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).

1059-1311/$ – see front matter © 2009 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.
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

Table 1
Specific aetiologies of remote symptomatic cases ($n = 111$) with findings in neuroimaging studies.

Aetiology	n	Neuroimaging findings	n
Neurocutaneous disorders[a]	6	Typical findings	6
Brain malformations[b]	15	Specific findings	15
Chromosomal abnormalities	4	Ventricular enlargement plus cortical atrophy	3
		Normal	1
Monogenic mendelian diseases[c]	5	Normal	5
Pre or perinatal hypoxic-ischemic lesions	25	Focal or diffuse multicystic encephalomalacia	12
		Periventricular leukomalacia	9
		Parasagittal necrosis	2
		Unilateral lateral ventricle enlargement	2
Postnatal acquired lesions[d]	9	Destructive lesions	9
Unspecific global developmental delay/intellectual disability[e]	39	Normal	39
Others	8	Various findings	7
		Normal	1

[a] Tuberous sclerosis: 5; Sturge-Weber syndrome: 1.
[b] Holoprosencephaly: 1; schizencephaly: 1; hemimegalencephaly: 1; corpus callosum agenesis: 2; periventricular heterotopia: 2; polymicrogyrias: 2; pachygyria: 1; lissencephaly: 1; hydrocephalus: 1; focal cortical displasia: 1; hydranencephaly: 1; arachnoid cyst: 1.
[c] Rett syndrome: 2; Angelman syndromes: 3.
[d] CNS tumours: 4; head traumatisms: 4; bacterial meningitis: 1.
[e] With normal MRI, no motor disability and no definite cause.

benign childhood occipital epilepsy, three generalized idiopathic epilepsies with infrequent generalized tonic-clonic seizures, eight cryptogenic localization-related epilepsies, one symptomatic localization-related epilepsy and three epilepsies without unequivocal partial or generalized seizures).

2.2. Overall probability of remission

For the overall sample ($n = 343$), at the end of the study period, 308 (90%) patients had achieved a 1-year initial remission, 271 (79%) a 2-year initial remission, 247 (72%) "seizure control" and 260 (76%) a 1-year terminal remission. For treated patients ($n = 309$) these figures were 275 (89%), 238 (77%), 216 (70%) and 229 (74%), respectively. For untreated patients ($n = 34$) these figures were 33 (97%), 33 (97%), 31 (91%) and 31 (91%), respectively.

Chi squared test showed that the following factors were significantly more frequent in treated than in untreated patients: age at onset of epilepsy <1 year ($p = 0.037$), remote symptomatic aetiology ($p = 0.001$), presence of global developmental delay or mental retardation ($p = 0.007$), abnormal neuroimaging ($p = 0.005$), a multiple first seizure ($p = 0.000$) and more than five seizures before diagnosis ($p = 0.000$). On the other hand, an idiopathic aetiology was more frequent in untreated patients ($p = 0.010$). There were no significant differences between both groups in sex, presence of motor deficit, presence of various seizure types, number of seizures during the first 6 months after diagnosis, first seizure as status or a history of prior febrile convulsions or neonatal convulsions.

At the end of the study period, 205 out of the overall sample (60%) and 202 out of 247 "controlled" patients (82%) were without antiepileptic treatment.

The probability of achieving a 1-year initial remission, a 2-year initial remission and "seizure control" in the overall sample ($n = 343$), calculated by Kaplan–Meier curves is shown in Table 2.

2.3. Response to antiepileptic treatment

Three hundred and nine patients were treated. The first AED used was valproic acid in 186 cases, carbamazepine in 64, oxcarbazepine in 18, phenobarbital in 15, phenytoin in 2, ethosuximide in 4, vigabatrin in 7, lamotrigine in 1 and topiramate in 1, in all cases in monotherapy. In 11 patients diagnosed as West syndrome, the first schedule consisted in oral corticosteroids or ACTH plus valproic acid. The second schedule was a monotherapy in 50 patients and a polytherapy with two drugs in 35. The third schedule was monotherapy in 13 children, polytherapy with two drugs in 27 and polytherapy with more than two drugs in 4. The fourth and subsequent schedules consisted in monotherapy in 2 patients, polytherapy with two drugs in 14 and polytherapy with more than two drugs in 10. 27 out of 518 drug treatments (5.2%) had to be suspended due to unacceptable adverse effects.

