Epilepsia, **40**(6):726–734, 1999
Lippincott Williams & Wilkins, Inc., Philadelphia

Clinical Research

The Early Prognosis of Epilepsy in Childhood: The Prediction of a Poor Outcome. The Dutch Study of Epilepsy in Childhood

*‖Willem F. M. Arts, †Ada T. Geerts, ‡Oebele F. Brouwer, §A. C. Boudewyn Peters, *Hans Stroink, and †Cees A. van Donselaar

*Departments of *Pediatric Neurology and †Neurology, Erasmus University Medical Center, Rotterdam; ‡Departments of Pediatric Neurology, Leiden University Medical Center, Leiden, and §University Hospital/Wilhelmina Children's Hospital, Utrecht, and ‖Departments of Neurology, Juliana Children's Hospital and Westeinde Hospital, The Hague, The Netherlands*

Summary: *Purpose:* To examine which variables available early in the course of childhood epilepsy are associated with a poor short-term outcome and to develop models to predict such an outcome.

Methods: We prospectively followed up 466 children with newly diagnosed epilepsy for 2 years. Variables were collected at intake and after 6 months. Outcome was defined as the duration of the terminal remission (TR): poor (<6 months) and not poor (≥6 months).

Results: Of the subjects, 31% had a poor outcome. Multivariate analysis based on the intake variables identified number of seizures, seizure type, and etiology as risk factors for a poor outcome. With the intake and 6-month variables combined, seizure type, etiology, the number of seizures, and not attaining a 3-month remission during these 6 months, and the EEG at 6 months were predictive variables. A predictive model based on the multivariate logistic-regression analysis with the intake variables was correct in 56% of the children in whom it predicted a poor outcome and in 73% of the children in whom it predicted a not-poor outcome. With the intake and 6-month variables together, these percentages were 66 and 79%, respectively. The sensitivity of these models was low (29 and 47%, respectively); the specificity was good (90 and 89%).

Conclusions: The 2-year outcome of childhood epilepsy is closely related to its early course. The prognosis is poor in ~30% of patients. By using our data, the prediction of a poor outcome is correct in almost two thirds of the patients; however, the models produce many false-negative predictions. **Key Words:** Epilepsy—Childhood—Prognosis—Prognostic model—Outcome.

About 25% of patients with epilepsy of all ages do not achieve a long-standing remission (1). Neurologic abnormalities, mental retardation, complex partial or secondarily generalized epilepsy or both (2–5), infantile spasms (6), remote symptomatic etiology (6), a large number of seizures (7), a high seizure frequency (4,8), and a history of status epilepticus (6) have been reported to be associated with a poor prognosis. Onset at older than 10 or 12 years has been related to a worse prognosis (2,7); in other studies, the risk of intractability decreased with later onset (5,6). Only one of these studies was completely prospective (5). The others were mostly (6) or partly (2–4,7,8) retrospective; a case–control method was used once (6). Two studies did not deal exclusively with children but concerned patients of all ages (2,3).

The Dutch Study of Epilepsy in Childhood (DSEC; 9) is a collaborative effort of two university, one children's, and one general hospital to study prospectively various aspects of childhood epilepsy in a hospital-based cohort consisting exclusively of primarily referred children with newly diagnosed epilepsy. The methods of patient recruitment, follow-up, and outcome definition were intended to establish a large, unselected, uncontaminated study cohort of children with epilepsy with a complete follow-up. Because chronic, intractable epilepsy is said to develop early in the course of the disease (10), prevention of intractability would require early identification of these patients followed by rapid and vigorous therapeutic intervention. Therefore we address two questions: what is the frequency of a poor outcome in newly diagnosed childhood epilepsy 2 years

Accepted November 20, 1998.
Address correspondence and reprint requests to Dr. W. F. M. Arts at Department of Pediatric Neurology, Erasmus University Medical Center, Dr. Molewaterplein 60, 3015 GJ Rotterdam, The Netherlands.

after the diagnosis? Is early identification of children likely to have a poor outcome possible, and if so, when?

METHODS

Setting

The study population consisted of a consecutive series of newly diagnosed children with epilepsy from two university hospitals, one general and one children's hospital in the western region of The Netherlands.

Diagnosis and classification

From August 1, 1988, to August 1, 1992, all children aged 1 month to 16 years seen in one of the participating hospitals with two or more unprovoked seizures or one status epilepticus were—after informed consent—enrolled in this arm of the DSEC, the "Prognosis Study" (Fig. 1). They were referred by their family physician (51%), the pediatrician of the participating hospital (25%), or came to the Emergency Room (16%). In 8%, the way of referral was different or unknown.

