Original article

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Childhood epilepsy with a small number of seizures may be left untreated: an international prospective study

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ABSTRACT – *Aims.* It is unknown whether treatment with antiepileptic drugs in children with epilepsy with a presumed good prognosis is always necessary. We aimed to study the course of newly diagnosed epilepsy in children with a presumed good prognosis who are managed without AED treatment.

Methods. A total of 151 children (one month to 12 years of age) with two to five lifetime unprovoked seizures (excluding febrile convulsions), were followed for three years. Treatment was initially withheld. Children with symptomatic epilepsy, or absence or myoclonic epilepsy, were excluded. AED treatment was started after >10 lifetime seizures or an episode of status epilepticus during follow-up, or if the parents or treating physician deemed it otherwise necessary.

Results. During follow-up, 113 children continued to meet our criteria for refraining from treatment with antiepileptic drugs, yet 30 started treatment at the request of the parents. Thirty-eight children at some time met the criteria to start treatment, but the parents of 16 declined treatment.

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In all, 99 (66%) children maintained the no-treatment regime. Ninety-eight children (65% of 151) reached terminal remission for at least one year, including 83 who did not receive antiepileptic drug treatment (84% of the untreated 99). Mean terminal remission was significantly longer in the group with a total of <10 seizures compared to those with >10 seizures. Treatment did not increase the length of terminal remission. Adverse events, including traumatic injury, occurred equally in the treated and untreated children. Measures of quality of life suggested a better outcome in those without treatment.

Conclusions. Children with newly diagnosed epilepsy with a presumed good prognosis may not need immediate AED treatment. Postponing treatment does not alter the chance of remission or the risk of accidents and adverse events and appears to be associated with a good quality of life.

Key words: childhood epilepsy, prognosis, no-treatment policy, antiepileptic drug, long-term evolution

Epilepsy can be diagnosed after two or more unprovoked seizures. Epidemiological evidence indicates that in children with a first unprovoked seizure, the risk of a second is approximately 50% (Stroink *et al.*, 1998). After a second seizure, the risk of additional seizures increases to approximately 75-85% (Camfield *et al.*, 1985; Shinnar *et al.*, 2000), justifying the diagnosis of epilepsy. Once the diagnosis of epilepsy in children has been made, it is common practice to start treatment with antiepileptic drugs (AEDs) with the exception of self-limited (benign) focal syndromes. However, only 28% of those with ≥two seizures will have more than 10 seizures during the next 10 years (Shinnar *et al.*, 2000). Moreover, prospective cohort studies of newly diagnosed childhood epilepsy have found that the outcome in selected untreated children was excellent (Camfield *et al.*, 1993; Arts *et al.*, 2004). In the Dutch study, 14% were not treated with AEDs and >90% of these were in long-term remission after 12 to 18 years of follow-up (FU) (Geerts *et al.*, 2010). These studies suggest that many children with epilepsy have only a few seizure recurrences and may not need AED treatment for what appears to be a self-limited disorder. On the basis of findings like these, it has been suggested more than 20 years ago that AEDs do not alter the prognosis of epilepsy, but instead only help to prevent seizures (Shinnar and Berg, 1996).

In the Nova Scotia (Canada) and Dutch cohort studies, the decision to start AED treatment was pragmatically taken by the treating physician and the patient's family. Combining these two cohorts allowed the development of prognostic models which predicted a good outcome (terminal remission [TR]) with a positive predictive value of about 0.7 (Geelhoed *et al.*, 2005). Variables predictive of a good outcome were idiopathic epilepsy of all types, focal epilepsy with cause unknown, a small number of seizures before initiation of AEDs, later age at onset, and absence of neurological and/or intellectual deficit. We reasoned that it might be possible at the time of diagnosis to identify children for whom a more conservative approach to starting treatment would be justified. Obviously, this approach would need to balance the risk of further seizures *versus* the advantage of avoiding AEDs with their risk of adverse events and the burden of daily medication. Several studies help to justify delaying AED treatment. First, in the Nova Scotia study, the long-term outcome did not vary with the number of pre-treatment seizures provided their number was <10 (Camfield *et al.*, 1996). Secondly, several studies support the contention that a few additional seizures do not lead to cognitive deterioration (Verity, 1998; Schouten *et al.*, 2002; Oostrom *et al.*, 2003).

The study reported here was the logical consequence of this reasoning and followed directly from the above mentioned Canadian and Dutch studies. Our hypothesis was that omitting or postponing AED treatment in children with a good prognosis at the time of diagnosis of childhood-onset epilepsy would not negatively influence epilepsy outcome, nor significantly increase the risk of accidents and adverse events or reduce quality of life (QoL).

Methods

Inclusion and exclusion criteria

This was a prospective study of 163 consecutive children with newly diagnosed epilepsy, recruited from the inpatient and outpatient departments of 11 hospitals. Patients were enrolled between 2000 and 2006 in three universities and seven general hospitals in the Netherlands and one university hospital in Canada, and followed for three years. All participating physicians were experienced paediatric epileptologists and

