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Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood

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Summary

Knowing the prognosis of epilepsy will undoubtedly influence the treatment strategy. This study aimed to define the prospects of newly diagnosed childhood epilepsy, assess the dynamics of its course, identify relevant variables and develop models to assess the individual prognosis. Four hundred and fifty-three children with newly diagnosed epilepsy were followed for 5 years. Terminal remission at 5 years (TR5) was compared with terminal remission at 2 years (TR2) and with the longest remission during follow-up. Variables defined at intake and at 6 months of follow-up were analysed for their prognostic relevance. In multivariate analyses, combinations of variables were tested to develop reliable models for the calculation of the individual prognosis. Data on treatment, course during follow-up and epilepsy syndromes were also studied. Three hundred and forty-five children (76%) had a TR5 >1 year, 290 (64%) >2 years and 65 (14%) had not had any seizure during the entire follow-up. Out of 108 children (24%) with TR5 <1 year, 27 were actually intractable at 5 years. Medication was started in 388 children (86%). In 227 of these (59%), anti-epileptic drugs (AEDs) could be withdrawn. A TR5 >1 year was attained by 46% on one AED, on the second AED by 19%, and by 9% on all additional AED regimes. Almost 60% of the children treated with a second or additional AED regime had a TR5 >1 year. Variables predicting the outcome at intake were aetiology, history of febrile seizures and age. For intake and 6-month variables combined, sex, aetiology, postictal signs, history of febrile seizures and TR at 6 months were significant. The model derived from intake variables only predicted TR5 <1 year correctly in 36% and TR5 >1 year in 85% (sensitivity 0.65, specificity 0.64). The corresponding values for the model derived from intake and 6-month variables were 43 and 88% (sensitivity 0.69, specificity 0.71). The course of the epilepsy was constantly favourable in 51%, steadily poor in 17%, improving in 25% and deteriorating in 6%. Intractability was in part only a temporary phenomenon. The outcome at 5 years in this cohort of children with newly diagnosed epilepsy was favourable in 76%; 64% were off medication at that time. Almost a third of the children had a fluctuating course; improvement was clearly more common than deterioration. After failure of the first AED, treatment can still be successful. Models predicting the outcome have fewer misclassifications when predicting a long terminal remission than when predicting continuing seizures.

Keywords: epilepsy; childhood; prognosis; treatment; course

Abbreviations: AED = anti-epileptic drug; CI = confidence interval; DSEC = Dutch Study of Epilepsy in Childhood; LR = longest remission during a defined period of follow-up; OR = odds ratio; RC = regression coefficient; ROC = receiver operant characteristic; TR = length of terminal remission existing at moment of evaluation; TR2 = terminal remission existing at 2 years; TR5 = terminal remission existing at 5 years.

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Introduction

The prognosis of childhood epilepsy has important epidemiological and clinical implications. Assessment of the risk profile of an individual patient may be used to tailor the treatment strategy. Not initiating anti-epileptic drug (AED) treatment after a first unprovoked seizure is now an evidence-based established practice (Hirtz *et al*., 2003). Conversely, decisions whether and, if so, when to start treatment in children with epilepsy are not based on firm clinical evidence since trials comparing different treatment strategies are lacking. Randomized studies to explore the way in which AEDs influence the natural course of epilepsy are usually considered unethical. The only exception so far is the Multicentre Study of Early Epilepsy and Single Seizures (MESS) trial, conducted in the UK, of which results will be available shortly. Although in recent years the opinion that AEDs only suppress seizures and have no influence on the course of the disease (Shinnar and Berg, 1996) has gained momentum, some authors have maintained that early vigorous treatment is essential to prevent intractability (Reynolds *et al*., 1983). The possibility of a self-perpetuating mechanism of untreated epileptic seizures (Gowers, 1881; Reynolds *et al*., 1983; opposed by van Donselaar *et al*., 1997) is in contrast with the results of large cohort studies indicating that about 60% of children with newly diagnosed epilepsy have a good prognosis (Camfield *et al*., 1993; Sillanpää *et al*., 1998). To resolve the controversy, it remains essential to gather entirely, prospective follow-up data in large cohorts of patients of all ages with different types of epilepsy, look for evidence adding to the already available knowledge, and develop instruments to assess the prognosis of an individual patient. This might ultimately provide a sound medical and ethical basis for trials addressing the issue more directly.

The Dutch Study of Epilepsy in Childhood (DSEC) provides some of the answers needed. We prospectively studied a cohort of children with newly diagnosed epilepsy, determined their outcomes, and identified factors associated with good and poor seizure outcomes. We also studied the dynamics of the course of the epilepsy and addressed the question of when and how to define intractability. Another goal was to identify children with newly diagnosed epilepsy who might benefit from immediate and vigorous treatment because of their poor prognosis, or in whom treatment could possibly be withheld or at least postponed because of the inherently favourable prognosis. In this paper, we present the data of the 5-year follow-up of the cohort, following up on our analysis of the 2-year outcome (Arts *et al*., 1999).

Methods

Composition of the cohort

The design of the study and the results of the 2-year follow-up have been described previously (Arts *et al*., 1999). A hospital-based cohort (n = 466) of children aged 1 month to 15 years with newly diagnosed epilepsy (defined as two or more unprovoked seizures within a 1-year period) was recruited after informed consent of the parents. Four Dutch hospitals participated: two University hospitals (Rotterdam and Leiden), one children's hospital and one general hospital (both in The Hague). The cohort comprised about 75% of the expected incidence in their referral areas. The attending paediatric neurologist completed an extensive questionnaire on the description of the event(s), possible provoking factors, previous medical history and the family history. Confirmation of the diagnosis of epilepsy by a committee of three paediatric neurologists, using predefined diagnostic criteria, was required for inclusion. The aetiology was classified according to the definitions of the International League Against Epilepsy (ILAE; Commission on Epidemiology and Prognosis of the International League Against Epilepsy, 1993) as idiopathic, cryptogenic or remote symptomatic. The aetiology of children with mental retardation was classified as remote symptomatic. Children with acute symptomatic seizures only were excluded. Epilepsy types and syndromes were classified according to the International Classification of Epilepsies and Epileptic Syndromes (ICES; Commission on Classification and Terminology of the International League Against Epilepsy, 1989). This was done at 2 years of follow-up, because the ICES had not yet been published when we started the study.