Table 2
Kaplan–Meier estimates of the probability of achieving a 1-year initial remission (1y.IR), a 2-year initial remission (2y.IR) and "seizure control" and of the cumulative probability of developing refractory epilepsy (Definition A). Overall sample ($n = 343$). 95% CI: 95% confidence interval.

	Years of follow-up									
	1	2	3	4	5	6	7	8	9	10
1y.IR%	50	74	83	87	91	92	93	94	95	95
(95% CI)	(45, 55)	(69, 79)	(79, 87)	(83, 91)	(88, 94)	(89, 95)	(90, 96)	(91, 97)	(92, 98)	(94, 98)
Number at risk	172	91	50	34	22	15	9	8	6	4
2y.IR%		44	64	76	81	85	87	88	89	90
(95% CI)		(39, 49)	(61, 69)	(71, 81)	(76, 86)	(81, 90)	(83, 92)	(84, 93)	(84, 94)	(86, 95)
Number at risk		192	106	60	39	26	16	15	10	8
Control%		39	55	65	70	75	78	81	83	86
(95% CI)		(34, 44)	(50, 60)	(60, 70)	(65, 75)	(70, 80)	(73, 83)	(76, 86)	(78, 88)	(80, 92)
Number at risk		209	136	91	64	45	31	22	18	10
Refractory epilepsy%		5%	–	7%	–	8%	–	11%	–	12%
(95%CI)		(3, 7)		(4, 10)		(5, 11)		(7, 15)		(7, 17)
Number at risk		325		239		197		103		64

Table 3
Response to subsequent treatment schedules. (A) Number of patients. (B) Number of patients responding to each schedule/overall sample (n = 309), % (95% CI). (C) Number of patients responding to each schedule/total number of patients treated with this schedule, % (95% CI). 1y.TR: 1-year terminal remission. 95% CI: 95% confidence interval.

		1st schedule n = 309	2nd schedule n = 85	3rd schedule n = 44	4 th schedule n = 26
A	1y.TR	188	26	10	4
	Seizure control	183	23	7	3
B	1y.TR	61% (56, 66)	8% (5, 11)	3% (2, 4)	1% (0, 3)
	Seizure control	59% (54, 65)	7% (4, 10)	2% (1, 3)	1% (0, 3)
C	1y.TR	61% (56, 66)	30% (20, 40)	23% (10, 35)	15% (6, 33)
	Seizure control	59% (54, 65)	27% (17, 36)	16% (5, 26)	12% (10, 23)

Table 4
Probability of finally achieving a 1-year terminal remission (1y.TR) and "seizure control" with subsequent treatment schedules after failing a regimen due to lack of efficacy. Calculated as number of patients responding to subsequent schedules/number of patients trying subsequent schedules. ([a]) Number of patients trying subsequent schedules. 95% CI: 95% confidence interval.

	1y.TR n (%) (95% CI)	Seizure control n (%) (95% CI)
Failure of first Schedule (n = 85)[a]	40 (47 %) (36, 58)	33 (39 %) (29, 49)
Failure of second schedule (n = 44)[a]	14 (32 %) (18, 46)	10 (23 %) (11, 35)
Failure of third Schedule (n = 26)[a]	4 (15 %) (1, 29)	3 (12 %) (3, 23)

Table 3 shows the number of patients responding to each treatment schedule (A), the proportion of patients responding to each treatment schedule in relation to total number of treated patients (B) and the proportion of patients responding to each treatment schedule in relation to the number of patients treated with this schedule (C). For example, 23 out of the 309 treated patients (7%) were controlled with the second schedule and 23 out of the 85 patients treated with a second schedule (27%) were controlled with this regimen. From another point of view, Table 4 shows the probability of response to subsequent regimens in patients failing treatment because of lack of efficacy. For example, 126 patients were not controlled with the first treatment schedule. In 85 cases there was enough time until the end of the study period to try at least one more regimen. 33 out of these 85 children (39%) were finally "controlled".