all had participated in the earlier studies (noted above). Patients were included if they had ≤five lifetime seizures (excluding febrile convulsions and with at least two unprovoked seizures within the 12-month period before enrolment), were between one month and 12 years of age, and had idiopathic (genetically determined) generalized or focal epilepsies or focal epilepsy with cause unknown, and no significant neurological and/or intellectual deficit. Two seizures within 24 hours with complete recovery after each seizure were considered separate events. Children with a single episode of non-febrile status epilepticus (SE) (defined as a seizure continuing for at least 30 minutes, or several seizures with a total duration of at least 30 minutes without regaining consciousness in-between the seizures; the usual definition at that time) were also included. Exclusion criteria were >five seizures before intake, symptomatic aetiology such as progressive brain or metabolic disorder, any clinical or radiological signs of brain damage, structural brain abnormalities identified with CT or MRI that could be linked to the epilepsy, or intellectual disability (clinically defined as IQ <70). The following epilepsy syndromes were also excluded: any absence or myoclonic epilepsy and the syndromes of Ohtahara, West, Lennox-Gastaut, Doose, Dravet, and Landau-Kleffner/CSWS. Other reasons for exclusion included: a history of neonatal convulsions, treatment with an AED in the past except for treatment of non-epileptic disease, ongoing treatment with an AED for a non-epileptic disorder, an ongoing disease that might have influenced the outcome measures, acute symptomatic aetiology (except for a history of febrile convulsions), or children or caregivers not able to comply with the study protocol or not able to understand its essential features.

Treatment strategies

The primary intention was not to start AED treatment until the end of FU unless there was an episode of SE or a tenth lifetime unprovoked seizure. AED treatment could also be initiated at the request of the child, parents/caregivers or attending physician for any reason (*e.g.* fear of further seizures, unacceptable number or severity of seizures, accident due to a seizure, or other concerns).

When treatment was initiated, monotherapy with one of the first-line drugs was used (target dosages: carbamazepine at 10-15 mg/kg, clobazam at 0.3-0.5 mg/kg, lamotrigine at 4-6 mg/kg, and valproate at 20-30 mg/kg). An AED was introduced over four weeks except for lamotrigine, which was introduced at a slower rate. Treatment was individualized with the expectation that it would be tapered and discontinued after one to two years of seizure freedom.

Evaluation

The following baseline variables were gathered for all participating children: gender, age, body weight, number of seizures and the dates of occurrence, date of diagnosis, and EEG and imaging results. EEG results (available for analysis for 148 out of the 151 children) were classified as normal (including mild abnormalities), a more than mildly abnormal background pattern, epileptic or epileptiform abnormalities (generalized, focal, unclassifiable, specific epilepsy syndrome), or other non-epileptiform abnormalities. After complete evaluation (including MRI or -if not possible- CT), seizure type, aetiology, and epilepsy syndrome were classified by the treating physician and reviewed by the first two authors, both at entry to the study and after three years of FU.

Children were prospectively followed in the outpatient departments for three years from the date of diagnosis at 3, 6, 12, 18, 24, 30, and 36 months. At each visit, the treating physician documented the interim history and completed both the physical examination and a questionnaire regarding seizures, medication (of any type and for any indication), and adverse events. The child and parent/caregiver completed questionnaires about symptoms and adverse events (each visit), seizure severity (0, 6, 18, 36-month visits), and QoL (0, 6, 18, 36-month visits). For the parental and child questionnaires, we used the modified Hague scale for symptoms and side effects (SSS) (Carpay *et al*., 1996; Geerts *et al*., 2010) and the Impact of Paediatric Epilepsy Scale (IPES) (Camfield *et al*., 2001). The SSS was used to examine the presence (mild, moderate or serious) or absence of 27 complaints that had occurred during the course of the epilepsy, whether caused by the epilepsy itself or by the treatment (*supplementary table 1*). The IPES contains a visual analogue scale (Likert Scale) of QoL ranging from 1 (poor) to 6 (excellent) and 11 questions that assess the impact of epilepsy on academic achievement, participation in activities, health, relationship with family and with peers and siblings, social activities, self-esteem, the relation between the parents, social life, and parental hopes for their child's future.

If AED treatment was started, the reason for abandoning the no-treatment policy was recorded. After three years of FU, the physician re-evaluated the classification of the aetiology and of the epilepsy syndrome and verified whether the child was, was not, or had been receiving AED treatment.

Definitions

Adverse events (AEs) were defined as any undesirable experience including accidents or diseases occurring to the child during the study period, whether or not

considered related to the current treatment policy. All AEs reported spontaneously by the child or the parents or observed by the treating physician were recorded on an AE data collection form. The intensity of these AEs was graded by the physician on a four-point scale defined as: mild (discomfort noticed but no disruption of normal daily activity), moderate (discomfort sufficient to reduce or affect normal daily activity), severe (inability to perform daily activities), or serious (SAE: any adverse event that was fatal, life-threatening, disabling, or required in-patient hospitalization, prolonging of hospitalization, or caused a malignancy). SAEs were immediately reported to the study coordinator and to the local Ethics Review Board. For each AE, the relationship to treatment policy (definite, probable, possible, unknown, definitely not), as judged by the treating physician as well as the actions taken, were recorded.

TR was defined as the interval between the last seizure and the end of FU.

Outcome measures

The main outcome measure was the proportion of untreated children after three years of FU. The TR at the end of FU was also determined as well as the number of untreated children who had a TR of at least 12 months, and the number of seizures during FU.

In the treated group, the delay between study entry and the initiation of treatment, the reason to start treatment, and the TR after three years were recorded. To establish better predictability for the no-treatment option, the untreated and the treated groups were compared to identify differences in the collected intake and early FU variables.

Analyses at the end of the three-year FU were also intended to reveal possible unfavourable consequences in the no-treatment group. To this end, we analysed the differences between the treated and untreated groups in terms of number of seizures experienced during the FU and after the start of AEDs, as well as accidents and adverse events, the -possibly drug-related- complaints, and QoL, as described above.

Statistical analyses

Data were analysed using SPSS Version 20 software. A Kaplan-Meier survival curve of the proportion of children left untreated was constructed from baseline to 36 months. Univariate and multivariate analyses of the differences between the untreated and treated groups at baseline and after six months of FU were performed. The differences in outcome (TR) between the treated and untreated groups were analysed with Analysis of Variance (ANOVA) statistics.