Follow-up and outcome

The follow-up of the original cohort (n = 466) was extended until 5 years after intake. We chose a fixed duration of follow-up for all children (instead of a variable length) to facilitate outcome comparisons at fixed intervals (6 months, 2 years, 5 years) and to examine the course of the epilepsy of all children during the entire follow-up.

Eight children died during the 5-year follow-up (Callenbach *et al*., 2001). They were not included in the present analyses. Five children (1.1%) were lost. Eventually, 453 patients remained for the analyses at 5 years.

We defined outcome as terminal remission (TR): the time from the last seizure to the moment of evaluation (i.e. 2 and 5 years after study entry). The TR at 5 years (TR5) was trichotomized (<1 year, 1–2 years, >2 years). We defined intractability at 2 and 5 years as a TR <1 year and longest remission (LR) <3 months during the last year of observation despite adequate treatment (Huttenlocher and Hapke, 1990; Berg *et al*., 2001; A. Berg, personal communication). Adequate treatment was defined as the optimal use of at least two AEDs, either alone or in combination.

The course during the follow-up was compared with TR5 in two ways. First, we compared TR5 with TR2. Next, we studied the duration of the LR during the entire 5-year follow-up in relation to the occurrence of seizure(s) during the last year of follow-up (TR5 <1 year).

Treatment

Treatment decisions were made by each child's treating paediatric neurologist. In children who needed AED treatment, we tried at least two first-choice AEDs in monotherapy (mostly sodium valproate and carbamazepine) before using a polytherapy regimen. In children who experienced long-term remission, we usually withdrew the AED(s) after 2 years without seizures. However, our cohort also contained 161 children in whom medication was withdrawn much earlier, selected on the basis of a rapid and complete response to AED therapy (Peters *et al*., 1998).

Determinants

A priori-defined variables, including EEG, were collected at intake and at 6 months of follow-up (Table 1). These possible determinants were analysed for their relevance for the outcome at 2 years (Arts *et al*., 1999) and 5 years after intake (see below). In the univariate analysis, age at intake was categorized in five groups (0–3, 3–6, 6–9, 9–12 and 12–16 years of age) to show more detail. In the multivariate analyses, age as a continuous variable was analysed both on linear and transformed scales to determine which scale best predicted the outcome. Since none of these was satisfactory, age was dichotomized (below and above 6 years of age). This also reduced the number of dummy variables.

The temporal seizure pattern before intake (Table 1) was studied as a possible determinant on the basis of a report by Shorvon (1984). We identified the following patterns: continuous (intervals between seizures $\leqslant$1 week); intermittent (intervals between seizures >1 week); multiple bursts (clusters of seizures within one week with >1 week between the clusters); status epilepticus (seizure with duration of >30 min); solitary burst (one cluster of seizures within a period of at most 1 week).

Statistical analyses

The correlation of intake and 6-month follow-up determinants with outcome (defined as TR5 less than or more than 1 year) was analysed with a modelling strategy (Harrell *et al*., 1996). When variables had missing values (e.g. family history), these were derived using imputation. Variables with many missing values (e.g. CT) were not considered in the multivariate analyses. After a stable model had been established, all second-order interaction terms of each determinant remaining in the model were tested. Significant interaction terms were added to the model. The goodness of fit of the models was determined by Pearson's χ^2 test. Bootstrapping techniques were used to determine the internal validity of the final models.

For each group that we analysed, we developed a model with intake variables only and a model with intake and 6-month variables combined.

From the odds ratios of the variables contributing to these models, regression coefficients (RC) can be derived. For each individual patient, the RCs of the applicable variables and a constant for the model can be summated to obtain the individual's sum score. From the sum score, the predicted probability of a poor outcome can be calculated using the formula $P = 1/1 + e^{-Z}$, in which Z is sum score/–100. The area under the receiver operant characteristic (ROC) curve (giving the relation between the sensitivity and the specificity of the predictions) is a measure of the ability of the model to discriminate between patients with and without a poor outcome. The value of P with the best combination of sensitivity and specificity is the probability cut-off. Any value of P above the cut-off predicts TR5 <1 year; any value below P predicts the opposite. Since P can be plotted against Z and, therefore, also against the sum score, one can use the sum score for the determination of the individual's prognosis. The cut-off value of P directly yields a cut-off value of Z and the sum score. Using the individual's value of the sum score (below or above the cut-off) facilitates the use of the model in daily clinical practice.

Results

Outcome

Of the 453 children, 345 (76%) attained a TR5 of at least one year, 290 (64%) of at least 2 years and 248 (55%) had not had any seizure since the 2-year outcome evaluation (Fig. 1). The moment of entering TR5 (i.e. the day of the last seizure during the 5-year follow-up) is presented as a Kaplan-Meier survival curve in Fig. 2. It shows that half of the cohort had reached terminal remission after 18.5 months of follow-up.

Sixty-five children (14%) were completely seizure-free since the intake (Fig. 1). In the univariate analyses, a number of significant variables distinguished this group from the 388 children with seizures after intake. They had had fewer seizures before intake, more often of a generalized tonic-clonic nature. Their EEG showed less often epileptiform discharges and they less often had symptomatic epilepsy. Their seizure pattern had more often been intermittent or a single burst and less often continuous.

