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Outcome of initial antiepileptic drug treatment in elderly patients with newly diagnosed epilepsy

Emmi Bruun[a,b,*], Reetta Kälviäinen[c,d], Tapani Keränen[e,f]

[a] Department of Neurology, University of Eastern Finland, Kuopio, Finland
[b] University of Oulu, Oulu, Finland
[c] NeuroCenter, Kuopio University Hospital, Kuopio, Finland
[d] Faculty of Health Sciences, School of Medicine, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland
[e] National Institute for Health and Welfare, Helsinki, Finland
[f] Science Service Center, Kuopio University Hospital, Kuopio, Finland

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ABSTRACT

Purpose: A study was carried out to assess the outcome of initial antiepileptic drug (AED) monotherapy in elderly patients with newly diagnosed epilepsy and to investigate the cumulative probabilities of ≥2- and ≥5-year complete seizure remission and the factors that may have an effect on the outcome of AED treatment and the response to successive AED regimens.
Methods: From the medical records of Kuopio University Hospital, Finland, the researchers identified a community-dwelling cohort of elderly subjects (aged 65 or above at the time of diagnosis; $n = 529$) with newly diagnosed epilepsy. The seizure outcome and the effect of initial prescription of AEDs were retrospectively studied.
Results: All told, 336 (64%) of the patients used the initial AED for the whole follow-up period, while the treatment was changed for 193 (36%) of the patients. In total, 456 (86%) of the 529 patients were treated with monotherapy until the end of follow-up. Four per cent of the patients developed refractory epilepsy. The response to the second monotherapy after failure of the first monotherapy was similar between patients whose treatment failed for reason of intolerable side effects and those showing failure due to inadequate seizure control. The estimated cumulative probability of achieving ≥2 years' remission was 83%, and that for achieving ≥5 years of remission was 79%. Early response to treatment was a statistically significant predictor of remission.
Conclusion: The prognosis of seizures in elderly patients with newly diagnosed epilepsy is good, and most patients can be successfully treated with the first AED. Patients who do not become seizure-free within the first year may be at risk of displaying a drug-resistant seizure disorder.

1. Introduction

Epilepsy reaches its highest incidence and prevalence rates in the elderly population (Forsgren et al., 2005; Sillanpää et al., 2011). At general-population level, more than 1% of those above 60 years of age have epilepsy, and the prevalence increases with advancing age (Forsgren et al., 2005). Diagnosis and treatment of epilepsy may be more complicated in the elderly than in younger adults, because of comorbidities, variations in the presentation of seizures, and co-medication (Besocke et al., 2013; Brodie et al., 2009). There are a limited number of clinical trials with antiepileptic drugs (AEDs) in the elderly (Brodie et al., 1999; Rowan et al., 2005; Werhahn et al., 2015). While a few studies have reported on the outcome for seizures in elderly patients with newly diagnosed epilepsy in real-world treatment situations, these have had relatively small sample sizes and no more than two years of follow-up (Besocke et al., 2013; Stephen et al., 2006; Tanaka et al., 2013).

The aim of the study reported upon here was to assess the outcome of initial AED monotherapy treatment in community-dwelling elderly patients with newly diagnosed epilepsy, investigate the cumulative probabilities for ≥2 and ≥5 years' complete seizure remission, and the factors that may influence the outcome of AED treatment and the response to successive AED drug regimens.

* Corresponding author. Address: Ylioppilaantie 2C 53, 90130 Oulu, Finland.
E-mail address: emmi.bruun@student.oulu.fi (E. Bruun).

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2. Subjects and methods

2.1. The population and setting

The methods applied for identification of subjects for the study have been described in detail previously (Bruun et al., 2015). The case-record register of Kuopio University Hospital (KUH) was used for retrospective identification of elderly patients with newly diagnosed epilepsy. One of five university hospitals in Finland, KUH serves as a secondary referral centre for epilepsy patients and also a national tertiary referral centre. The population of the primary catchment area of KUH is 250,000, with around 50,000 of those covered being aged 65 years old or above. National guidelines on the diagnosis and treatment of epilepsy recommend that all patients with suspected seizures be referred to a neurology department for evaluation (Kälviäinen et al., 2014).

Included in the study were community-dwelling patients who had been diagnosed for the first time, on either an outpatient or inpatient basis, as having epilepsy between 1.1.2000 and 31.12.2013; were aged 65 or above at the time of diagnosis of epilepsy; had not previously been treated with an AED; and had their AED treatment started as monotherapy. All those patients from whom data were available from at least one follow-up visit were included. The study excluded patients who lived in institutions at the time of diagnosis, because such patients are often not referred for hospital specialist consultation. In total, 529 persons meeting the inclusion criteria were identified.

