Epilepsy Research (2014) **108**, 295—304

journal homepage: www.elsevier.com/locate/epilepsyres

Outcome prediction of initial lamotrigine monotherapy in adult patients with newly diagnosed localization related epilepsies

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Received 12 July 2013; received in revised form 21 October 2013; accepted 3 November 2013
Available online 17 November 2013

KEYWORDS
Epilepsy;
Lamotrigine;
Treatment outcome;
Prognosis;
Effect modifiers

Summary
Objective: To develop and test model to predict outcome of treatment with initial lamotrigine monotherapy in adult patients with newly diagnosed localization — related epilepsy, using data available at the time of diagnosis.
Methods: Prospective longitudinal study included consecutive series of adult patients with newly diagnosed localization — related epilepsy started of lamotrigine monotherapy. Logistic regression analysis using backward procedure was performed with treatment failure as the outcome variable. We evaluated both calibration and discrimination of the model. Internal validation of the model was performed with bootstrapping techniques.
Results: A total of 159 patients on lamotrigine monotherapy have been included in final analysis. Among them 78 (49.06%) patients had persistent seizures. Finally fitted multivariate model included: 1) age at therapy start, 2) presence of complex partial seizures, 3) aetiology of epilepsy and 4) interaction of age and epilepsy aetiology. Estimated odds ratio for seizure relapse in old patients with symptomatic epilepsy is lower than for the old patients with cryptogenic epilepsy, despite strong positive covariate effect of epilepsy aetiology. The model correctly classified 69.23% patients with seizure relapses and 81.48% of patients with seizure freedom, with estimated *c* — statistic of 0.80. Testing practical application we observed threefold increase or reduction of odds for the seizure relapse after model's positive or negative prediction respectively.

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0920-1211/$ — see front matter
http://dx.doi.org/10.1016/j.eplepsyres.2013.11.008

Conclusion: Standard clinical data were modesty adequate to predict response to the initial trial of lamotrigine in adult patients with localization related epilepsy. Better markers of antiepileptic failure are required to guide optimal patient counselling and clinical decisions. Formal interaction analysis of variables improves outcome prediction and may be a key to correct interpretation of data.

Introduction

At least 30—40% of patients newly treated for a seizure disorder experience further seizures despite taking appropriate antiepileptic drug (AED) therapy (Brodie et al., 2012). Several studies have found that the response to the initial AED trial carries significant implications for long-term prognosis (Kwan and Brodie, 2000; Dlugos et al., 2001). Therefore, identifying clinically useful predictors of individual drug response to AED treatment would have major clinical benefits. This could serve both for patient counselling and for prompt identification of drug-resistant epilepsy and early referral of patients to nonpharmacologic treatments such as epilepsy surgery or vagal nerve stimulation.

Previous studies investigating such predictors have examined for clinical (Mohanraj and Brodie, 2006; Pittau et al., 2009; Varoglu et al., 2009; Aguglia et al., 2011; Bonnett et al., 2012), EEG (Elwes et al., 1984; Shafer et al., 1988; Pittau et al., 2009), imaging (Semah et al., 1998; Spooner et al., 2006; Pittau et al., 2009) or genetic biomarkers (Petrovski et al., 2009). Among them only few studies have gone beyond measurement of isolated factors and have identified an array of prognostic items, which together can form the elements of a predictive models (Camfield et al., 1993; Arts et al., 2004; Dlugos and Buono, 2004; Bonnett et al., 2012; Serrano-Castro et al., 2012). However, their results show modest discriminatory power of the models, which illustrate the complex interplay of factors determining the course of epilepsy.

Interaction is one of the fundamental concepts of statistical analysis and the basics of modelling interaction effects in the regression analysis of data are now widely understood (Rothman et al., 1980; Berrington de González and Cox, 2007) and the term ''effect modifiers'' have been recently introduced in to the Medical Subject Headings (2013). The most common frameworks use the concepts of adjustment, confounding, interaction, and effect modification (Hosmer and Lemeshow, 2000). An interaction effect is said to exist when the effect of an independent variable on a dependent variable differs depending on the value of a third variable. When interaction effects are present, it means that interpretation of the individual variables may be incomplete or misleading e.g. when a covariate is an effect modifier, its status as a confounder is of secondary importance (Kleinbaum and Klein, 2010). Therefore, establishing the presence or absence of interaction may be a key to correct interpretation of data (Berrington de González and Cox, 2007). However, previous studies investigating predictors for treatment response in newly diagnosed epilepsy have primarily considered the main effects of predictors on the outcome, without a formal interaction analysis.

Furthermore, actual evidences are not strong enough to support the immediate choice of any single AED for all new patients with focal epilepsy and the choice of initial monotherapy for the same epilepsy syndrome mainly depends on several factors like comorbidity, gender issues, drug adverse effect profile etc. (Perucca and Tomson, 2011). Therefore, in nonrandomized studies patients allocated to different AED can also have different risk profiles with potentially diverse confounding or effect modifier consequences. For this study we included patients treated with the same AED as initial therapy in order to analyze a homogeneous cohort of patients and to avoid the variability derived from groups treated with the different AEDs.

The goal of this study was to develop and test prediction models for the identification of adult patients with newly diagnosed localization — related epilepsy, destined to fail their initial trial of the same AED, based on information available at their initial diagnosis of epilepsy. We also aimed to compare the fits of models with and without concerning variable interactions with age and gender as potentially main biological effect modifiers. The study focused on patients with localization — related epilepsy, because such patients could potentially be candidates for early surgical intervention if AEDs are unlikely to control seizures and paid attention on patients receiving lamotrigine (LTG) as possible first line therapy for this syndrome.

Methods

Collection and processing of data

We analyzed a prospective registry including all adult patients with epilepsy evaluated at our tertiary care academic department. Local Ethic committee approved collection and use of patient database and informed consent was obtained from each patient and/or from parents/caregivers. We analyzed consecutively unselected group of patients with newly diagnosed localization — related epilepsy, from January 1st, 2003 to December 31st, 2009, and those who fulfilled the inclusion and had no exclusion criteria were encompassed in this study.

Patients older than 16 years were eligible for inclusion if satisfied all of the following criteria: 1) at least two well documented, unprovoked, clinically evaluated and classified partial seizures (with or without secondary generalization) within last 12 months, 2) EEG within 12 months compatible with focal onset seizures (to exclude patients with generalized electroclinical syndromes). In addition some patients with normal interictal EEG have also been suitable for inclusion, 3) Computed tomography (CT) and/or magnetic resonance imaging (MRI) scan within 12 months, and 4) no previous use of AED and planned start of LTG monotherapy.