Seizure 18 (2009) 412–416

Contents lists available at ScienceDirect

Seizure

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

Early prediction of refractory epilepsy in childhood

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ARTICLE INFO

Article history:
Received 30 December 2008
Received in revised form 6 February 2009
Accepted 27 February 2009

Keywords:
Epilepsy
Refractory
Intractable
Prognosis

ABSTRACT

Purpose: To investigate early predictors (6 months after diagnosis) of refractory epilepsy.
Methods: Study design: prospective cohort study. Inclusion criteria: all consecutive children <14 years with two or more unprovoked seizures 24 h apart, who were seen at our hospital between 1994 and 2004. Exclusion criteria: patients previously examined in other centres. Definitions: refractory epilepsy: failure of >2 drugs plus >1 seizure/month for ≥18 months. Analysis: risk of developing refractory epilepsy was calculated using Kaplan–Meier survival curves. Univariable and multivariable analyses of potential predictors of developing refractory epilepsy were carried out using Cox proportional hazards model.
Results: 343 patients were included. Mean age at diagnosis was 4.8 years (±3.8 SD). Mean follow-up period was 76.2 (±35.2 SD) months (range 24–139). Risk of developing refractory epilepsy was 8% at 6 years. Risk for idiopathic syndromes was 2%. For non-idiopathic syndromes the risk was 38% for patients with age at onset <1 year plus >1 seizure during the first 6 months after diagnosis, 9% for age at onset <1 year plus 0–1 seizures during the first 6 months, 22% for age at onset ≥1 year plus >1 seizures during the first 6 months and 3% for age at onset ≥1 year plus 0–1 seizures during the first 6 months.
Conclusion: Risk of developing refractory epilepsy is very low in idiopathic syndromes. For the rest of patients, a simple model comprising three variables allows more accurate prediction of risk of refractoriness.

1. Introduction

Most children with epilepsy do well on antiepileptic treatment. However, some patients respond poorly to antiepileptic drugs (AEDs) and develop refractory (intractable) epilepsy. Early identification of children at risk of developing refractory epilepsy is important for parents' counselling and consideration of alternative treatments. Some studies investigating prognostic factors of refractory epilepsy have been published, but most of them have a case–control design.[1–9] This type of study does not allow estimation of the risk of developing refractory epilepsy in patients with a given risk factor. Only three prospective cohort studies are available.[2,7,9] One of them did not include patients younger than 2 years old[7], a group of children particularly at risk of developing refractory epilepsy, and the other one used broad criteria for defining refractory epilepsy.[9] Therefore, a prospective cohort study is needed. The objective of the present work is to investigate the value of potential prognostic factors identifiable at 6 months from diagnosis in a prospectively followed cohort of children younger than 14 years old with recent-onset epilepsy.

2. Methods

2.1. Definitions and classification criteria

Seizures were considered unprovoked when they occurred in the absence of any known proximate precipitant. More than one seizure within a period of 24 h was considered to be a single seizure (multiple seizure). Epilepsy was defined as the occurrence of two or more unprovoked seizures. *Status epilepticus* was defined as a seizure lasting more than 30 min or recurrent seizures lasting a total of more than 30 min without the patient fully regaining consciousness. The type of seizure was classified according to the 1981 ILAE criteria.[10] We considered that a patient had various seizure types when he/she had both partial and generalized seizures, various types of partial seizures (for example simple partial and secondarily generalized seizures) or various types of generalized seizures (for example absences and generalized tonic–clonic seizures). Epilepsies were classified according to their

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doi:10.1016/j.seizure.2009.02.006

aetiology as idiopathic, cryptogenic or remote symptomatic, following the ILAE criteria.[11] In particular, epilepsies were classified as remote symptomatic when they occurred in a patient with a history of a static encephalopathy of pre- or perinatal origin or a prior neurological insult such as central nervous system infection, stroke or significant head trauma.[11] Classification of patients by epileptic syndrome was also performed according to the ILAE revised 1989 classification.[12] Into the category "without unequivocal partial or generalized seizures" we classified all patients with apparently generalized tonic–clonic seizures and a normal EEG. Two new syndromes, not included in this classification, were also diagnosed: benign infantile seizures and early-onset benign childhood occipital epilepsy (Panayiotopoulos type). EEGs were classified as normal or abnormal; the latter category includes both epileptiform (focal or generalized spike-waves) and nonepileptiform (focal or generalized slowing) abnormalities. A family history of unprovoked seizures was defined as seizures occurring in a first-degree relative (parent or sibling). Neuroimaging was classified as abnormal only when the observed abnormality was considered the cause of epilepsy. Global developmental delay was defined as a developmental quotient below 70% and mental retardation as an intelligence quotient below 70. When formal intelligence tests were not available, intelligence was clinically assessed. Motor deficit was considered as present if there was hemiplegia, quadriplegia or diplegia.