The diagnosis of a seizure was based on predefined criteria, adapted from Van Donselaar et al. (11). A panel of three pediatric neurologists had to agree on the epileptic nature of the events on the basis of the information provided in a questionnaire and in the letter to the family physician, without knowledge of the results of additional examinations (11). If these details were insufficient, the results of one or two EEGs also were considered (see the following). Ninety-two percent of the children were included on the basis of their history alone. The panel evaluated 850 children with one or more possible seizures (Fig. 1). Of these, 412 were immediately confirmed to have epilepsy. Seventy children, seen after August 1, 1988, of a cohort of 139 with a single seizure (12), were included after a recurrence. In only three of these 482 children, the diagnosis of epilepsy was later rejected, whereas in 17, the diagnosis was doubted after follow-up. In 178 children, the diagnosis of epilepsy was still uncertain after discussion of the history and the EEGs by the committee. These "uncertain cases" were followed up for 1 year. Twelve of them were included after more episodes and repeated discussion by the panel. Altogether, therefore, 494 children were eligible for the study. The mean age at intake in this group was 5.9 years (SD, 4.2 years; median, 5.5 years).

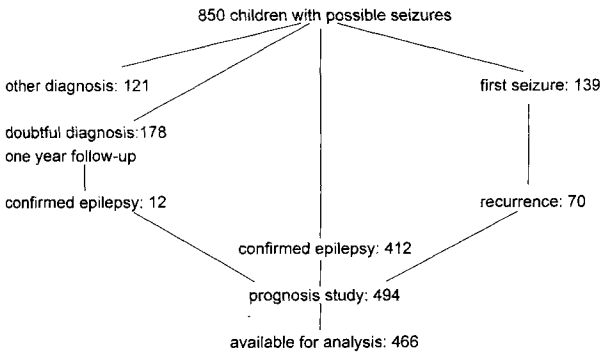

FIG. 1. Composition of the inception cohort. The First-Seizure Study (12) started January 1, 1988. Its complete cohort consisted of 170 children (85 children had a recurrence). The figure mentions only the 139 children who entered the First-Seizure Study after the starting date of the Prognosis Study (i.e., August 1, 1988).

The seizures were classified according to the ILAE criteria (13). The original classification of the type of epilepsy according to Gastaut (generalized vs. partial and idiopathic vs. symptomatic; 14) was at the end of the 2-year follow-up replaced by the 1989 ILAE classification of epilepsy and epileptic syndromes (15). In addition, the etiology was reclassified according to the guidelines of the committee on epidemiology of the ILAE (16). "Remote symptomatic" meant either that the child had preexisting neurologic abnormalities, including mental retardation (considered to be present when the child needed specialized care or schooling for the retarded; presumed IQ <70) or that a definite etiology was established (17).

Variables and investigations

A priori defined variables were collected at intake, after 6 months (Table 1), and at the end point of this study (2 years after intake). Four hundred eighty-seven (99%) children had an EEG. In children without epileptiform abnormalities, a second EEG was made after partial sleep deprivation. A standard EEG was repeated after 6 months. Imaging was performed with computed tomography (CT), sometimes supplemented with magnetic resonance imaging (MRI); it was omitted if the child had typical absences or if the treating physician did not consider it necessary.

Treatment

The patient's pediatric neurologist made the decision whether to treat the child and selected the antiepileptic drug (AED). According to the protocol, at least two first-line and one second-line drug had to be tried consecutively up to maximal tolerated dosages. Patient compliance was tested with repeated drug-level monitoring.

Follow-up and outcome

Of the 494 children in the Prognosis Study, 28 were excluded from this analysis. Seven children were lost before 2-year follow-up had been completed. The outcome of 11 children could not be defined correctly, usually because they had both epileptic and pseudo-seizures, impossible to distinguish on the basis of the history. Seven participants in the first-fit study had a recurrence after the closure of the intake period, and therefore were not followed up for 2 years. Three children in whom a diagnosis other than epilepsy was made during follow-up