Twenty-seven (6%) out of 108 children (24%) with a TR5 of less than one year fulfilled our criteria for intractability. Of these, seven children had symptomatic partial and seven others cryptogenic partial epilepsy; five had cryptogenic generalized and one symptomatic generalized epilepsy. Three had been classified as idiopathic generalized epilepsy with (mainly) absences, and four as idiopathic generalized epilepsy with (mainly) generalized tonic-clonic seizures.

Treatment

Sixty-five children (14%) were not treated with AEDs. Most of these suffered from sporadic generalized tonic-clonic seizures. Of the 65 untreated children, 61 (94%) achieved a TR5 $\geqslant$1 year, and 53 (82%) $\geqslant$ 2 years.

Medication was prescribed to 388 (86%) children. Of these, 206 (53%) received only one AED and 182 (47%) two or more (up to nine) AEDs or AED regimens (Fig. 3). Of the 388 treated children, 46% attained a TR5 >1 year on one AED, 19% reached this end-point on two AED regimes and 9% on three or more.

Medication was withdrawn in 227 (59% of 388 treated) patients of whom 13 had a TR5 less than one year and 214 a TR5 of $\geqslant$1 year. At 5 years of follow-up, 161 (36% of 453) patients were still using AEDs (TR5 <1 year, 91; $\geqslant$1 year, 70).

Predictive variables

The determinants of seizure outcome at 5 years were largely identical to those found in the 2-year analysis (Table 1).

Few variables showed substantial changes in outcome when the TRs at 2 and 5 years were compared. Most conspicuously, patients with simple partial seizures had a significantly worse outcome at 2 years in comparison with patients with generalized tonic–clonic seizures, but at 5 years of follow-up their outcome was better, although not significantly so.

Multivariate analyses of the 5-year outcome with logistic regression models are presented in Table 2A. The model with intake variables only retained sex, age at intake, initial EEG, aetiology, history of febrile seizures and postictal signs. Aetiology and history of febrile seizures interacted. Children with cryptogenic or remote symptomatic aetiology without a history of febrile convulsions had a worse prognosis than those with

Table 1 *Univariate analysis*

	Number of children	% with TR2 <1 yr	% with TR5 <1 yr	OR for TR5 <1 yr (95% CI)
Intake				
Overall	453	43	24	
Sex				
Male	221	42	22	1.00
Female	232	44	26	1.26 (0.81, 1.94)
Age at intake (years)				
0–3	145	48	28	1.00
3–6	90	46	30	1.13 (0.63, 2.01)
6–9	99	39	15	0.47 (0.24, 0.91)*
9–12	73	34	18	0.57 (0.28, 1.15)
12–16	46	41	28	1.03 (0.49, 2.17)
No. of seizures before intake				
<25	285	42	22	1.00
>25	168	44	26	1.23 (0.79, 1.91)
Seizure type				
Generalized tonic–clonic	272	38	22	1.00
Complex partial	49	51	35	1.88 (0.97, 3.63)
Simple partial	29	69	17	0.74 (0.27, 2.02)
Absences	59	32	19	0.81 (0.40, 1.66)
Infantile spasms, myoclonic/atonic seizures, etc.	44	57	34	1.83 (0.92, 3.65)***
Type of epilepsy				
Generalized idiopathic	193	32	16	1.00
Generalized cryptogenic	31	52	42	3.92 (1.70, 9.06)***
Generalized symptomatic	32	47	28	2.13 (0.89, 5.08)
Partial idiopathic	28	39	0	0.00
Partial cryptogenic	86	48	34	2.76 (1.51, 5.07)***
Partial symptomatic	67	63	39	3.45 (1.80, 6.59)***
Unclassifiable	16	38	6	0.36 (0.05, 2.87)***
Aetiology				
Idiopathic	232	33	14	1.00
Remote symptomatic	126	56	33	2.91 (1.70, 4.98)***
Cryptogenic	95	48	36	3.36 (1.89, 5.98)***
Pre-existing neurological signs				
Absent	396	41	22	1.00
Present	57	54	33	1.72 (0.94, 3.15)
Postictal signs				
Absent	407	42	22	1.00
Present	46	52	39	2.26 (1.19, 4.30)*
History of febrile convulsions				
No	406	42	23	1.00
Yes	47	51	32	1.58 (0.82, 3.04)
Family history				
Negative	395	44	24	1.00
Positive	58	31	24	1.02 (0.53, 1.94)
Standard intake EEG				
Normal	111	36	20	1.00
Epileptiform	267	45	25	1.32 (0.76, 2.27)
Other abnormalities	69	45	28	1.54 (0.76, 3.13)
CT scan				
Normal	245	40	24	1.00
Abnormal	67	61	34	1.69 (0.94, 3.03)
Not obtained	141	38	19	0.76 (0.46, 1.28)
Temporal seizure pattern				
Continuous	189	41	25	1.00
Intermittent	162	43	19	0.71 (0.43, 1.20)
Multiple bursts	17	59	47	2.69 (0.97, 7.45)*
Solitary status epilepticus	24	46	33	1.51 (0.61, 3.77)
Solitary burst	61	39	23	0.90 (0.45, 1.78)
6 months after intake				
No. of seizures within 6 months				
<25	288	40	21	1.00
>25	165	47	27	1.56 (1.00, 2.43)*

Table 1 *Continued*

	Number of children	% with TR2 <1 yr	% with TR5 <1 yr	OR for TR5 <1 yr (95% CI)
3-month remission ever in 6 months				
No	123	67	42	1.00
Yes	330	34	17	0.28 (0.17, 0.45)***
6-month EEG				
Normal	122	32	17	1.00
Epileptiform	110	55	32	2.24 (1.20, 4.21)**
Other abnormalities	58	43	24	1.53 (0.71, 3.30)
Not obtained	163	42	23	1.46 (0.81, 2.66)
TR at 6 months				
6 months	141	28	13	1.00
2–6 months	171	38	17	1.46 (0.77, 2.74)
0–2 months	141	51	43	5.23 (2.77, 9.89)***