To test for differences between groups regarding the number of seizures before intake, the non-parametric Mann-Whitney U test was used. The Pearson Chi-Square test or Fisher's Exact test were used to test for differences when categorical variables were evaluated.

The analysis of the Impact of Paediatric Epilepsy Scale (IPES) and the QoL visual analogue scale included the General Linear Model (GLM) Repeated Measures analysis, allowing both between-subjects and within-subject analysis of repeatedly measured variables at intake and the 6, 12, 18 and 36-month FU visits. For missing values, imputation using means was applied if subjects had completed the scales at least three times. A significance level of 0.05 was used for all statistical tests.

Ethical approval

Ethical approval for this study was obtained from the ethics review boards of all participating hospitals. At intake, the parents or caretakers of all participating children signed a detailed informed consent form.

Results

Description of the cohort

Five of the 163 recruited children began medication at the request of their parents within 1-4 days after the diagnosis of epilepsy and therefore were not considered to have remained untreated. They were not followed further. Seven children were followed for <three years; two of these started medication after their tenth seizure and five had <10 seizures and had not started an AED at the time of last contact. The mean FU period for these seven children was 1.9 years (median: 2.0; range: 1.15-2.86). Consequently, 151 remained initially untreated, completed the three-year FU, and were available for analysis. The baseline demographic characteristics and the epilepsy classifications at intake and after three years of FU for these 151 children are presented in *table 1* ; characteristics of the initial seizures before diagnosis are presented in *table 2*.

After three years, the classification of the epilepsy changed in 44 children (29%) (*table 1*). The cohort contained three major groups of epilepsy syndromes: self-limited focal epilepsies (*n*=28 at intake, 35 after reclassification after three years of FU), focal epilepsy with cause unknown (45 at intake, 39 after three years), and genetic generalized epilepsy with tonic-clonic seizures (TCS) only (54 at intake, 44 after three years). At intake, 25, and after three years 24 children could

Table 1. Characteristics of the 151 children at intake and after three years of follow-up (*n* [%]).

	Entire cohort	**Group A Treatment according to protocol**	**Group B Treatment before 10th seizure**	**Group C No treatment despite >10 seizures**	**Group D No treatment according to protocol**	***p***
Total number	151	22	30	16	83	
Boys	87 (58) *p*=0.073	13 (59)	14 (47)	11 (69)	49 (59)	*p*=0.499
Age at intake (years)	Mean: 6.7 (0.4-13.1)	Mean: 6.7 (0.5-11.9)	Mean: 7.3 (0.4-13.1)	Mean: 7.04 (0.9-12.8)	Mean: 6.4 (0.4-13.0)	*p*=0.679
Number of seizures before enrolment						
2	69 (46)	7 (32)	*19 (63)*	4 (25)	39 (47)	*p=0.043**
3	49 (33)	8 (36)	6 (20)	*7 (44)*	28 (34)	
4	21 (14)	3 (14)	4 (13)	*3 (19)*	11 (13)	
5	12 (8)	*4 (18)*	1 (3)	2 (13)	5 (6)	
History of febrile convulsions	31 (21)	6 (27)	6 (20)	4 (25)	15 (18)	*p*=0.772
Positive family history for epilepsy 1st degree (*n*=148)	21 (14)	6 (30)	4 (13)	2 (13)	9 (11)	*p*=0.180
EEG (*n*=148)						
- Normal	57 (39)	8 (36)	6 (21)	4 (27)	39 (48)	*p*=0.054 (abnormal/normal)
- Abnormal	91 (62)	14 (64)	23 (79)	11 (73)	43 (52)	
- More than mildly abnormal background pattern or other non-epileptic abnormalities	13 (9)	1 (5)	5 (17)	1 (7)	6 (7)	*p*=0.129 (normal/epileptic/ other abnormalities)
- Epileptic +/- other abnormalities	78 (53)	13 (59)	18 (62)	10 (67)	37 (45)	
→ Generalized	14 (18)	2 (14)	*7 (39)*	0 (0)	5 (12)	*p=0.009**
→ Localization related	60 (77)	11 (85)	*9 (50)*	8 (80)	32 (87)	
→ Unknown	4 (5)	0	2 (11)	2 (20)	0 (0)	
Classification of the epilepsy at intake						
- Self-limited focal epilepsies	28 (19)	6 (27)	3 (10)	6 (38)	13 (16)	
- Focal epilepsy, cause unknown	45 (30)	5 (23)	10 (33)	4 (25)	26 (31)	***p*=0.916
- Idiopathic generalized epilepsies with TCS only	53 (35)	7 (32)	12 (40)	5 (31)	29 (35)	
- Epilepsies without generalized or focal features	25 (17)	4 (18)	(17)	1 (6)	15 (18)	

Table 1. Characteristics of the 151 children at intake and after three years of follow-up (*n* [%]) *(continued)*.

	Entire cohort	Group A Treatment according to protocol	Group B Treatment before 10th seizure	Group C No treatment despite >10 seizures	Group D No treatment according to protocol	>*p*
Classification of the epilepsy after 3 years:						
- Self-limited focal epilepsies	35 (23)	7 (32)	4 (13)	7 (44)	17 (20)	
- Focal epilepsy, cause unknown	39 (26)	5 (23)	8 (27)	3 (19)	23 (28)	
- Idiopathic generalized epilepsies with TCS only	44 (28)	4 (18)	14 (47)	3 (19)	23 (28)	
- Benign myoclonic epilepsy of infancy	1 (1)	0	0	0	1 (1)	**p=0119
- Juvenile myoclonic epilepsy	1 (1)	1 (5)	0	0	0	
- Epilepsy with myoclonic-astatic seizures	1 (1)	1 (5)	0	0	0	
- Symptomatic focal epilepsies	4 (3)	1 (5)	3 (10)	0	0	
- Epilepsies without generalized or focal features	24 (16)	3 (14)	1 (3)	2 (13)	18 (22)	
- No epilepsy	3 (2)	0	0	1 (6)	2 (2)	

*p is based on a non-parametric test; **p is based on the contingency coefficient.
TCS: tonic-clonic seizures

Table 2. Characteristics of seizures before intake.