TABLE 1. *Distribution of the variables at intake and after 6 months*

	Total	TR <6 mo "poor"	OR "poor" (95% CI's)[a]
Intake			
Overall	466	146 (31)	
Sex			
Male	225 {48}	66 (29)	1.00
Female	241 {52}	79 (33)	1.15 (0.78, 1.70)
Median age at intake (yr)	5.5	5.0	0.96 (0.91, 1.00)
25–75% range	2.3–9.1	1.6–8.7	
Median patient delay (mo)	2.6	2.7	1.00 (0.98, 1.02)
25–75% range	0.5–6.2	0.4–5.9	
No. of seiz. before intake			[b]
≤25	293 {63}	87 (30)	1.00
>25	173 {37}	58 (34)	1.17 (0.79, 1.76)
Seizure type			[c]
General. tonic–clonic	277 {59}	71 (25)	1.00
Complex partial	47 {10}	18 (38)	1.80 (0.94, 3.44)
Simple partial	25 {5}	13 (52)	3.14 (1.37, 7.21)[d]
Absences	59 {13}	13 (22)	0.82 (0.42, 1.61)
Inf. spasms, myocl./atonic seiz., etc.	58 {12}	31 (53)	3.33 (1.86, 5.96)[c]
Type of epilepsy			[d]
General. idiopathic	194 {42}	42 (22)	1.00
General. cryptogenic	34 {7}	17 (50)	1.96 (0.92, 4.18)
General. symptomatic	37 {8}	13 (35)	3.62 (1.70, 7.69)[d]
Partial idiopathic	28 {6}	6 (21)	0.99 (0.38, 2.59)
Partial cryptogenic	86 {19}	32 (37)	3.13 (1.75, 5.61)[d]
Partial symptomatic	69 {15}	32 (46)	2.14 (1.23, 3.74)[e]
Unclassifiable	18 {4}	4 (22)	1.03 (0.32, 3.31)
Etiology			[c]
Idiopathic	235 {50}	51 (22)	1.00
Remote symptomatic	136 {29}	58 (43)	2.68 (1.69, 4.25)[c]
Cryptogenic	95 {20}	37 (39)	2.30 (1.37, 3.86)[d]
Pre-existing neurol. signs			
Absent	403 {87}	115 (29)	1.00
Present	63 {14}	31 (49)	2.43 (1.42, 4.16)[d]
Postictal signs			
Absent/unknown[f]	418 {90}	128 (31)	1.00
Present	48 {10}	18 (37)	1.36 (0.73, 2.53)
History of febrile conv.			
No/unknown[g]	417 {90}	132 (31)	1.00
Yes	49 {11}	14 (29)	0.86 (0.45, 1.66)
Family history			
Negative/unknown[h]	408 {88}	131 (32)	1.00
Positive	58 {12}	15 (26)	0.74 (0.40, 1.38)
Standard intake EEG			
Normal	111 {24}	28 (25)	1.00
Epileptic ± other abn.	277 {59}	91 (33)	1.45 (0.88, 2.38)
Other abn./not done[i]	78 {17}	27 (35)	1.57 (0.83, 2.96)
CT scan			[d]
Normal	251 {54}	73 (29)	1.00
Abnormal	73 {16}	35 (48)	2.25 (1.32, 3.83)[d]
Not obtained	142 {31}	38 (27)	0.89 (0.56, 1.41)
Temporal seizure pattern[j]			
Continuous/not clear[k]	207 {44}	71 (34)	1.00
Intermittent	162 {35}	43 (27)	0.69 (0.44, 1.09)
Multiple bursts	10 {2}	5 (50)	1.92 (0.54, 6.84)
Solitary status epil.	26 {6}	7 (27)	0.71 (0.28, 1.76)
Solitary burst	61 {13}	20 (33)	0.93 (0.51, 1.71)
6 Months after intake			
No. of seiz. within 6 mo			[b]
≤25	294 {63}	74 (25)	1.00
>25	172 {37}	72 (42)	2.14 (1.43, 3.20)[d]
3-mo remission			
No	130 {28}	76 (58)	1.00
Yes	336 {72}	70 (21)	0.19 (0.12, 0.29)[c]

TABLE 1. *Continued*

6-mo EEG			
Normal	125 {27}	22 (18)	1.00
Epileptic ± other abn.	117 {25}	51 (44)	3.62 (2.01, 6.51)[c]
Other abn.	60 {13}	19 (32)	2.17 (1.06, 4.42)
Not obtained	164 {35}	54 (33)	2.30 (1.31, 4.04)

Number of children with a poor outcome and odds ratio for a poor outcome in the univariate analysis for each of the intake and 6-month variables (n = 466). The odds ratios are calculated as the chance of a poor outcome with that particular value of the variable considered versus the chance of a poor outcome with the reference value of that variable (see Methods section). Between {}, column percentages; between (), row percentages.

[a] Odds ratio and (between parentheses) 95% confidence interval for a poor outcome for that particular value of the variable vs. the reference value in the univariate analysis; the reference values are scored 1.00.

[b] OR for log (no. of seizures before intake): 1.23 (0.95, 1.58); for log (no. of seizures in first 6 months after intake): 1.57 (1.21, 2.02).

[c] $p < 0.001$.

[d] $p < 0.01$.

[e] $p < 0.05$.

[f] Unknown, 10.

[g] Unknown, 6.