Refractory epilepsy was defined as failure, due to lack of seizure control, of more than 2 AED at maximum tolerated doses, with an average of more than 1 seizure per month for $\geq$18 months and no more than 3 consecutive months seizure-free during this interval.[2] Drugs withdrawn due to intolerable adverse effects in patients without recurrences were not taken into account.

2.1.1. Cohort selection

Torrecárdenas Hospital is the reference hospital of the province of Almería (Spain). The only EEG laboratory and paediatric neurology unit in the province are located in this hospital. Between June 1, 1994 and December 31, 2004 all patients aged less than 14 years who were consecutively seen at our institution for two or more unprovoked seizures were enrolled in a prospective study. Patients with seizures limited to the neonatal period, inborn errors of metabolism, neurodegenerative disorders, children already on antiepileptic treatment and those who had previously been examined in other centres were excluded. Consequently, all patients were directly referred by primary care paediatricians or were first seen in the emergency department of our hospital. The study was approved by the ethical committee of the hospital and informed consent was obtained to participate in it.

2.2. Initial evaluation

For every patient, family and medical history were taken, a physical and neurological examination was performed and a standard EEG was obtained at diagnosis of epilepsy. When the standard EEG was normal, a sleep record was performed.

Computed tomography or magnetic resonance imaging was performed at least in the cases with abnormal findings in the neurological examination, partial seizures, focal abnormalities on the EEG (except in the case of benign childhood epilepsy with centro-temporal spikes) or West syndrome.

2.2.1. Follow-up

All patients were followed through personal interviews at regular intervals until December 31, 2006 (to allow for a minimum of 2 years' follow-up) or until they attain a remission of 3 years without AEDs (i.e. 3 years without either relapses or treatment). Patients in remission were thereafter contacted by telephone until a follow-up of 5 years without antiepileptic treatment was completed. Then, patients were instructed to contact us if a relapse occurred. Otherwise the patient was considered in remission.

2.2.2. Predictors of refractoriness

The following variables, all measured at 6 months of follow-up, were explored: sex, age at onset of epilepsy in years, prior febrile seizures, prior neonatal seizures, family history of epilepsy in first-degree relatives, aetiology, global developmental delay/mental retardation, motor deficit, abnormal neuroimaging (compared to normal or not done), *status epilepticus* at diagnosis, multiple seizures at diagnosis, abnormal EEG, various seizures types, West syndrome, number of seizures before diagnosis and number of seizures during the first 6 months after diagnosis. For treated patients the date of diagnosis was the same as the date of treatment onset. For patients with epilepsies characterised by a high frequency of seizures, such as absence epilepsy or West syndrome, seizures during the initial medication titration phase were not considered as recurrences.

2.2.3. Analysis

Risk of developing refractory epilepsy was calculated using Kaplan–Meier survival curves. Patients entered the study on the date of diagnosis of epilepsy. The event under study was fulfilling the criteria of refractory epilepsy. Cases were considered censored if, at the end of the study, the event under observation had not occurred or if contact with the patient was lost. We carried out univariable and multivariable analyses of potential predictors of developing refractory epilepsy using Cox proportional hazards model. Calculations were performed by means of statistical software SPSS for Windows, version 15.0. The level of statistical significance was established at $p < 0.05$.

3. Results

3.1. General features of the sample

Three hundred and fifty-three children were enrolled in the study. 8 patients were lost to follow-up before completing a minimum follow-up period of 2 years and 2 children died within 2 years of diagnosis. Therefore, 343 patients were followed-up for more than 2 years and they constitute the sample of this study. Thereafter, another 6 patients were lost to follow-up and 4 children died. Overall, we lost contact with only 4% (8 + 6) cases from the initial sample. Mean age at diagnosis was 4.8 ($\pm$3.8 SD) years. 68 (20%) of the children were younger than 1 year of age at diagnosis of epilepsy, 236 (69%) between 1 and 9 years old and 39 (11%) were 10 years of age or older. 191 (56%) were male and 152 (44%) female. 34 (9.9%) patients were not treated. Mean follow-up period was 76.2 ($\pm$35.2 SD) months (range 24–139). Of the 343 children, 249 (73%) were followed for more than 4 years, 168 (49%) for more than 6 years and 104 (30%) for more than 8 years.

3.1.1. Overall risk of developing refractory epilepsy

Thirty out of 343 patients (8.7%) met the criteria of refractory epilepsy. The Kaplan–Meier estimate of the risk of developing refractory epilepsy was 5% (95% CI: 3–7), 7% (95% CI: 4–10), 8% (95% CI: 5–11), 11% (95% CI: 7–15) and 12% (95% CI: 7–17) at 2, 4, 6, 8, and 10 years respectively.

3.1.2. Epileptic syndromes

The risk of developing refractory epilepsy was higher in West syndrome and in symptomatic generalized and symptomatic partial groups, it was lower in idiopathic partial and idiopathic generalized groups and it was intermediate in cryptogenic partial