	1st seizure	2nd seizure	3rd seizure	4th seizure	5th seizure
No. of children	151	151	85 (56%)	38 (25%)	12 (8%)
Last seizure before intake		16 (11%)	35 (23%)	26 (17%)	12 (8%)
Time of day					
During sleep	48 (33%)	46 (32%)	27 (33%)	9 (27%)	3 (25%)
On awakening	30 (21%)	32 (23%)	14 (17%)	5 (15%)	0
While awake	66 (46%)	64 (45%)	41 (50%)	20 (59%)	9 (75%)
Data not available	7	9	3	4	0
Type of seizure					
Focal with intact awareness	12 (8%)	12 (8%)	7 (9%)	6 (16%)	3 (25%)
Focal with impaired awareness	21 (15%)	22 (15%)	14 (18%)	5 (14%)	3 (25%)
Focal to bilateral tonic-clonic	25 (17%)	25 (17%)	11 (14%)	4 (11%)	0
Generalized tonic-clonic	83 (57%)	85 (57%)	45 (57%)	21 (57%)	6 (50%)
Atonic	2 (1%)	3 (2%)	1 (1%)	0	0
Unclassified	2 (1%)	2 (1%)	1 (1%)	1 (3%)	0
Data not available	6	2	6	1	0

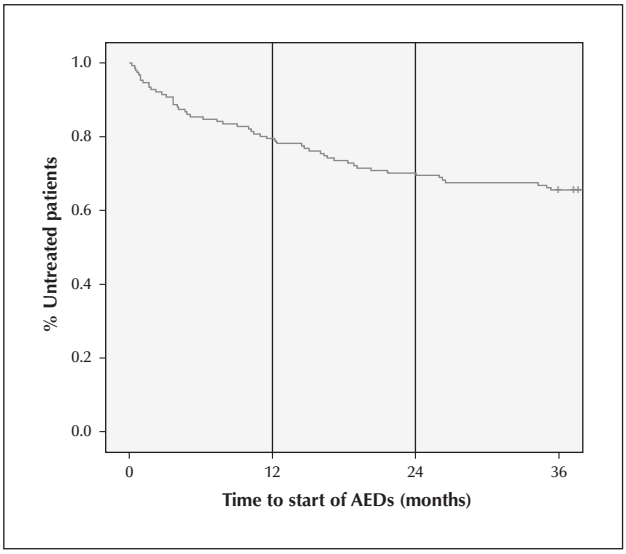

Figure 1. Kaplan-Meier survival curve of the cumulative proportion of children remaining without AED treatment during follow-up (*n*=151).

not be classified because of a lack of specific generalized or focal features. In seven children (4.0%), the initial epilepsy type or syndrome diagnosis was revised in such a way that they would have met the exclusion criteria, if the correct diagnosis would have been made at intake (benign myoclonic epilepsy of infancy in one, juvenile myoclonic epilepsy in one, a change from cause unknown to symptomatic epilepsy in five [one with Lennox-Gastaut syndrome, one proven and one probable Dravet syndrome, one undetermined but with the development of intellectual disability during FU, and one symptomatic focal epilepsy -a child with initially undiscovered cortical dysplasia]). In three patients, the diagnosis of epilepsy was rejected (they had either reflex syncope or cardiovascular syncope). Data for these ten children were retained in the analysis according to the "intention to treat" principle. Thirty-one children had had convulsions associated with a febrile illness before enrolment. Six of them also had febrile seizures during FU. Additionally, 10 children without febrile convulsions before intake had seizures with fever during FU.

Treatment initiation

All 151 children were initially left untreated with AEDs and followed prospectively. The number of untreated children during FU is presented in *figure 1* as a Kaplan-Meier survival curve. At one year after enrolment, the cumulative proportion remaining off medication was 79.5% (95% CI: 73.0-86.0), at two years 70.2% (95% CI: 62.9-77.5), and at three years 65.6% (95% CI: 58.0-73.2).

Fifty-two children started AED treatment (25 with valproic acid, 23 with carbamazepine, two with lamotrigine, and two with clobazam) after study entry; 37 children remained on monotherapy and 15 used multiple AEDs. Reasons for starting AEDs during FU were the occurrence of ≥10 seizures (*n*=20), SE (*n*=2), or a parental request to start medication earlier than the tenth seizure because of fear of additional seizures or increasing severity of the seizures (*n*=30) (*figure 2*). The mean interval between enrolment and start of medication in these 52 children was 338 days (median: 291; range: 7-1076). The period of time corresponding to AED treatment delay did not differ between children with focal epilepsy, generalized epilepsy with TCS only, or epilepsy with focal and generalized seizures combined (p=0.56), and was not related to the number of seizures prior to enrolment (on the basis of the inclusion criteria, this could vary between 2 and 5; p=0.973). Four groups emerged: Group A (*n*=22) consisted of children treated with AEDs according to the protocol (after ≥10 seizures or an episode of SE); Group B (*n*=30) of children treated before a tenth seizure; Group C (*n*=16) of children continuing without AED treatment despite ≥10 seizures; Group D (*n*=83) of children completing three years of FU without AED treatment according to the protocol. In summary, 97 children (64.2%) had <10 seizures between epilepsy onset and the end of FU. The strategy of not starting AED treatment was achieved in 83 of these 97 (85.6%) children. Fifty-four children had ≥10 seizures of whom 16 (29.6%) continued without AED treatment upon parental request (Group C) (*figure 2*).
Table 1 also shows the characteristics of these four groups at the time of initial diagnosis. Only a few significant differences were noted. Children who ultimately experienced ≥10 seizures (Groups A and C) were more likely to have had four or five seizures before intake (p=0.043). Group D was less likely to have an abnormal EEG than the other three groups (p=0.054), and Group B was more likely to show generalized spike-wave discharges while the other three groups had predominantly focal abnormalities (p=0.009).