[h] Unknown, 14.

[i] Not done, 7.

[j] Definition: continuous, intervals between seizures ≤1 week; intermittent, intervals between seizures >1 week; multiple bursts, clusters of seizures within 1 week with >1 week between the clusters; status epilepticus, seizure with a duration of >30 min; solitary burst, one cluster of seizures within a period of ≤1 week.

[k] not clear, 11.

also were omitted. The remaining 466 children were all followed up for 2 years.

The follow-up was usually done at visits to the outpatient clinic. Telephone interviews were allowed for children who were seizure free and without medication. The outcome after 2 years was assessed according to the duration of the terminal remission (TR): ≥12 months, "good," 6–12 months, "fair," and <6 months, "poor." We compare the outcome "poor" with the outcome "not-poor."

Statistics

The predictive significance for the outcome after 2 years was analyzed separately for the intake variables and for the intake and 6-month variables combined. Univariate and multivariate logistic-regression analyses were performed with SPSS. For multivariate analysis, a model with stepwise backward elimination of variables was used. A variable was eliminated if its removal statistic had a probability ≥0.10. We used simple parameter coding (each category of any particular variable was compared with the reference category of that variable). The analysis was done with a model comparing a remission of <6 versus >6 months ("poor" vs. "not poor"). Odds ratios were calculated as the chance of the outcome with that particular value of the variable considered versus the chance of the outcome with the reference value of that variable.

The type of epilepsy according to the ILAE classification (15) and the EEG after partial sleep deprivation were not used as independent variables in the multivariate analyses. The correlations between type of epilepsy and etiology and between the standard EEG and the EEG after partial sleep deprivation were too high. All other intake and 6-month variables were included in the logistic-regression analyses. The number of seizures before intake and the number of seizures in the first 6 months of follow-up were in these analyses modeled as continuous variables but log-transformed, because they did not have a normal distribution (18). For the second variable, this was done as log (seizures during first 6 months + 1) to avoid log (0). Moreover, indicator variables were added to code for excessive numbers of seizures. We found that reported numbers of seizures >25 were very inaccurate, especially in the case of absences and myoclonic seizures; therefore, we considered >25 seizures to be excessive in terms of both these variables. For patients with excessive amounts of seizures either before intake or in the first 6 months of follow-up, the log (no. of seizures) was coded as zero.

After stepwise deletion, all possible interaction terms were tested for significance, but both interaction terms that we found to be significant could not be used in the models because of the occurrence of colinearity. One clinically important but not significant variable was added to the models to include too many rather than too few variables. For the model with only intake variables, this was "preexisting neurologic signs," and for the model with the intake and 6-month variables combined, this was "EEG1."

The variables remaining in the two models (intake

variables only and intake and 6-month variables combined) after stepwise deletion were used to calculate each individual's chance of having a poor outcome according to the formula $P = 1/1 + e^{-Z}$. Z is a score resulting from adding values for the applicable category of each of the relevant variables plus a constant for the particular model. The values are computed on the basis of values derived from the logistic-regression coefficients of each category multiplied by the individual's coded characteristics from the simple parameter coding scheme. To prevent overoptimism in the interpretation of the results, we used a correction (shrinkage) factor for the regression coefficients in the final models. All coefficients were multiplied by the shrinkage factor $k = 1 - (p - 2)/C$, where p is the number of degrees of freedom and C the global χ^2 statistic for the multivariate full model (19). For the model with only intake variables, p was 23, and χ^2 was 53.217, resulting in the shrinkage factor $k = 0.605$. For the model with intake and 6-month variables combined, p was 29, χ^2 was 116.635, and therefore k was 0.769.

All 466 children were used for the development of the final models. We did not use a split-sample technique, because using a smaller group for the development of the model would result in a less accurate and reliable model (20). Instead, we decided to recruit a new cohort for the validation of the models. This validation study is currently under way.

RESULTS

Overall

For the 466 children, the distribution of the outcome categories at 2 years was poor, 146 (31%); good, 264 (57%); and fair, 56 (12%; not-poor 69%). Table 1 details the total number and the number with a poor outcome for each intake and 6-month variable.

During the 2-year follow-up, two patients died. The intervals until death were 16.6 and 20.4 months. Both children were classified as poor because neither of them achieved any significant remission during the follow-up. One of these children had a progressive metabolic disorder; the other died of the complications of a congenital brain anomaly. Progressive disorders were diagnosed in four other children, one with a cerebral tumor and three with a progressive metabolic affection.