The table shows the distribution of the possible determinants collected at intake and after 6 months, percentages of children with a TR2 and TR5 <1 year and odds ratios for TR5 <1 year for each value of the intake and 6-month variables compared with the reference value of that variable, scored as 1.00. OR = odds ratio; CI = confidence interval. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

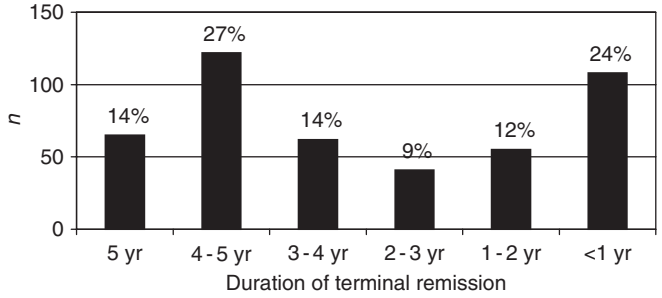

Fig. 1 Outcome of 453 children with newly diagnosed epilepsy at 5 years of follow-up.

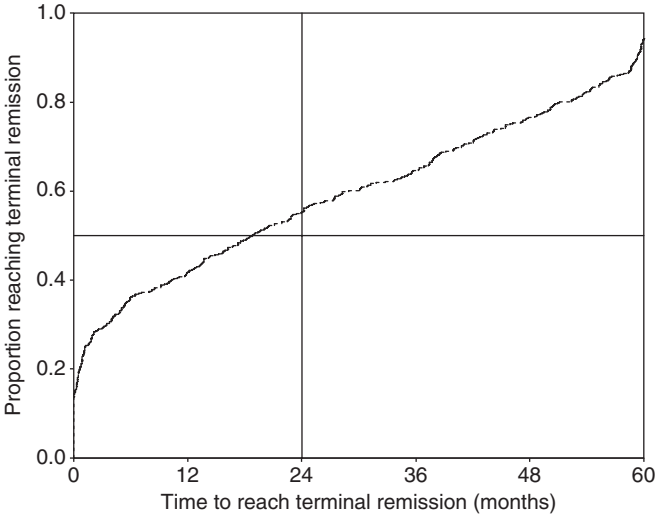

Fig. 2 Moment (time in months) of the last seizure before entering the terminal remission existing at 5 years of follow-up for 453 children in the cohort. Kaplan–Meier survival curve.

idiopathic aetiology and no febrile convulsions. On the other hand, a history of febrile convulsions was a significant predictor of a worse outcome in all children with idiopathic epilepsy, but not in the children with non-idiopathic epilepsy. The

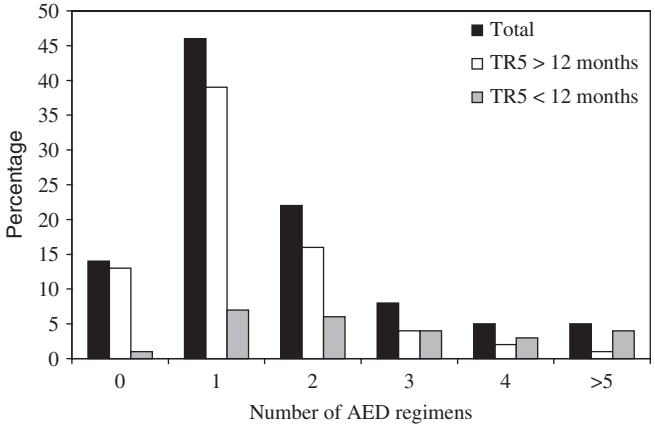

Fig. 3 Number of anti-epileptic drug (AED) regimens during 5 years of follow-up in the entire cohort and in each of two 5-year outcome categories, all expressed as percentage of the entire cohort ($n = 453$).

model with intake and 6-month variables combined retained the above variables except for the initial EEG, and, in addition, the number of seizures and the longest remission during the first 6 months of follow-up, and the duration of terminal remission at 6 months. The following variables attained significance. The outcome was worse for girls than for boys, as well as in children with postictal signs, a TR at 6 months of <2 months, non-idiopathic aetiology and a history of febrile seizures. Again we found a significant interaction between aetiology and febrile convulsions.

Based on the models presented here, it is possible to determine the individual prognosis of children with newly diagnosed epilepsy by calculating the sum score (Table 2B). In these models, the value of the sum score for an individual reflects his or her chance of having a TR5 <1 year. In the model with intake variables only, the sum score cut-off equals 110, which is derived from $P = 0.25$. This P value corresponds to the best combination of sensitivity (0.65) and specificity (0.64), resulting in a predictive value for TR5 <1 year of 0.36 and predictive

Table 2A *Multivariate analyses*

	Intake variables	Intake and 6-month variables
Number of children	453	453
Number of covariate patterns	43	119
Pearson χ^2 (74)	35.30	93.63
Probability > χ^2	0.45	0.84
Area under ROC curve	0.70	0.77
Variables	OR (95% CI)	OR (95% CI)
Sex (male/female)	1.49 (0.93, 2.37)	1.64 (1.00, 2.70)*
Age at intake (<6/≥6 years)	0.62 (0.39, 0.99)*	0.87 (0.52, 1.43)
EEG at intake (normal/abnormal)	1.34 (0.77, 2.34)	
Aetiology (idiopathic/not idiopathic)		
If no febrile seizures occurred	3.72 (2.20, 6.30)***	3.58 (2.05, 6.27)***
If febrile seizures occurred	0.63 (0.17, 2.30)	0.56 (0.14, 2.18)
History of febrile seizures (no/yes)		
If aetiology idiopathic	4.37 (1.70, 11.26)**	5.28 (1.92, 14.51)***
If aetiology non-idiopathic	0.74 (0.27, 2.08)	0.82 (0.28, 2.4)
Postictal signs (no/yes)	1.83 (0.93, 3.60)	2.23 (1.08, 4.63)*
No. of seizures in 1st 6 months (<25/>25)		0.77 (0.42, 1.41)
3-month remission (no/yes)		0.58 (0.29, 1.13)
Terminal remission at 6 months		
6 months (no/yes)		1.00
2–6 months (no/yes)		1.57 (0.78, 3.17)
0–2 months (no/yes)		4.47 (2.00, 9.99)***

