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Family history and frontal lobe seizures predict long-term remission in newly diagnosed cryptogenic focal epilepsy

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Summary
Purpose: Cryptogenic focal epilepsy (CFE) is a heterogeneous clinical disorder including patients with severe refractory forms and patients with a fairly good prognosis. Predictors of prognosis in CFE are poorly understood. The aim of this retrospective study is to identify long-term (5-year) prognostic predictors in patients with newly diagnosed CFE.
Methods: Subjects with cryptogenic focal epilepsy (CFE) seen from April 1987 to September 2011 in two twin Epilepsy Centres located in Reggio Calabria and Catanzaro, Calabria, Southern Italy, were screened. Patients were excluded if they had psychogenic seizures, major psychiatric disorders presence of brain lesions except for non-specific white matter T2-hyperintensities, short follow-up (less than five years) or for having received the diagnosis of CFE elsewhere. One hundred and eighty-six patients, firstly diagnosed in our Centres, constituted the study sample. Survival curves were generated according to the Kaplan—Meier method and compared with the log-rank test. The endpoint was the cumulative time-dependent chance of 5-year remission after treatment start. Independent predictors of remission were tested by multivariate analysis using Cox proportional hazards function models. The accuracy of the resulting model was tested with Receiver Operating Characteristics (ROC) curve analysis.

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Key findings: The cumulative incidence of remission was 23%. At Kaplan—Meier analysis, the only factor predicting remission was family history of epilepsy or febrile seizures (FS; $p = 0.02$). At Cox regression, family history and frontal lobe epilepsy showed to be independent predictors of outcome ($p = 0.02$ and 0.03, respectively). The accuracy of these predictors was good (area under ROC curve 0.648, 95% CI 0.575—0.716). Interestingly, we also found a considerable (7 years) diagnostic delay that did not result in a worse prognosis.
Significance: About one quarter of subjects with newly diagnosed CFE attains 5-year seizure remission during follow-up. Family history of epilepsy or FS and frontal localization are independent prognostic predictors.

Introduction

The presence of a cerebral lesion predicts poor prognosis and pharmacoresistance in focal epilepsies (Semah et al., 1998; Dhamija et al., 2011; Wirrell et al., 2011; Berg et al., 2011). The absence of a demonstrable cerebral lesion defines cryptogenic focal epilepsy (CFE) that represents a very common type of focal epilepsy as verified in many population studies (Hauser et al., 1991; Kwan and Brodie, 2000; Cossu et al., 2012; Garcia-Martin et al., 2012) and in a systematic review (Forsgren et al., 2005). Heterogeneous prognostic features have been described in different studies including CFE (Cockerell et al., 1997; Aguglia et al., 1998; Wirrell et al., 2011; Berg et al., 2011). Indeed, little is known about electro-clinical prognostic predictors in CFE. In a longitudinal prospective study of children with ''nonsyndromic epilepsy'' followed up for a long time (Berg et al., 2011), early remission and absence of underlying brain disorders were predictors of complete remission, defined as 5-year seizure and medication freedom. A retrospective study, that included patients with a single seizure (Cockerell et al., 1997), showed high rates of long-term remission, without identifying any prognostic predictor. Another study (Del Felice et al., 2010) was conducted prospectively on patients with new-onset epilepsy of any kind, and showed high rates of early (in the first 24 months since treatment start) and late (2-year seizure freedom at least after 24 months) remission, probably reflecting a high proportion of idiopathic generalized or focal epilepsies (about one-third of the sample). In that study, the only predictor of late remission was the interaction between type and number of seizures prior to starting treatment. In a longitudinal study on prognostic predictors in subjects with temporal lobe epilepsy (Aguglia et al., 2011) age at onset was the only predictor of outcome in this group of patients, with earlier onset associated with poorer outcome.

Remarkably, only the study from Berg et al. (2011) and, partially, that from Cockerell et al. (1997) took into consideration a long-term outcome (5-year seizure and medication freedom), while all other researchers considered a shorter time-frame for seizure freedom.

Identifying 5-year predictors of remission in patients with new-onset CFE would offer a valuable tool to both physicians and patients. The aim of this retrospective study was to evaluate 5-year predictors of terminal remission in a cohort of patients with newly diagnosed CFE, regardless of age of onset.

Patients and methods

Assessment, inclusion and exclusion criteria

One thousand, four hundred and one subjects with cryptogenic focal epilepsy (CFE) were consecutively screened from April 1987 to September 2011 in two twin Epilepsy Centres located in Reggio Calabria and Catanzaro, Calabria, Southern Italy, sharing the same study design and the electronic database. Patients were mostly recruited from the surrounding community, as they were addressed to our Centres by general practitioners, paediatricians, an emergency department (Reggio Calabria Hospital only) or they referred on their own. In this retrospective study, criteria for inclusion were a history of two or more unprovoked focal seizures and non-lesional aetiology (as determined by brain MRI imaging), regardless of the age of onset; all patients met the 1989 ILAE criteria for CFE (Commission on Classification and Terminology of the ILAE, 1989). Brain MRI studies (1.5 Tesla for all subjects, 3 Tesla for 8 subjects), performed at diagnosis and/or during follow-up, included 3D T1-weighted spoiled gradient echo (SPGR) sequences, axial T2-weighted images, axial fast fluid-attenuated inversion-recovery (FLAIR) images and coronal IR images, with the following parameters: TR = 15.2 ms; TE = 6.7 ms; flip angle 15°; matrix size 256×256; FOV = 24 cm; slice thickness = 2 mm. Patients with non-specific white matter scattered T2-hyperintense spots on brain MRI were included, while patients with evidence of hippocampal sclerosis were excluded. The MRI diagnosis of hippocampal sclerosis (HS) was based on the occurrence of the neuroimaging alterations which are considered reliable indicators of HS (Labate et al., 2006). One thousand, two hundred and fifteen subjects were excluded; of these, 409 (34%) because of loss of follow-up or short follow-up (less than 5 years), 655 (54%) for having received the diagnosis of CFE elsewhere (prevalent cases), and 151 (12%) for the occurrence of psychogenic seizures and/or major psychiatric disorders. Thus, the study sample included 186 subjects with newly diagnosed CFE (incident cases). The following variables were considered: age, gender, age at onset of epilepsy (further divided in childhood: <18 years, adulthood: 18—70 years, and old age: >70 years), diagnostic delay (difference between age at first observation and age at onset of seizures, further divided in short: $\leq$1 year or long: >1 year), family history of epilepsy or febrile seizures (FS) in first or second-degree relatives, perinatal (infectious, traumatic,