Two years after the intake, 74 children still had not been treated with AEDs. These children had a significantly better outcome than the treated group (poor outcome in 16% vs. 34%) (21). Among the 12 untreated children whose outcome was poor, two had benign rolandic epilepsy, and five, infrequent generalized tonic–clonic seizures, not necessitating prolonged AED treatment. On the other hand, children needing more successive AEDs or polytherapy to gain seizure control generally had a worse outcome: 25% of children with monotherapy and 70% of children with any type of polytherapy did not achieve a 6-month TR (21).

Compliance did not significantly affect the outcome. Moderate or poor compliance was demonstrated at some time in 18% of those treated. Of these, 31% had a poor outcome.

Poor outcome

One hundred forty-six children had a TR <6 months. To describe this group in more detail, in Table 2, the distribution of this group according to TR and longest remission (LR) during the last 6 months of follow-up is presented.

Table 1 documents the odds ratios of a poor outcome (TR) and their confidence intervals for each variable as resulting from the univariate analysis. Table 3 presents the results of the stepwise backward multivariate analyses, first for the intake variables only and subsequently also for the intake and 6-month variables combined. In the analysis restricted to the intake variables, seizure type and log (number of seizures) were significant predictors for a poor outcome. The number of seizures and the etiology remained in the model with a p level between 0.05 and 0.1. Combining the intake and 6-month variables, not attaining a 3-month remission during the first 6 months of follow-up and log (number of seizures in the first 6 months after intake) were the most powerful predictors for a TR of <6 months. Seizure type, etiology, and the result of the EEG after 6 months remained in the model with p values between 0.05 and 0.1.

On the basis of the intake variables only, a computer prediction "poor outcome" was correct in 42 (55%, likelihood ratio 2.9) of 76 cases. A prediction "not-poor" was correct in 286 (73%, likelihood ratio 0.79) of 390 cases. The sensitivity of this model was 29%; the specificity was 89%. Altogether, 30% of the patients were misclassified. With the intake and 6-month variables combined, the positive predictive value for a poor out-

TABLE 2. *Comparison of terminal remission and longest remission during the last 6 months of follow-up in 139 children with a poor outcome according to the definition*

	LR						
TR	≤1 mo	1–2 mo	2–3 mo	3–4 mo	4–5 mo	5–6 mo	Total
≤1 mo	29	11	5	5	6	13	69
1–2 mo		4	2	5	10		21
2–3 mo			5	8			13
3–4 mo				8			8
4–5 mo					11		11
5–6 mo						17	17
Total	29	15	12	26	27	30	139

In seven children, it was not possible to define the exact length of either TR or LR.

TR, terminal remission; LR, longest remission.

TABLE 3. *Poor outcome*

	Odds ratios (95% CI)	
	Intake variables	Int. + 6-mo variables
+ No. of seizures before intake		
>25 vs. ≤25	1.19 (0.57, 2.46)	
+ Log (no. of sz. before intake)	1.51 (1.05, 2.19)[a]	
+ Seizure type	[b]	
Compl. part. vs. GTC Sz.	1.64 (0.80, 3.36)	1.05 (0.49, 2.21)
Simple part. vs. GTC Sz.	3.15 (1.32, 7.51)[a]	2.72 (1.07, 6.89)[a]
Absences vs. GTC Sz.	1.43 (0.60, 3.41)	0.58 (0.24, 1.39)
Infant. spasms, myocl./atonic seiz. vs. GTC Sz.	3.01 (1.45, 6.23)[b]	1.53 (0.74, 3.18)
+ Etiology		
Remote sympt. vs. idiop.	1.90 (1.06, 3.39)[a]	1.48 (0.83, 2.64)
Cryptogenic vs. idiop.	2.20 (1.25, 3.87)[b]	1.95 (1.05, 3.61)[a]
+ Preexisting neurol. signs, yes vs. no	1.67 (0.87, 3.19)	
+ EEG at intake		
Epil. abn. vs. normal		1.33 (0.71, 2.48)
Other abn./not obtained vs. nl.		2.09 (0.98, 4.47)
+ No. of seizures during first 6 mo after intake, >25 vs. ≤25	n.a.	2.20 (1.06, 4.56)[a]
+ Log (no. of sz. in first 6 m. + 1	n.a.	1.99 (1.39, 2.85)[c]
+ Remission of 3 mo during 6 mo after intake, + vs. −	n.a.	0.32 (0.18, 0.58)[c]
+ EEG 6 months after intake	n.a.	
Epil. abn. vs. normal		2.21 (1.12, 4.36)[a]
Other abn. vs. normal		1.28 (0.57, 2.88)
Not obtained vs. normal		1.73 (0.92, 3.27)

Odds ratios (OR) and (between parentheses) 95% confidence intervals of the intake, and the intake and 6-month variables, respectively, for a terminal remission (TR) of <6 months during 2 years of follow-up. Variables with a removal statistic of ≤0.1 have been included (see Methods section). Multivariate stepwise backward logistic regression analysis.