The table shows odds ratios (OR) and 95% confidence intervals (CI) for the models with intake variables only and with intake and 6-month variables for a terminal remission (TR5) of <1 year at 5 years of follow-up. Logistic regression model with interaction according to Harrell *et al*., 1996. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

value for TR5 ⩾1 year of 0.85. The interpretation of these figures is that for sum scores more than 110, a TR5 >1 year is predicted with few false predictions (15%). However, the prediction of TR5 <1 year (sum score lower than 110) yields a large number of false predictions (64%). The number of misclassifications amounts to 38 (false prediction of TR5 >1 year) + 124 (false prediction of TR5 <1 year) = 162 (36%).

For the model with intake and 6-month variables combined, the sum score cut-off equals 132 derived from a $P = 0.21$. The resulting values for sensitivity, specificity, positive and negative predictive value are 0.69, 0.71, 0.43 and 0.88. One can see that this model is more reliable than the one with intake variables only, but suffers from the same deficit: too many false predictions of TR5 <1 year. The number of misclassifications amounts to 33 + 101 = 134 (30%). A simplified way of calculating the individual prognosis with the help of these data is given in Table 2B.

For children with a defined epilepsy syndrome, it may not be necessary to use a complicated model to determine the prognosis, because the syndrome itself largely determines the prognosis. Therefore, we analysed the group that remained after removal of all children with a well-defined epilepsy syndrome and with idiopathic generalized epilepsy not otherwise defined. The 182 residual children had cryptogenic (86) or symptomatic (67) partial epilepsy, and symptomatic or cryptogenic generalized epilepsy (29). Multivariate analysis of the 153 children with symptomatic or cryptogenic partial epilepsy retained sex, age, family history, postictal signs, 3-month remission during and terminal remission at 6 months in the model. Only the determinant postictal signs was significant. After bootstrapping, the following results were found: the best cut-off value for P with the highest sensitivity (0.65) and specificity (0.67) is at 0.39. The predictive value for TR5 <1 year for any value above this cut-off is 0.53 and the predictive value for TR5 >1 year for any value below the cut-off is 0.78. This amounts to 19 + 32 = 51 misclassifications (33%).

Comparison of the results at 2 and at 5 years

The correlation of the outcomes 2 and 5 years after intake, measured as continuous variables, was highly significant. For the 442 children whose outcome could be measured this way both at 2 and at 5 years, Kendall's tau-b correlation coefficient was 0.591 ($P < 0.0001$).

The correlation between the categorical remissions at 5 and 2 years is presented in Fig. 4. In two children, the outcome at 2 and at 5 years could not be compared.

TR5 was >1 year in 231 of the 259 children with a TR2 of >1 year (89%, or 51% of the entire cohort). In univariate analyses, this was associated with seizure type (absences and tonic–clonic seizures), epilepsy type (idiopathic generalized epilepsy), aetiology (idiopathic), EEG (normal), remission of 3 months in the first 6 months of follow-up and absence of postictal signs, pre-existing neurological signs and imaging abnormalities. A deteriorating course was seen in 28 of the 259 children (11%, or 6% of the entire cohort). All of these had a TR2 of >1 but seizures during the fifth year. Significantly

Table 2B *Simple formula for the calculation of the prognosis with the above models*

	Model with intake variables only	Model with intake and 6-month variables
If female, add	−37	−45
If age at intake >6 years, add	45	13
If epileptiform features on first EEG, add	−28	
If non-idiopathic aetiology, add	−123	−115
If history of febrile seizures, add	−139	−150
If postictal signs present, add	−57	−72
If >25 seizures in first 6 months of follow-up, add		24
If ⩾3 months remission in first 6 months, add		49
If TR at 6 months 2–6 months, add		−41
If TR at 6 months 0–2 months, add		−135
If combination of non-idiopathic aetiology and history of febrile seizures, add	166	167
Constant × 100	228	256
Calculate sum score of individual child		
Cut-off value sum score	110	132
Good outcome predicted	Sum score >110	Sum score >132
Poor outcome predicted	Sum score <110	Sum score <132

The numbers in the table are the RCs of each contributing variable multiplied by (−100) and the shrinkage factor. For the model based on intake variables only, the shrinkage factor derived from bootstrapping was 0.94 and for the model with intake and 6-month variables combined it was 0.90. For each variable, enter the number given in the table if the child has the defined category or property, but 0 if the child does not. For example, for a girl, enter 37 in the model with intake variables only and 45 in the model with intake and 6-month variables, but for a boy enter 0. The value for the interaction term can only be entered if both terms (non-idiopathic aetiology and history of febrile seizures) are present. Adding the numbers for any particular child results in its sum score. This sum score has to be compared with the sum score cut-off value which was derived from the probability cut-off with the highest values for sensitivity and specificity. For the model with intake variables only, the cut-off was 110 and for the model with intake and 6-months variables it was 132. Values below the cut-off indicate a higher probability of TR5 <1 year and values above the cut-off indicate a smaller probability.