Terminal remission and number of seizures

Thirty-six (23.8%) children had no further seizures during the entire FU and another 36 (23.8%) had their last seizure within the first year after intake.
Ninety-eight children (64.9%) reached a TR of ≥one year, 83 of them (54.3%) without AED treatment at 36 months (73 from Group D, four from Group C, and six from Groups A and B together; in the latter six, the AEDs had already been withdrawn). *Figure 3A* shows the cumulative proportion of children attaining TR for at least one year. The mean period of TR at the end of

three years of FU was 1.7 years (95% CI: 1.5-1.9; median: 1.9; range: 0.0-3.0). However, the four groups differed significantly. Those with ≥10 seizures or SE (Group A, treated and Group C, untreated) had the shortest TR and Group D (untreated according to protocol) had the longest period of remission ($p<0.001$) (*table 3*).

The cumulative probability of reaching one-year TR for the four groups is presented *figure 3B*.

The duration of TR was not significantly different between the three major syndrome groups (self-limited focal, focal with cause unknown, and genetic with TCS only) (*table 1*).

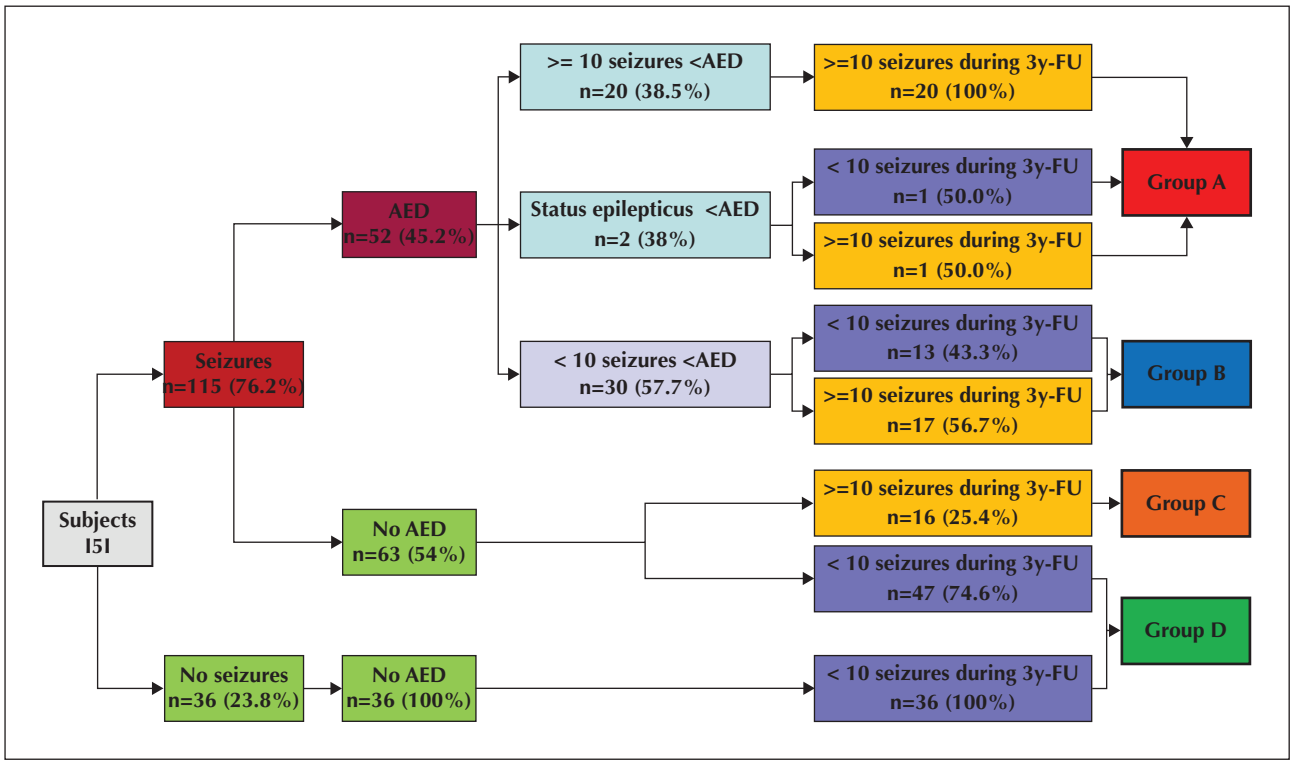

Figure 2. Flow diagram of the 151 children from intake until the end of FU.

Table 3. Number of children with terminal remission (TR) of >one year and mean length of TR after three years of follow-up.