2.4. Refractory epilepsy

Table 5 shows the proportions of patients meeting the different definitions of refractory epilepsy in our study and the proportions observed in the original studies using these criteria.

The cumulative probability of meeting the Definition A of refractory epilepsy, calculated by Kaplan–Meier curves, is shown in Table 3. 16 (53%) of the patients who fulfilled criteria of refractory epilepsy did so before 24 months, 18 (60%) before 36 months and 24 (80%) before 48 months from the diagnosis. Four cases (13%) met the criteria of refractory epilepsy after a period of remission of at least 2 years. On the other hand, two patients (7%), achieved a period of remission of at least 2 years after having met the Definition A for refractory epilepsy.

Table 5
Proportion of patients meeting the different definitions of refractory epilepsy compared with proportion obtained in the original studies where these definitions were used.

Refractory epilepsy	Our study n (%)	Prior studies (reference)
Definition A	30 (8.7%)	13.8 % (4)
Definition B	30 (8.7%)	6 % (2)
Definition C	30 (8.7%)	8.4 % (1)
Definition D	83 (24.2%)	40.7 % (6)

3. Discussion

The main limitation of this study is that it is hospital-based. Nevertheless, it has been designed to obtain a sample as representative of general population as possible. In Spain, primary care pediatricians do not treat children with epilepsy. There are three hospitals in the province of Almería. Torrecárdenas Hospital is the reference hospital and it has the only EEG laboratory and pediatric neurology division in the province. Consequently, most patients in the province with epileptic seizures are cared for in Torrecárdenas Hospital. However, some patients are seen in the other two hospitals due to decision of their parents or primary care physician. In this case, difficult-to-treat patients are referred to our hospital. To avoid a selection bias, patients previously examined in other centres were excluded. There is no other institution in the province that treats patients with epilepsy. Therefore, our sample is based exclusively on direct referrals by primary care pediatricians and patients first seen at the emergency department of our hospital. In addition, features of our sample are in accordance with those found in population-based incidence cohort studies and other prospective cohort studies usually considered reasonably representative of the general population.[9–12]

Patterns of recurrence and remission of seizures in epilepsy depend on the specific policies about medication withdrawal in each centre. Usually, in discussion with parents, we propose stopping medication in patients who are seizure-free for 2 years. For this reason, we have chosen the achievement of a period of 2 years without seizures and without further relapses except those related to attempts of medication withdrawal ("seizure control"), as the main measure of patient's response to AED. Other authors have used a 1-year terminal remission: a seizure-free interval of at least one year at the end of the study period. In our study, the probability of achieving "seizure control" was only slightly lower than the probability of attaining a 1-year terminal remission. However, we consider that the variable "seizure control" gives a more precise notion of the efficacy of antiepileptic medication. For example, it is more informative to say that 72% of patients achieve a seizure-free period of 2 years and do not have more seizures or only have seizures related to attempts of medication withdrawal, than to say that 76% have been seizure-free for more than one year at the end of the study period (both results observed in our series).

The present study shows an excellent outcome in childhood epilepsy. The probability of achieving a 2-year initial remission was 81% and 90% at 5 and 10 years, respectively. Some studies,[13,14] including a large population-based one[15] and two studies dealing exclusively with children[16,17] have found similar results (probability of achieving a 2-year remission in the range of 81–90% at 5–9 years). Moreover, seizures were "controlled" in 70% of patients at 5 years and in 86% at 10 years. 60% of the overall sample and 82% of the "controlled" patients were without antiepileptic treatment at the end of the study period. In addition, 10% of our patients were not treated at all.

