Seizure 18 (2009) 620–624

Contents lists available at ScienceDirect

Seizure

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

Response to sequential treatment schedules in childhood epilepsy Risk for development of refractory epilepsy

J. Ramos-Lizana *, P. Aguilera-López, J. Aguirre-Rodríguez, E. Cassinello-García

Pediatric Neurology Unit, Department of Pediatrics, Torrecárdenas Hospital, Almería, Spain

ARTICLE INFO

Article history:
Received 6 April 2009
Received in revised form 30 June 2009
Accepted 10 July 2009

Keywords:
Epilepsy
Prognosis
Refractory
Intractable
Antiepileptic drugs

ABSTRACT

Purpose: To investigate response to sequential treatment schedules and risk of development of refractory epilepsy in childhood.
Methods: All children younger than 14 years with two or more unprovoked seizures seen at our hospital between 1994 and 2004 were included and prospectively followed. "Seizure control" was defined as a 2-year seizure-free interval without further recurrences except those related to attempts of medication withdrawal and "refractory epilepsy" as failure of >2 drugs plus >1 seizure/month for ≥18 months.
Results: 343 Patients were included, 191 males and 152 females. Mean age at diagnosis was 4y 10 mo (SD 3 year 10 month). Mean follow-up period was 76.2 mo (SD 35.2). The probability of achieving "seizure control" was 70% and 86% at 5 and 10 years. 59% of patients were "controlled" with the first drug used. Among patients failing the first, second and third therapeutic regimen due to lack of efficacy, 39%, 23% and 12% respectively were finally "controlled" with subsequent treatment schedules Risk of development of refractory epilepsy was 8% and 12% at 6 and 10 years.
Conclusion: After failing a first drug, a significant proportion of children can still be controlled with subsequent therapeutic schedules. Only a small proportion develops refractory epilepsy.

Knowing how epilepsy responds to antiepileptic drugs (AEDs) is important in decision making and in providing information for patients and/or their parents. Most patients with epilepsy do well on antiepileptic treatment. However, a proportion of patients ranging between 6% and 41% in different studies, do not respond adequately to AED and develop refractory (intractable) epilepsy.[1–6] At least in part, this variability could reflect the use of different definitions of refractory epilepsy. On the other hand, it is known that failure of the first AED used diminishes the probability of response to subsequent AEDs. In a study with adolescents and adults, only 21% of patients in whom the first drug failed due to lack of efficacy were controlled with subsequent therapeutic schedules.[5,6] Other studies in children suggest a higher probability of success.[1,2] These are important and unsatisfactorily answered questions. Consequently, the main objectives of the present work have been to study response of childhood epilepsy to sequential treatment schedules and risk for the development of refractory epilepsy.

1. Methods

1.1. Definitions and classification criteria

Seizures were considered unprovoked when they occurred without any known proximate precipitant. Epilepsy was defined as occurrence of two or more unprovoked seizures at least 24 h apart. Epilepsies were classified according to their etiology as idiopathic, cryptogenic or remote symptomatic, following the ILAE criteria.[7] In particular, epilepsies were classified as remote symptomatic when they occurred in a patient with a history of a neurological deficit of pre or perinatal origin or a prior neurological insult such as CNS infection, stroke or significant head trauma.[7] Therefore, this group included patients with global developmental delay/mental retardation and cerebral palsy. Classification of patients by epilepsy syndrome was also performed according to the ILAE revised 1989 classification.[8] Classifications were performed with data available at 6 months after diagnosis. "Initial remission" was defined as a seizure-free period of *x* years, with or without further recurrences until the end of the study period. "Terminal remission" was defined as a seizure-free interval of *x* years without further recurrences. Consequently, the difference between "initial" and "terminal" remission is that in the first case the patient may be or not in remission at the end of the study period whereas in the second, the patient is always in remission. In this study we examined 1 and 2-year initial remission and 1-year terminal remission. "Seizure

* Corresponding author at: Unidad de Neurología Pediátrica. Servicio de Pediatría, Hospital Torrecárdenas. Almería, Paraje de Torrecárdenas s/n, 04009 Almería, Spain. Fax: +950016856.
E-mail addresses: jramoslizana@telefonica.net (J. Ramos-Lizana), paguileralopez@gmail.com (P. Aguilera-López), javieraguirrerodriguez@orange.es (J. Aguirre-Rodríguez), elicassinello@hotmail.com (E. Cassinello-García).

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doi:10.1016/j.seizure.2009.07.001

control" was defined as a seizure-free period of 2 years without further recurrences except those related to attempts of medication withdrawal. We considered as recurrences related to attempts of medication withdrawal, those occurring after the onset of medication withdrawal and not repeated after reinitiating antiepileptic medication. A patient was considered "controlled" with antiepileptic drugs if he/she attained a 2-year seizure-free period without further relapses and also if he/she attained a 2-year seizure-free period, had a seizure after medication withdrawal, reinitiated medication and did not have more seizures until the end of the study period. In other words, "seizure control" is like a terminal remission, but seizures related to drug withdrawal are not taken into account because they can not be attributed to drug failure. Untreated patients were considered "controlled" when they reached a 2-year seizure-free period without further relapses. As can be noted, the operational definition of "controlled" in this study includes seizure-free patients both on and off medication.