	Total	TR ≥1 yr N (%)	Mean TR 95% CI (years)
Group A: >10 seizures and treated (according to protocol)	22	5 (23)	0.65 0.36 - 0.95
Group B: treated before 10th seizure	30	16 (53)	1.35 0.92 - 1.77
Group C: not treated despite >10 seizures	16	4 (25)	0.66 0.24 - 1.08
Group D: <10 seizures and not treated (according to protocol)	83	73 (88)	2.31 2.12 - 2.51
Total	151	98 (65)	1.71 1.52 - 1.89

For number of children with TR >1 year: $p=0.000$.
For mean length of TR: $p<0.00$.

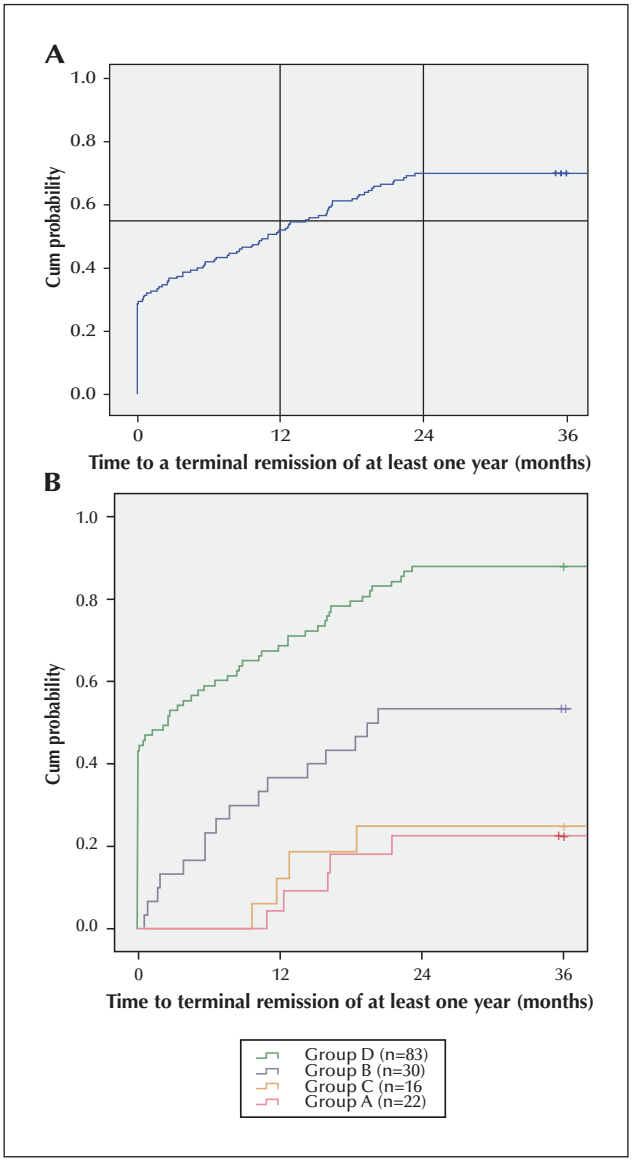

Figure 3. (A) Kaplan-Meier survival curve of the cumulative proportion of children reaching one-year terminal remission at three years (*n*=151). (B) Kaplan-Meier survival curve of the cumulative proportion of the children in each of the four groups reaching terminal remission of at least one year. Group A (≥10 seizures, treatment according to protocol), Group B (<10 seizures, earlier treatment on request), Group C (≥10 seizures, request to continue the no-treatment policy), Group D (<10 seizures, no treatment according to protocol) (Test of Equality of survival distributions: Log Rank [Mantel-Cox] 57.12, df=3; $p<0.0001$).

Most children had a limited number of seizures, with a notable exception in the treated groups in which the proportion of children with >15 seizures was clearly higher than the proportion with a smaller number (*supplementary figure 1*). This is only partly explained by the fact that these groups contained the five children in whom the original epilepsy syndrome diagnosis had been incorrect and was modified to a type of symptomatic focal or generalized epilepsy.

Accidents, injuries, and other adverse events (AEs)

Before enrolment, 20 children (13.2%) had experienced ≥one complication, accident or injury as a result of a seizure. Nineteen of the 23 reports (83%) concerned head injuries. The intensity was reported as mild (*n*=12), moderate (*n*=5), and severe (*n*=2; one cerebral concussion and one hospitalization).

During FU, 58 children reported a total of 91 AEs of all kinds. Thirteen (in 10 children) were classified as SAEs (*table 4A*). All SAEs involved hospitalizations. Three were seizure-related; one was already treated with an AED at the time of the SAE, one was hospitalized because of postictal drowsiness, and another because of SE (both started AEDs on the day of the hospitalization). Seven additional children were hospitalized for disorders unrelated to epilepsy. No deaths occurred.

More specifically, accidents and injuries were reported 56 times by 37 children (*table 4B*). One was classified as an SAE, but it was unclear in this case whether this accident (a fall with serious head trauma) was due to a seizure. Eight were considered to be severe, 13 moderate, and 34 mild. Twenty-three accidents (41.1%) were considered to be seizure-related; in two, the cause was unclear. Of note, 12 of the 23 children with a seizure-related accident were at the time not receiving AED treatment.

Non-accidental AEs were reported 35 times by 25 children. Only two of these were seizure-related. An association with AED treatment at the time of the AE was also not identified; 24 were reported while the child was not receiving AEDs, two during AED treatment, and for nine, the treatment status at the time of the incident was unclear.

Symptoms, impact of epilepsy, and quality of life

As noted in the methods, at each visit, the families completed a check list of neurological and general symptoms. This check list did not attempt to relate symptoms to seizures or AED treatment. Therefore, we analysed the number of symptoms noted at each visit, subtracting the number of symptoms at baseline. The mean number of symptoms compared to baseline did not vary significantly between the four groups ($p=0.101$), throughout the clinical course ($p=0.101$), or between the groups receiving one of the four AEDs mentioned in the protocol.