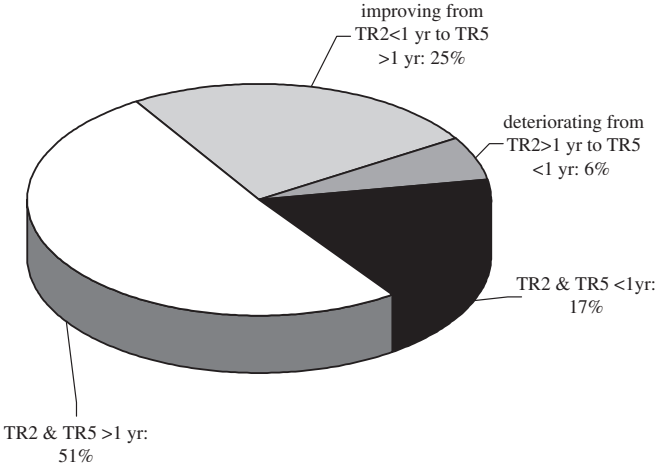

Fig. 4 Correlation between the categorical outcomes at 2 and 5 years for 453 children in the 5-year analysis. The outcome measures are terminal remission <1 year or >1 year at 2 and 5 years of follow-up.

associated with a deteriorating course were age at onset >4 and the presence of postictal signs.

On the other hand, an improving course was seen in 113 out of 193 children with TR2 less than one year (59%, or 25% of the entire cohort) but TR5 >1 year. Six of these had been intractable at 2 years. An improving course was associated with seizure type (simple partial seizures), negative family history and abnormalities in imaging studies. A constantly poor course was observed in 78 children (17%) who attained a 1-year terminal remission neither at two nor at 5 years. Age at onset (<6 years), a large number of seizures before and in the 6 months after intake, seizure type (complex partial seizures, infantile spasms and myoclonic and atonic seizures), epilepsy type (symptomatic partial and cryptogenic partial and generalized), aetiology (non-idiopathic), a history of febrile seizures and absence of remission during the first 6 months of follow-up were all associated with a constantly poor course.

Fifteen out of the 27 children who were intractable at 5 years had also been intractable at 2 years. Some other intractable children had had at least one long-term remission during the 5-year follow-up, but relapsed (Table 3). Two of these had had a remission of >2 years. More than half of the 108 children having seizures during the fifth year had had an intercurrent remission of at least 1 year.

Results at the level of epileptic syndromes

For virtually every syndrome, the largest group did well from the onset, and the second largest group showed an outcome improvement at 5 compared with 2 years (Fig. 5). This was most obvious for benign partial epilepsy with rolandic spikes and for idiopathic generalized epilepsies. Much smaller groups of children doing poorly from the onset or showing a worse

outcome at five than at 2 years were found mainly in the categories of symptomatic or cryptogenic epilepsies.

Since the epileptic syndromes were classified in retrospect 2 years after the intake, syndromes were not included as a variable in the multivariate analyses. In the model with intake variables only, age (<6 versus ⩾6 years or older) was significant. Epileptic syndromes occurring at certain ages may have caused this. Therefore, we looked at the relation between age and outcome. In univariate analysis, age >6 years was associated with a significantly better outcome [odds ratio (OR) 0.46 with 95% confidence interval (CI) 0.23–0.92]. Stratifying for epilepsy syndrome did not yield a significant association between age and outcome [Mantel–Haenszel common odds ratio estimate: 0.71 (asymptotically 95% CI, 0.44, 1.14)], with one exception: age at intake <6 years had a worse prognosis if the child had symptomatic partial epilepsy. Stratifying for age according to the five groups shown in Table 1 demonstrated also that symptomatic partial had a worse outcome below the age of 6 years (significantly so between 3 and 6 years), whereas cryptogenic partial had a significantly worse outcome between 3 and 9 years. Idiopathic generalized syndromes had a better outcome in the younger age groups (significant at the ages of 3–9 years). Without exception, all idiopathic partial syndromes (mostly occurring between 6 and 12 years) had a good outcome. Our finding that age at intake was significant in the model with intake variables only may have been caused by the occurrence of epileptic syndromes at the various ages.

Table 3 *Longest remission ever during 5 years of follow-up of 27 children matching the definition of intractable at 5 years, of 108 children with TR5 <1 year and of the remaining children with a TR5 of >1 year*

Longest remission during 5 years	Number of children (%)		
	27 intractable children	108 children with TR5 <1 year	345 children with TR5 ⩾1 year
0–3 months	11 (41)	13 (12)	0
3–6 months	6 (22)	9 (8)	0
6–12 months	3 (11)	19 (18)	0
12–24 months	5 (19)	30 (28)	29 (8)
>24 months	2 (8)	37 (34)	316 (92)

Discussion

The data presented here provide some insight in the evolution of childhood epilepsy over the years and in the variables that may influence the outcome. We hypothesized that we would be able to predict the outcome of childhood epilepsy based on (combinations of) determinants that can be identified at the moment of the diagnosis of epilepsy or shortly thereafter. Such