As expected, a previous study showed that the probability of response to subsequent therapeutic regimens after failure of a first

AED is higher if the first treatment failed because of adverse effects than if it failed due to lack of efficacy.[5] We have chosen to focus on treatment failure due to lack of efficacy.

In our study, the probability of achieving "seizure control" was 59% with the first treatment schedule, 27% with the second, 16% with the third and 12% with the fourth and subsequent (number of patients controlled with a treatment schedule/number of patients treated with this schedule). From another point of view, among patients who failed the first treatment schedule because of lack of efficacy, 39% were "controlled" with subsequent schedules. Among those who did not respond to the second schedule, 23% were finally "controlled". Among children who did not respond to the third, 12% were finally "controlled". The probability of success of subsequent treatment schedules is considerably better in our study than in the recently updated hospital-based study with adolescents and adults by Mohanraj and Brodie.[5,6] In this study, 21% of the patients in whom a first treatment schedule failed because of lack of efficacy finally achieved a 1-year terminal remission (47% in our study), 8% of the patients who did not respond to a second schedule attained a 1-year terminal remission (32% in our series) and 4% of patients in whom a third schedule failed finally entered 1-year terminal remission (15% in our sample). Our results are in line with another study in patients less than 16 years old.[2] Although this work was not specifically designed to investigate the response to sequential therapeutic regimens, the authors report that 58% of patients, who did not attain a 1-year terminal remission with the first drug used, finally did it with subsequent therapeutic schedules. Another study in children younger than 16 years old also suggested a more favourable outcome.[1] It must be noted that overall outcome is also better in our study than in the study by Mohanraj and Brodie. In the latter study only 59% of patients achieved a 1-year terminal remission compared with 76% in our study.

In our series, 8.7% of the patients met our criteria for refractory epilepsy. Definitions of refractory epilepsy vary in different studies. Those studies in children using stringent criteria, similar to those used in our study, have found refractory epilepsy in 6% to 14% of the cases.[1–4] When applying the different definitions of refractory epilepsy used in these studies, we have found the same proportion of refractory epilepsy. The different figures in these studies do not appear to be related to the criteria used but probably are due to different sample features and follow-up duration. A recent population-based study in adults using stringent criteria has shown a rate of refractory epilepsy of 16%.[18] With a broad definition (failure to reach a 1-year terminal remission), the proportion of intractable cases raises in our series to 24%. This figure is similar to that found in one of the previously cited cohort of children[19] but lower than the 41% observed in the study by Mohanraj and Brodie with adolescents and adults.[6] Another study in children with a broad definition (no 5-year remission ever during a follow-up of at least 10 years) found a rate of refractory epilepsy of 19%.[20] This latter definition was not tested in our study because a more prolonged follow-up is needed.

Nineteen per cent of our patients could not be "controlled" with antiepileptic drugs but did not fulfil our intractability criteria. This is an intermediate group that includes both patients with occasional seizures and patients with frequent seizures. A significant proportion of these patients would be labelled by other authors as refractory.

If we defined refractory epilepsy as the failure of two or more drugs with an average of more than one seizure per month for 18 months and no more than 3-months seizure free during this interval,[3] refractoriness becomes a dynamic process. In our study, the risk of having developed refractory epilepsy increased with time from 5.2% at 2 years to 12.1% at 10 years. 40% of refractory patients met the criteria for refractoriness after 3 years from diagnosis. Moreover, in 13% of the cases, intractability developed after a period of remission of at least 2 years. On the other hand, 6.6% of patients that met intractability criteria achieved thereafter a period of remission of at least 2 years. The same finding was observed in the original study using this definition[3,4] where refractory epilepsy criteria were met after 3 years in 32% of the cases and 13% of the patients who met intractability criteria were in remission when last contacted.