GTC Sz, generalized tonic–clonic seizures; n.a., not applicable.

[a] $p < 0.05$.

[b] $p < 0.01$.

[c] $p < 0.001$.

come was 66% (likelihood ratio, 4.27), the negative predictive value 79% (likelihood ratio, 0.67), with a sensitivity of 47% and specificity of 89%. Misclassified were 24% of the children.

Another way to look at these data is to determine the individual's chance of a poor outcome. To do this, one can use the formula $P_{poor} = 1/1 + e^{-(z)}$ (see Methods section). Table 4 gives the values for each category of the relevant variables and the constants of both models, rounded to one decimal and multiplied by 10 to make computations easier. From the sum score for any given individual patient, the exact corrected Z score can be calculated by dividing the sum score by 10. Multiplying this figure with the shrinkage factor gives the corrected Z score. The use of the models is made easier by the graphic presentation in Figs. 2 and 3, in which the chance of a poor outcome is plotted against the sum score. In these graphs, the shrinkage factor has already been taken into account.

DISCUSSION

This is a study of a hospital-based cohort followed up prospectively from the first visit at which the diagnosis of epilepsy was suspected. The 494 children in the cohort were collected over a period of 4 years. The estimated number of under-16s in the catchment area is ~410,000 (data from the Dutch Statistical Office). Recent data point to an incidence of childhood epilepsy of ~40 per 100,000 (22). If this number approximates the Dutch situation, ~160 children with newly diagnosed epilepsy per year would be expected in our referral area. Therefore the recruitment rate in our study may have been ~75% of the expected annual incidence.

The outcome assessment needs discussion. Outcome definitions used so far are heterogeneous: criteria such as numbers of seizures, seizure frequency, the attainment of a remission of a certain length ("remission ever"), time to remission, time to recurrence of seizures, and length of "terminal remission" have all been used. We chose seizure freedom as the main criterion, defined here as TR. This had the practical advantage of easy applicability. Moreover, seizure freedom has a direct bearing on a patient's quality of life, whereas having, for example, half as many seizures may not be an important gain in the opinion of the patient or his or her parents. The objection might be that the proportion of children with a poor

TABLE 4. *Calculation of the sum score for an individual patient*

	Intake variables only	Intake + 6-mo variables
Constant	−5	−6
Log (no. of sz. before intake)	4 × log(no. of sz.)	
No. of seiz. before intake		
≤25	−1	
>25	1	
Seizure type		
GTC Sz.	−6	−2
Complex partial	−1	−1
Simple partial	5	8
Absences	−3	−7
Other	5	2
Etiology		
Idiopathic	−5	−4
Remote symptomatic	2	0.4
Cryptogenic	3	3
Preexisting neurologic signs		
No	−3	
Yes	3	
Log (no. of sz. in first 6 mo after intake + 1)		7 × log(no. of sz. + 1)
No. of seizures in first 6 mo after intake		
≤25		−4
>25		4
3-mo remission in first 6-mo follow-up		
No		6
Yes		−6
EEG at intake		
Normal		−3
Epileptiform abnormalities		−0.6
Other abnormalities		4
EEG 6 mo after intake		
Normal		−4
Epileptiform abnormalities		4
Other abnormalities		−1.5
Not done		1.5
Sum score		

The values in the table are the actual constants and regression coefficients, rounded and multiplied by 10. To get the Z score, divide the sum score by 10, and correct with the shrinkage factor by multiplying with 0.6 (intake variables only) or 0.8 (intake and 6-month variables combined).

See Methods section, paragraph on statistics.

outcome was higher than necessary, because the occurrence of only one or a few seizures in the last 6 months of follow-up resulted in classification in the poor group. This may have happened to 13 children who had a TR of <1 month but a LR of >5 months in the last 6 months of follow-up (see Table 2). The use of the longest remission ever (LRE) for outcome assessment could be a solution to this problem, but if the epilepsy becomes resistant to treatment after a prolonged period without seizures, a good LRE outcome will not be relevant.