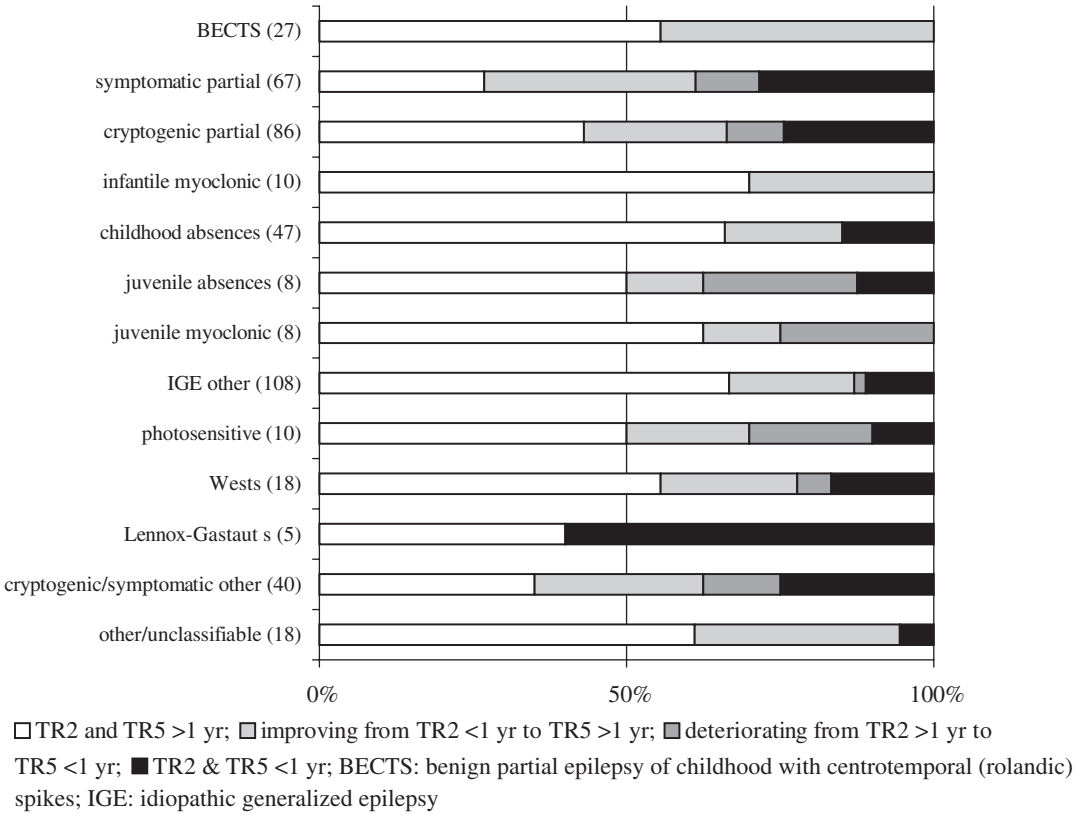

Fig. 5 Outcome at 2 and 5 years of 453 children followed for 5 years, according to epileptic syndrome (Commission on Classification and Terminology of the International League Against Epilepsy, 1989) as defined 2 years after intake. Numbers in parentheses are numbers of patients.

a strategy might lead to individualized treatment regimens depending on the prognosis of the child. Evaluating this possibility, we were able to elaborate on the concept of 'smooth-sailing epilepsy' (Camfield *et al*., 1990) on the one hand and of intractability (Huttenlocher and Hapke, 1990; Berg *et al*., 2001) on the other.

Outcome and response to treatment

There seems to be a general consensus that both adults and children with newly diagnosed epilepsy have a 65–75% chance of entering long-term remission (Annegers *et al*., 1979; Beghi and Tognoni, 1988; Camfield *et al*., 1993; Cockerell *et al*., 1997, Sillanpää *et al*., 1998). About 10–15% are due to become really intractable and 10–25% end up somewhere in between. This is rather surprising in view of the large discrepancies in patient selection, duration of follow-up and outcome definitions in the cohorts described so far. In our cohort, we find a large proportion with an improving course over time whereas the proportion with a deteriorating course is relatively small. Eventually, the outcome figures resemble the general beliefs. Our data clearly show that this is a dynamic process, and that outcome is more dependent on the duration of follow-up than may previously have been thought.

The response to treatment with AEDs follows a pattern that bears superficial resemblance to the one that has recently been described in the retrospective study by Kwan and Brodie (2000) in a hospital-based patient group aged 9 to 93 years, but our final results are better. They found a success rate (seizure-free for at least 1 year at the time of last follow-up) for the first AED in 47% of all patients treated, for the second in 13%, and in 4% for any further AED regime. They do not state the number of patients who were not treated. In our childhood cohort, the 388 treated children have similar results: 46% had a TR5 >1 year on the first AED, 19% on the second and 9% on any further AED regime. However, the success rate of any further AED or AED combination after the first AED had failed was almost twice as high (58%; Kwan and Brodie, 32%). The better results found by us and by Camfield *et al*. (1993) were probably largely caused by the different composition of the groups investigated: children versus all ages, and (largely) population-based versus hospital-based. Therefore, we want to stress that, at least in children, failure of one (or two) AED(s) certainly is a risk factor for a poor outcome, but that a considerable proportion of these patients will do well in the end.

Course during the follow-up

In more than two-thirds of patients, the 5-year outcome mirrored the 2-year outcome (in 51% both >1 year, in 17% both <1 year). For the best seizure–outcome group, the relevant variables pointed heavily to all qualities of 'idiopathic' as the main predictor. For the worst outcome group, indications for a symptomatic or cryptogenic aetiology and for malignant types of seizures or epilepsy, an early age at onset and a history of febrile seizures (despite the absence of children with severe myoclonic epilepsy of childhood in our cohort) were the leading variables.

An improving course was seen in one quarter of the cohort. The association of the improvement with simple partial seizures may be partly explained by the presence of a considerable number of children with benign partial epilepsy in this group. In this clinical epidemiological study, their long-term outcome was invariably good (Fig. 5), in contrast to the outcome at 2 years. This finding is in agreement with a recent meta-analysis of studies on benign partial epilepsy of childhood with rolandic spikes (Bouma *et al*., 1997). But the number of children with a remote symptomatic aetiology, who attained a TR5 of >1 year, also increased by almost 25% in comparison with TR2 (Table 1). Deterioration after a favourable early course was much less frequent (6% of our entire cohort) than improvement after an initially poor course. This was associated with the variable age at onset above 9 years.