The IPES includes one single question for assessing global QoL. Parents were asked to rate the QoL of their child on a Likert scale from 1 (poor) to 6 (excellent). We compared this global measure at intake and at the six,

Table 4A. Serious adverse events leading to hospitalization (*n*=13).

Nature of SAE	AED treatment at time of SAE
2x hospitalization because of serious immunodeficiency and cytomegalovirus infection	No
3x hospitalization: first for tonsillectomy and ear drums, then because of pharyngitis with dehydration, and seven months later because of a generalized infection with mycoplasma pneumonia	No
Streptococcal tonsillitis	No
Tonsillectomy	Unknown
Tonsillectomy	No
Gastro-enteritis with dehydration	No
Acute psychotic episode	No
Fall while at school, seizure uncertain	Yes
Status epilepticus	No
Long-lasting postictal drowsiness	Unknown

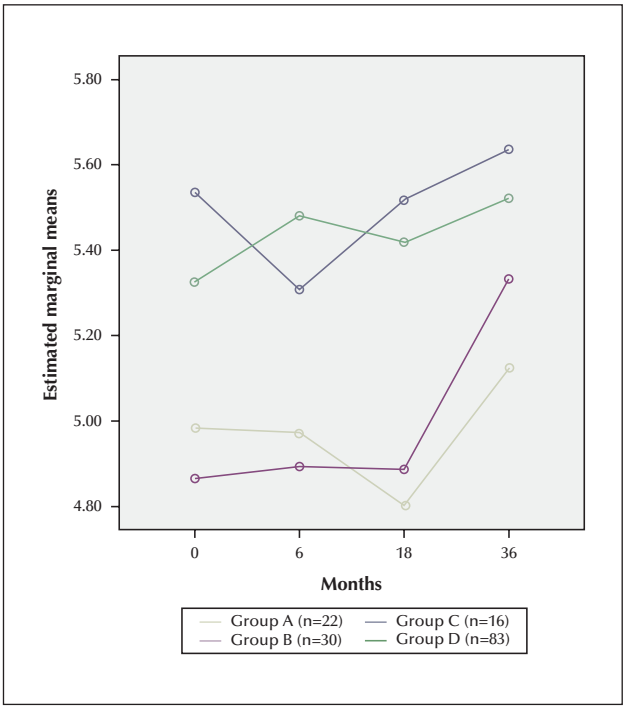

Figure 4. Development of QoL scores as measured with the IPES for the four groups of children during follow-up.

18, and 36-month visits. The between-subjects analysis revealed a significant difference between the groups, and the groups without AED treatment had a better Likert Scale QoL (p=0.006) (*figure 4*). These findings were largely confirmed by analysis of the answers to the other 11 questions of the IPES. For eight of the questions, there were significant differences between the groups, most often with a markedly higher score for the two groups without medication.

Discussion

It is common practice to withhold AED treatment in children with a single unprovoked seizure. We are of the impression that an increasing number of clinicians refrain from treatment in children with only a few solitary seizures, notably in self-limited epilepsy with centrotemporal spikes and other syndromes with

Table 4B. Types of accidents/injuries during follow-up (the last column corresponds to the number of seizure-related injuries occurring when the child was not treated).

	Total	Severe	Seizure-related	Untreated at time of injury
Soft tissue injuries	26	0	14	7/14
Laceration	3	0	1	0/1
Dental injury	1	0	1	1/1
Head injury	18	2	5 + 1 unknown	4/6
Any other fracture	7	6	0	
Fall in water	1	0	1 unknown	0/1
Total	56	8	21 + 2 unknown	12/23

a known good outcome. Until now, the evidence to justify this approach has been limited. The only study known to the present authors in which immediate and delayed treatment have been compared is the MESS study (Marson *et al*., 2005). In this study, both adult- and childhood-onset patients were followed, and the authors did not distinguish between patients with one solitary seizure or multiple seizures. In the present study, we have systematically and prospectively examined a no-treatment approach in a selected group of children newly diagnosed with epilepsy with characteristics strongly suggesting a self-limited course.

General cohort

The no-treatment strategy was successful in 83 out of 151 children (Group D; 55.0%) in the sense that they did not start AED treatment and had <10 seizures and no episodes of SE during the three years of FU. Nearly all children in this group had at least one year of TR -a self-limited course without AED treatment. The clinical course of the remainder of the cohort was more complex with some families choosing AED treatment after <10 seizures and others having >10 seizures but choosing to continue without treatment.

In the overall cohort, almost two thirds of the children were seizure-free in the last year of FU (TR ≥one year: 64.9%). This is comparable with other outcome studies, but might have been higher after longer FU, as the natural course of childhood epilepsy may require more than two years to reach seizure freedom. In addition, many of the children without remission during the third year of FU had only rare seizures with long inter-seizure intervals (data not shown). Based on this data in children fulfilling our entry criteria, postponement of AED treatment seems to be justified. On the other hand, the outcome prediction based on our entry criteria was far from perfect since 38 children had >10 seizures and 10 had >20. Therefore, to be certain that a strategy of omitting or postponing AED therapy was justified on the basis of the selection criteria used in this study (in our opinion the best we have at the moment), we also needed to demonstrate that postponement of treatment did not harm our patients.