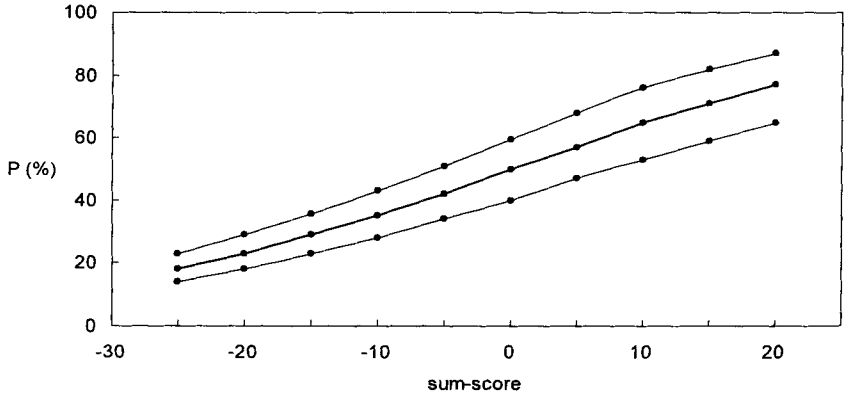

FIG. 2. Corrected chance of a poor outcome for any given sum score in the model with intake variables only. The sum score is computed by adding the values (derived from the actual regression coefficients, rounded and multiplied by 10) for each applicable category of the relevant variables (see Table 4). This sum is divided by 10 and corrected with the shrinkage factor (0.6). The resulting value is the corrected Z score. The chance of a poor outcome, P, can be calculated with the formula $P = 1/1 + e^{-(z)}$. In the figure, P is plotted against the sum score (*thick line*). Also given are the lower and upper limits of the 95% confidence interval (thin lines).

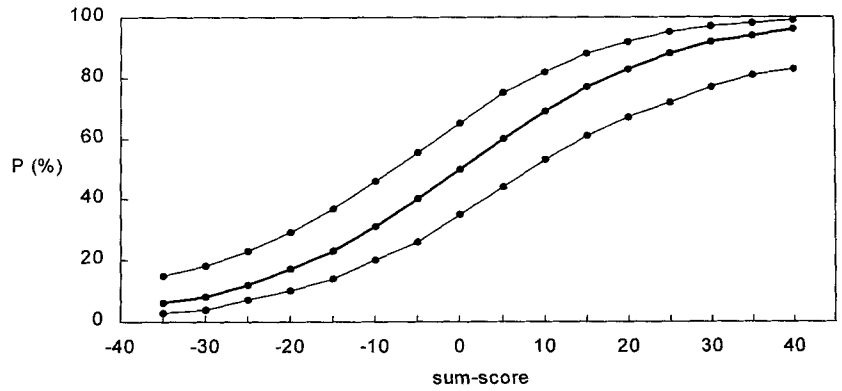

FIG. 3. Corrected chance of a poor outcome for any given sum score in the model with intake and 6-month variables. See Fig. 2 for details. The shrinkage factor for this model is 0.8.

On the other hand, it is clear that not all children fulfilling our criteria for a poor outcome will be equally poor. Table 2 illustrates this point. When one takes a certain duration of terminal remission as the main outcome criterium, this problem can never be completely solved, because one needs a fixed cut-off point. Shortening the TR period in the definition of poor outcome may be a solution to get a more homogeneous group of patients, but in this way, the problem remains of the patients with one or a few solitary seizures at the end of the follow-up. Perhaps a combination of TR and LRE would be able to sort out the children with a really poor outcome. One should recognize, however, that statistical methods will always twist the representation of reality in studies like this. The differences between various outcome-assessment methods after shorter or longer follow-up (e.g., 2 and 5 years) should be studied systematically, and the best method validated. Its use would then facilitate a comparison between the results of different studies.

This was a pragmatic study. Decisions about treatment (immediate treatment, delayed or no treatment) were left to the treating physician. The intake of the patient was chosen as the most consistent and pragmatic moment to start the follow-up. Only 12 children of 146 with a poor outcome had not been treated at all during the 2-year follow-up. In five children, the start of treatment had been delayed for >12 months. Therefore decisions of the treating physician and the parents to withhold treatment may have influenced the outcome in 17 of the 146 children.

The general outlook of epilepsy in childhood is favorable. In our study, the prognosis after 2 years was good in almost 60% and poor in ~30%. One may expect the proportion with a poor outcome to become smaller after longer follow-up, in accordance with the results of earlier studies (4,7,8,23) that concentrated on the long-term outcome. One of the most conspicuous findings of our study is the relatively good outlook early in the course of the disease (i.e., at 2 years of follow-up). Nevertheless, an important goal remains to reduce the number of patients who will eventually become intractable. In this study, we tried to identify those children at the intake and 6 months later.