In conclusion, most childhood epilepsies can be controlled with AED, more than half with the first drug used. Among those patients that do not respond to the first drug, a significant proportion can still be controlled with subsequent therapeutic schedules. Only a small proportion of children develop refractory epilepsy.

Conflict of interest

None.

References

1. Camfield PR, Camfield CS, Gordon K, Dooley JM. If a first antiepileptic drug fails to control a child's epilepsy, what are the chances of success with the next drug? J Pediatr 1997;131:821–4.
2. Arts WF, Brouwer OF, Peters AC, Stroink H, Peeters EA, Schmitz P, et al. Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood. Brain 2004;127:1774–84.
3. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rappaport S, Beckerman B. Early Development of intractable epilepsy in children: a prospective study. Neurology 2001;56:1445–52.
4. Berg AT, Vickrey BG, Testa FM, Levy SR, Shinnar S, DiMario F, et al. How long does it take for epilepsy to become intractable?. A prospective investigation. Ann Neurol 2006;60:73–9.
5. Kwan P, Brodie M. Early identification of refractory epilepsy. N Eng J Med 2000;342:314–9.
6. Mohanraj R, Brodie MJ. Diagnosing refractory epilepsy: response to sequential treatment schedules. Eur J Neurol 2006;13:277–82.
7. Commission on Epidemiology and Prognosis, International League Against Epilepsy: Guidelines for Epidemiologic Studies on Epilepsy. *Epilepsia* 1993; 34: 592–596.
8. Commission on Classification and Terminology of the International League Against Epilepsy: Proposal for revised classification of epilepsies an epileptic syndromes. *Epilepsia* 1989; 30: 389–399.
9. Berg AT, Shinnar S, Levy SR, Testa FM. Newly diagnosed epilepsy in children: presentation at diagnosis. Epilepsia 1999;40:445–52.
10. Arts W, Geerts A, Brouwer F. The early prognosis of epilepsy in childhood: the prediction of a poor outcome. The Dutch Study of Epilepsy in Childhood. Epilepsia 1999;40:726–34.
11. Braathen G, Theorell K. A general hospital population of childhood epilepsy. Acta Paediatr 1995;84:1143–6.
12. Hauser WA. Seizure disorders: the changes with age. Epilepsia 1992;33(suppl. 4):S6–14.
13. Elwes RD, Johson AL, Shorvon SD, Reynolds EH. The prognosis for seizure control in newly diagnosed epilepsy. N Eng J Med 1984;311:944–7.
14. Collaborative Group for the Study of Epilepsy: Prognosis of epilepsy in newly referred patients: a multicenter prospective study of the effects of monotherapy on the long-term course of epilepsy. *Epilepsia* 1992;33:45–51.
15. Cockerell OC, Johnson AL, Sander JWAS, Shorvon SD. Prognosis of epilepsy: a review and further analysis of the first nine years of the British National General Practice Study of Epilepsy, a prospective population-based study. Epilepsia 1997;38:31–46.
16. Ramos Lizana J, Cassinello García E, Carrasco Marina LL, Vázquez López M, Martín González M, Muñoz Hoyos A. Remisión de la epilepsia tras el comienzo del tratamiento: estudio prospectivo en la infancia. Rev Neurol 2001;33: 1021–6.
17. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, Beckerman B, et al. Two-year remission and subsequent relapse in children with newly diagnosed epilepsy. Epilepsia 2001;42:1553–62.
18. Picot MC, Baldy-Moulinier M, Daures JP, Dojols P, Crespel A. The prevalence of epilepsy and pharmacoresistant epilepsy in adults: a population-based study in a Western European country. Epilepsia 2008;49:1230–8.
19. Arts WFM, Geerts AT. When to start drug treatment for childhood epilepsy: the clinical-epidemiological evidence. *European Journal of Paediatric Neurology* 2008, doi:10.1016/j.ejpn.2008.02.010.
20. Sillanpää M, Schmidt D. Natural history of treated childhood-onset epilepsy: prospective, long-term population-based study. Brain 2006;129:617–24.