We considered "treatment failures" those changes of medication due to persistence of seizures at maximum tolerated doses. Drugs withdrawn due to intolerable adverse effects in patients without seizures were not included as "treatment failures" for the purposes of this study".

We defined refractory epilepsy as failure, due to lack of seizure control, of more than 2 AED with an average of more than 1 seizure per month for $\geq$18 months and no more than three consecutive months seizure-free during this interval (definition A).[3,4] We chose this definition as the main definition because it is suitable for using in a survival analysis. To compare it with previously published studies we used three other definitions. Definition B: terminal remission $<$1 year and longest remission $<$3 months during the last year of observation despite the optimal use of at least two AED, either alone or in combination.[2] Definition C: failure of three or more AED and more than one seizure per month during the final 12 months of follow-up.[1] Definition D: failure to achieve a 1-year terminal remission.[5,6] Different criteria were retrospectively applied using the prospectively collected data about frequency of seizures.

1.2. Cohort selection

Torrecárdenas Hospital is the reference hospital of the province of Almería (Spain). The only EEG laboratory and pediatric neurology division in the province are located in this Hospital. Between June 1st, 1994 and December 31st, 2004 all patients younger than 14 years of age seen consecutively at our hospital due to two or more newly-diagnosed unprovoked seizures at least 24 h apart were enrolled in a prospective study. Patients with seizures limited to neonatal period, inborn errors of metabolism, neurodegenerative disorders, children already on antiepileptic treatment and those who had been examined previously in other centres were excluded. Consequently, all patients were directly referred by primary care pediatricians or were first seen in the emergency department of our hospital.

Informed consent to participate in the study was obtained and the study was approved by the ethical committee of the Hospital.

1.3. 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. EEG records were read by independent neurophysiologists.

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.

Since this was an observational study, the treating physician chose the AED to be used. Some patients were not treated.

1.4. Follow-up

All patients were followed by personal interviews, at least at 6 to 12 months intervals, until December 31st, 2006 (to allow for a minimum of 2 year follow-up) or until they attained a remission of 3 years without AED (i.e 3 years with neither treatment nor relapses). Patients in remission were thereafter contacted by telephone until a follow-up of 5 years without antiepileptic treatment was completed. After that, patients were instructed to contact us if a relapse occurred. Otherwise patients were considered in remission. We did so to simplify the follow-up process, because previous studies showed that recurrence risk $>$5 years after medication withdrawal is very low.

Patients failing treatment due to lack of efficacy either had the original drug substituted or were offered combination therapy. In general, medication withdrawal was attempted after a seizure-free period of 2 years. In case of relapse, the same drug was reinitiated.

Mean follow-up period was 76.2 (SD 35.2) months (range 24 to 139). Out of 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. 66 patients achieved a 5-years remission period without antiepileptic treatment. Only one of these patients contacted us afterwards due to a relapse. This happened 85 months after treatment withdrawal.

1.5. Analysis

The probabilities of achieving a 1-year initial remission, a 2-years initial remission, a 1-year terminal remission and the risk of developing refractory epilepsy (Definition A) were calculated using Kaplan–Meier survival curves. Patients entered the study on the date of diagnosis of epilepsy. Probability of response to different treatment schedules was calculated as percentages. For latter analysis only treatments initiated before December 31st, 2004 were taken into account, to allow for a minimum of 2 years of follow-up. Calculations were performed by means of SPSS for Windows, version 15.0, statistical software.

2. Results

2.1. General features of the sample

Three hundred and fifty three children were enrolled in the study. Eight 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. This left 343 patients who were followed-up for more than 2 years and constituted the sample of this study. Thereafter, another six patients were lost to follow-up and four children died. Overall, we lost contact with only 4% (8+6) cases of the initial sample. Mean age at diagnosis was 4 years and 10 months (SD 3 years and 10 months). 68 (20%) of the children were younger than 1 year of age at diagnosis of epilepsy, 236 (69%) were between 1 and 9 years and 39 (11%) were 10 years of age or older. 191 were male and 152 female. A neuroimaging study was carried out in 291 (85%) patients: computed tomography was carried out in 105, magnetic resonance imaging in 113 and both in 72 patients. Etiology was remote symptomatic in 111 (32%) cases, cryptogenic in 86 (25%) and idiopathic in 146 (43%). Details of specific aetiology in remote symptomatic cases are shown in Table 1.

Thirty four (10%) patients were not treated (17 benign childhood epilepsies with centrotemporal spikes, two early-onset