models for binary data [24]. For the multivariable model, relevant predictors were selected on the basis of univariate analyses, and the final model was obtained using backward selection: all variables with univariate $p \leq 0.1$ were included in the first model, and those with $p > 0.1$ were excluded one by one starting from the predictor with the highest p-value. With epilepsy being a symptom complex, pairwise interactions of etiology and early treatment seizure frequency to all other predictors were examined in

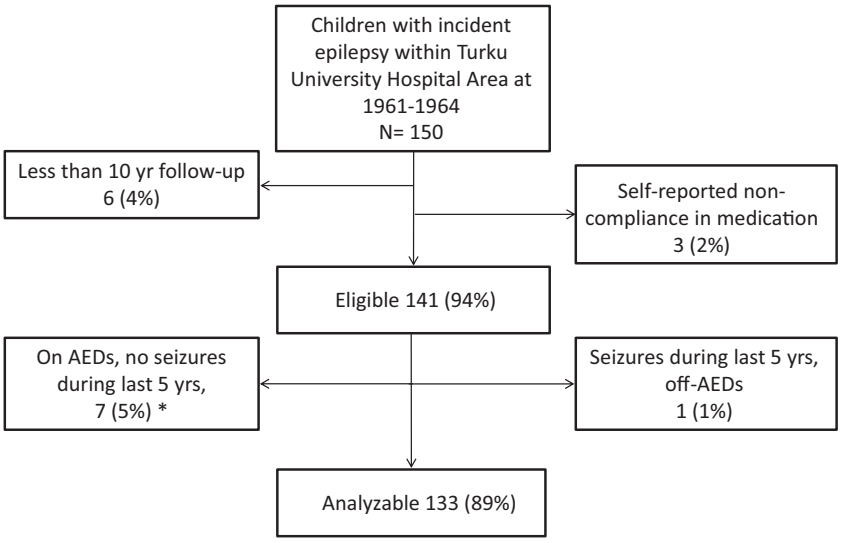

Fig. 1. Subjects of the study. Only 7 of 141 eligible patients on AEDs in remission, five declined to withdraw AEDs mainly because they were afraid of losing their driver's license and to be dismissed from work in case of relapse. Two patients preferred to continue AEDs for psychological reasons; they feared the social consequences of a relapse. As a result, cure could be ascertained in 133 (94%) of the 141 eligible patients.