Detailed data on the patients' medical and demographic characteristics, including the aetiology of the epilepsy and the seizure and epilepsy type, were gathered from the case records. The number of seizures before AED treatment and the initial AED were recorded also. Follow-up data were gathered from the diagnosis of epilepsy until the last clinic visit with available data, death, or the end of the follow-up period (31.12.2013). Data on the occurrence of seizures was gathered from patient records at outpatient visits, and possible treatment periods in the hospital or at the emergency room. Seizures reported by the patients or witnessed by health care personnel were recorded. Descriptions of the events were carefully reviewed from the records in order to exclude non-epileptic seizures.

2.2. Definitions

For purposes of the study, epilepsy was defined as a disorder with 1) at least two unprovoked (or reflex) seizures, occurring >24 h apart, or 2) one unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures occurring over the next 10 years on account of, for example, underlying aetiology or *status epilepticus* (Fisher et al., 2014). Patients with acute symptomatic seizures – i.e., seizures secondary to substance (including alcohol) abuse or withdrawal or due to an acute illness (Beghi et al., 2010) – were excluded.

Refractory epilepsy was defined in accordance with the criteria of the International League Against Epilepsy (ILAE) (Kwan et al., 2010), as failure of adequate trial of two tolerated, appropriately chosen and used AED schedules (whether as monotherapy or in combination) to achieve sustained seizure-freedom. The conditions entail observation of a seizure-free period that is either at least 12 months or at least three times the longest inter-seizure interval prior to the initiation of a new intervention.

Epilepsy was categorised as focal, generalised, or unclassified (Berg et al., 2010). Epileptic seizures were classified as focal seizures, generalised seizures, or unclassified seizures.

The aetiology of the epilepsy was recorded as indicated in the case records.

2.3. Measurements

Patients were deemed responsive to medication if they were seizure-free from initiation of the initial AED or achieved seizure-freedom during the follow-up period. Patients were classed as having uncontrolled epilepsy if they did not achieve seizure remission during the follow-up. Failure of seizure control for reason of inadequate seizure control was defined as lack of efficacy in patients who were able to tolerate the medication.

Remission was defined as being free of all seizures by self-report according to patient files. The date of the start of seizure-freedom was obtained from the patient chart, or, in cases wherein no exact date had been recorded in the chart, the first clinic visit at which no seizure was reported was considered to represent the start of remission. The remission curve includes patients from whom follow-up data were available until the last clinic visit within the follow-up period or death.

2.4. Statistical analysis

The analysis of categorical data used a chi-squared test. To estimate achievement of a cumulative probability of $\geq$2 years' or $\geq$5 years' remission, Kaplan–Meier analysis was employed. Time to remission was defined as the time from the day the initial monotherapy AED started to the start date of two years' or five years' seizure remission. The 'event' was defined as seizure-freedom for at least two or five years. Cases were defined as censored if a seizure had not recurred by the end of follow-up. The observations were censored from the date of the last clinic visit. The Cox proportional hazards model was used to obtain a hazard ratio (HR) for each independent variable. The hazard rate and its 95% confidence interval (CI) for certain presumed risk factors for seizure remission were calculated from the standard errors of Cox regression coefficients. The following factors were included: Sex, age at diagnosis, etiology (classified as unknown or known), EEG prior to the start of AED treatment (categorized as normal, abnormal non-epileptiform changes or epileptiform discharges), seizure type (classified as focal generalized seizures or focal seizures), number of seizure types (single seizure type or more than one seizure types), number of seizures prior to AED treatment, time from first seizure to initiation of the first AED, seizure remission after initiation of the first AED (categorized as remission achieved within one year or not achieved within one year). The level for significance was determined to be $P < 0.05$. All statistical analyses were performed with Microsoft Excel and SPSS 21.

2.5. Ethics considerations

The study was conducted in accordance with the principles of the World Medical Association's Declaration of Helsinki. This non-interventional study was based on individual-level hospital patient data, and the corresponding authorisation for using these data was received from the regulatory authority responsible for the administration of said data at KUH. According to the Finnish legislation on medical research, an opinion of an ethics committee is not required for this kind of study.

3. Results

The study cohort, 529 patients, comprised 253 (48%) females and 276 (52%) males. Their age range at the onset of epilepsy was 65–94 years. With the exception of two patients, whose exact epilepsy type remained unknown, all of them had focal epilepsy. The most common known aetiological factors for epilepsy were stroke (45%), central nervous system tumour (10%), and Alzheimer's disease (8%). For 33% ($n = 175$) of the patients, AED treatment was