Our data suggest that the two main outcome groups at 5 years (the first 'good to excellent', the second 'poor') predominate numerically and that the in-between group is relatively small (Fig. 1). After a longer follow-up, the outcomes become better more often than worse for children who do not have a stable course of their epilepsy. The improvement found in about one-quarter of the children adds to the good result of the children with smooth-sailing epilepsy. On the other hand, the number of children found to be intractable had not decreased when we compared the outcome at 2 and 5 years. Children who deteriorated took the place of children who had improved. Further follow-up is mandatory to find out whether the intractability leading to an indication for epilepsy surgery at adult age may arise after a (much) longer delay (Berg *et al*., 2003).

Intractability

Our finding that the number of children with a worsening course was relatively small confirms our idea that childhood epilepsy is generally not a progressive disease (van Donselaar *et al*., 1997). This is in contrast to the opinion of those authors adhering to Gowers' dictum that 'seizures beget seizures' (Gowers, 1881; Reynolds *et al*., 1983). However, fluctuations during the course do occur and even fulfilling criteria for intractability may be a temporary phenomenon. Of the 419 patients with a seizure-free period of at least 12 months at any time during the follow-up, 74 (18%) did not reach a TR5 of >1 year and seven (2%) became intractable (Table 3). On the other hand, 10 of the 25 children considered intractable at 2 years were not intractable at 5 years and six even had a TR5 of >1 year. In the Connecticut study (Berg *et al*., 2001), there was no fixed duration of follow-up but the range and median duration of follow-up were given. Intractability was considered to be early if it began within the first 2 years of follow-up and was observed during at least 18 months. Ten per cent of the children fulfilled their criteria for early intractability, comparable to our findings (6%). Of their 60 children with early intractability, seven (12%) went on to attain a remission

of at least 1 year. In our cohort, this was 24% (six out of 25 children). Other authors found that in a group of children that had been refractory to AED therapy for at least 2 years, about 4% entered remission during each year of further follow-up (Huttenlocher and Hapke, 1990). A recent editorial comment (Holmes and Engel, 2001), therefore, rightly cautions against an early rush to aggressive intervention, but on the other hand acknowledges the possibly adverse effects of a period with continuing seizures, fitting the definition of at least temporary intractability, on the patient and his or her family. Improvement in the course of lesional epilepsy in childhood may come late, and our findings clearly underscore the need for a careful decision about which children should be referred for epilepsy surgery and when.

It is difficult to give an accurate and broad definition of medical intractability. Not being in remission is insufficient, since treatment, duration of remission, number and/or frequency of seizures and the time interval during which seizures were counted should be specified. To predict intractability correctly, there should not be too many false-negatives and false-positives. It would be worthwhile to develop a consensus on the definition or definitions of intractability, enabling investigators to compare the results of various studies. The definitions applied in this study were used in various publications by Berg and colleagues and also in our former study on the 2-year outcome of childhood epilepsy.

Smooth course

A considerable proportion of our cohort fulfilled one or more criteria for an uncomplicated course. Sixty-five (14%) children were completely seizure-free since the intake (28 without treatment, 35 successfully withdrawn from AEDs), and 122 (27%) came into terminal remission during the first year of follow-up (17 without treatment, 95 successfully withdrawn). For such a favourable course, Camfield and colleagues coined the term 'smooth-sailing epilepsy' (Camfield *et al*., 1990). By this, they meant the children who became seizure-free immediately after the start of AED treatment and remained seizure-free during the follow-up, even after the withdrawal of medication. In their cohort (Camfield *et al*., 1993), this group comprised 20% of the entire sample. To this could be added a group that had never been treated at all (3%). It can be concluded from their and our data that smooth-sailing epilepsy does exist and accounts for at least a quarter—more probably a third or more—of all children with newly diagnosed epilepsy.

Determinants, outcome prediction

Both in the univariate and in the multivariate analysis, the variables reaching significance in the prediction of the outcome were largely identical at 5 years compared with 2 years of follow-up. The modelling strategy used in the present analysis, including interaction terms, seems to predict the outcome better than the variables *per se*. Notably, we found a dichotomy concerning aetiology. In the group with idiopathic aetiology, febrile seizures were a significant predictor of a worse outcome. In the group with non-idiopathic aetiology, this predictor was no longer significant. As far as we know, this has not been reported before.

Variables predictive of the outcome of childhood epilepsy in multivariate analyses were found to be aetiology, seizure type, early response to treatment (Sillanpää *et al*., 1998), number of pretreatment seizures, age at onset and a history of neonatal convulsions (Camfield *et al*., 1993). In these and our studies, children with clear mental retardation were considered to have remote symptomatic epilepsy. Except for age at onset and history of neonatal convulsions (which was not recorded by us), our findings were similar. Camfield and colleagues found age at onset below 12 years to be predictive of remission. Our group of patients older than 12 years was perhaps too small to confirm this finding. In our cohort, secondary deterioration was associated with age at intake above 9 years. Otherwise, the influence of age seemed to be correlated with epilepsy syndromes and the age at which they usually occur.

A model with determinants identified at intake was able to predict the outcome at 5 years correctly in 64% of our cohort. With the model based on the intake and 6-month variables together, the outcome was correctly classified in 70% of the cohort. In our earlier study, the outcome at 2 years of follow-up was predicted correctly in 70 and 76% (Arts *et al*., 1999). These data suggest that predictive models have a place in the determination of the prognosis of childhood epilepsy, especially in the prediction of a long terminal remission. When the models predict a long terminal remission, the chance that the prediction will be incorrect is much smaller than when they predict a short terminal remission. The resulting expectations may be used to inform the parents, and as a basis for the choice of treatment strategy. Caution with the interpretation of such predictions is warranted, however, because the number of those misclassified (especially children predicted to have a poor outcome) is considerable due to the lack of sensitivity of the models. Nevertheless, it is justified to ask whether AED treatment really would be necessary if the prognosis is good, and whether early aggressive intervention could prevent the development of expected intractability. Our findings indicate that there are no ethical or practical objections against designing studies that aim to test hypotheses based upon these questions.

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