No treatment *vs.* treatment

The patients in Group D had, by definition, <10 seizures from the onset of their epilepsy until the end of FU, and those in Groups A and C had ≥10 seizures or an episode of SE. Overall, the children with ≥10 seizures, whether treated or untreated, were less likely to have substantial TR. Even though this confirms earlier findings by Camfield *et al*. (1996), our results also suggest that the natural course of the epilepsy, but not AED treatment, determines the seizure outcome, at least in this relatively small cohort with its specific entry criteria. This tends to confirm the contention that AED medications do not alter the chance of remission -they are anti-seizure and not antiepileptic medications. Reassuringly, we found that the time to onset of ≥one-year TR was the same in Groups A and C. Both groups had ≥10 seizures but Group A was then treated with AEDs and Group C continued without treatment (*figure 3B*). In these children also, AED treatment did not seem to influence the chance or timing of TR. We conclude that from a seizure remission perspective, our avoidance or delay in AED treatment was not harmful. These findings are comparable with those of the MESS study (Marson *et al*., 2005), in which the long-term outcome of groups with immediate and deferred treatment was largely equal.

Is delay of treatment detrimental?

Beyond seizure recurrence, we were concerned that a no AED or delayed AED treatment approach might lead to more injuries from seizures. About two thirds of reported injuries were not related to seizures. Of the seizure-related injuries, about one half occurred in untreated patients. It is possible that AED treatment might have prevented a few of these injuries. Fortunately, none of the "serious accidents" were definitely related to a seizure.

Complaints other than accidents and injuries could have been caused both by continuing seizures as well as side effects of the AEDs. Our analyses show that there was no clear pattern or trend in the number of symptoms when compared to baseline throughout the eight visits of the study. Surprisingly, we did not find an increase in complaints from children on AED treatment, despite the fact that we used a pre-formatted questionnaire to detect side effects at each visit to the outpatient clinic.

Somewhat in contrast with this, parents considered the general QoL of their children to be better when they were not treated with AEDs, and this did not change during FU. Possible explanations are the absence of AED-related side effects and, perhaps more likely, the smaller number of seizures that most of these children had. We conclude that whichever treatment strategy was followed, the FU did not reveal any improvement or deterioration in injuries, complaints, or QoL that could be related to the treatment strategy.

A final issue to be considered with either no or delayed treatment is the risk of SUDEP. There were no deaths in this three-year cohort study. Parental and physician concerns about SUDEP are vital in the decision to start or delay AED treatment. Fortunately, a combined study of four large population-based cohorts (*n*=2,239) found

that seizure-related death or SUDEP was exceedingly rare in childhood-onset epilepsy (Berg *et al*., 2013). In "uncomplicated" childhood epilepsy, the overall risk of death was the same as in the general population. In a long-term study from Finland, there were no deaths within five years of epilepsy onset and none under 14 years of age in the idiopathic and cryptogenic epilepsy groups (Sillanpää and Shinnar, 2010). Therefore, our findings are reassuringly consistent with the extremely low risk of SUDEP in the childhood-onset epilepsy types that we studied.

Limitations of this study

Our study has some limitations. First of all, this was not a randomized controlled study. When we began this study, it was designed to be randomized with entry and exclusion criteria, as mentioned in the Methods section. We had intended to compare the outcomes of initially untreated children with those of children treated from the moment of diagnosis. This plan failed because after reading the information leaflet and hearing the explanation from the treating physician, almost all parents refused to consent to randomization and preferred the no-treatment option. After recruiting only 40 children over several years, we concluded that a randomized trial was simply not feasible, thus our project became a prospective FU cohort study. The lack of randomization may have introduced some bias in decisions taken during the FU and interpretation of the results. Secondly, our sample size may have been too small to detect small effects of the no-treatment strategy, in particular, the very small risk of SUDEP in self-limited childhood epilepsies (as noted above).

Many families chose not to follow the protocol and to start AEDs before 10 seizures or to continue without AED treatment despite ≥10 seizures. Apparently, there are strong parental opinions about the benefits and risks of drugs in countries such as Canada and The Netherlands. In Group B (treated before 10 seizures), there were more patients with generalized epilepsy with generalized tonic-clonic seizures only, with a predominance of generalized spike waves on initial interictal EEG. The perceived impact of generalized seizures on the children and their parents may have stimulated this group to ask for AED treatment before 10 seizures. The strategy of delayed AED treatment is apparently more palatable to families with children with other types of seizures.

A further limitation was that reports by the children themselves or information on their behaviour and school performance were not systematically collected during this study and QoL was not extensively assessed. However, we had the impression that QoL was better in children who did not use AEDs, and deterioration of behaviour or school performance was not reported by any parent. It is uncertain whether this is the result of the no-treatment policy. Alternatively, children with a better QoL may have been more likely to remain untreated (as noted above).

Finally, the duration of FU was limited to three years. The possibility of long-term remission after longer FU could not be excluded in children with TR of <one year. Therefore, we presume that an increased duration of FU would have strengthened our results.

The FU of the cohort described here was concluded in 2009. Unforeseen circumstances delayed the publication of the results. However, we believe that the results remain important and confirm earlier findings indicating that treatment at the time of initial diagnosis of childhood epilepsy, with a high likelihood of a self-limited course, may be safely omitted or at least postponed. To our knowledge, a similar study has not been performed elsewhere. Since 2009, several newer AEDs have become available that may have fewer side effects than those on the market when we started our study. It is conceivable that this might have altered parents' interest in a no-treatment strategy.

General conclusions

Based on this study, we believe there is a group of children with newly diagnosed epilepsy in whom AED treatment can be safely withheld without risk of a negative impact on the epilepsy itself or QoL of the children. Our findings indicate that in this "epilepsy-only" group of patients predicted to have a self-limited course, the chance of remission is, apparently, not determined by AED treatment. However, current knowledge does not enable us to identify these children at intake with absolute certainty. Therefore, careful monitoring of untreated children remains necessary. □

Supplementary data.
Supplementary table and figure are available on the www.epilepticdisorders.com website.

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