We found a poor outcome to be significantly associated with seizure type ["other" seizures (infantile spasms, atonic spells, atypical absences, etc.) and simple partial seizures, as compared with generalized tonic–clonic seizures] and the number of seizures (log-transformed). These findings are somewhat different from those of other authors reporting studies on the prognosis of childhood epilepsy. Annegers et al. (2) found remote symptomatic etiology and partial seizures; Brorson and Wranne (8), the number of seizures and neurologic abnormalities, including mental retardation; Sillanpää (4), remote symptomatic etiology and a history of a large number of seizures; Hauser et al. (5), in a prospective study, remote symptomatic etiology and neurologic abnormalities; and Berg et al. (6), in a case–control study, seizure type (only infantile spasms) and remote symptomatic etiology. The common denominator, though, seems to be the presence of some kind of brain abnormality, whether it be expressed as remote symptomatic etiology, the presence of partial seizures or one of the seizure types associated with the malignant epilepsies of childhood, or the presence of neurologic abnormalities at examination. The number of seizures was relevant in a number of studies (4,8), including ours. When log-transformed, a larger number of seizures was associated with a worse prognosis. Interestingly, we did not find a number of other variables to be of prognostic significance for a poor outcome, whereas others had, notably early age at onset (5,6) and a presentation with status epilepticus (4,6). A good explanation for this finding is lacking.

After addition of the 6-month variables to the analyses, etiology and seizure type remained in the model but lost importance. The course of the disease during these 6 months was relatively more important, especially when it was expressed as not achieving a 3-month remission during that follow-up period, and as the number of seizures in these 6 months, log-transformed. The EEG done at 6 months also had a significant impact on the prognosis

(epileptic abnormalities vs. normal). These findings raise the question whether it is the "epileptic disposition" of the patient—making him refractory to treatment both immediately after treatment onset and later—or the persistence of seizures, aggravating the course of the epilepsy, which really determines the prognosis in this group of predominantly symptomatic and cryptogenic epilepsies. To explore this question, one would have to study a group identified early as having a poor prognosis and try to prevent such an outcome by early vigorous intervention. Current knowledge suggests that prevention of intractability should start as early as possible (10). With this in mind, we conclude that our study presents models with which one will be able to identify candidates for such an approach as early as possible.

Acknowledgment: The EEGs were reviewed by Drs. R.J. Schimsheimer, A.W. de Weerd, and J. Zapletal. Dr. A.B. Johnson gave statistical advice. Secretarial assistance was given by Mrs. M. Westendorp-de Serière and Mrs S. Looman. This study was supported by grants no. A72 and A86 from the Dutch National Epilepsy Fund.

REFERENCES

1. Hauser WA. The natural history of drug resistant epilepsy: epidemiologic considerations. In: Theodore WH, ed. *Surgical treatment of epilepsy.* Amsterdam: Elsevier, 1992:25–8.
2. Annegers JF, Hauser WA, Elveback LR. Remission of seizures and relapse in patients with epilepsy. *Epilepsia* 1979;20:729–37.
3. Elwes RDC, Johnson AL, Shorvon SD, Reynolds EH. The prognosis for seizure control in newly diagnosed epilepsy. *N Engl J Med* 1984;311:944–7.
4. Sillanpää M. Remission of seizures and predictors of intractability in long-term follow-up. *Epilepsia* 1993;34:930–6.
5. Hauser E, Freilinger M, Seidl R, Groh C. Prognosis of childhood epilepsy in newly referred patients. *J Child Neurol* 1996;11:201–4.
6. Berg AT, Levy SR, Novotny EJ, Shinnar S. Predictors of intractable epilepsy in childhood: a case-control study. *Epilepsia* 1996; 37:24–30.
7. Camfield C, Camfield P, Gordon K, Smith B, Dooley J. Outcome of childhood epilepsy: a population-based study with a simple predictive scoring system for those treated with medication. *J Pediatr* 1993;122:861–8.
8. Brorson LO, Wranne L. Long-term prognosis in childhood epilepsy: survival and seizure prognosis. *Epilepsia* 1987;28:324–30.
9. Brouwer OF, Van Donselaar CA, Stroink H, Arts WFM, Geerts AT, Peters ACB. The Dutch Study of Epilepsy in Childhood: design of the study. *Epilepsia* 1995;(suppl 3)36:S28.
10. Reynolds EH. The prevention of chronic epilepsy. *Epilepsia* 1988;(suppl 1)29:S25–8.
11. Van Donselaar CA, Geerts AT, Meulstee J, Habbema JDF, Staal A. Reliability of the diagnosis of a first seizure. *Neurology* 1989; 39:267–71.
12. Stroink H, Brouwer OF, Arts WF, Geerts AT, Peters ACB, Van Donselaar CA. The first unprovoked, untreated seizure in childhood: a hospital based study of the accuracy of the diagnosis, rate of recurrence, and long term outcome after recurrence: Dutch study of epilepsy in childhood. *J Neurol Neurosurg Psychiatry* 1998;64: 595–600.
13. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981;22:489–501.
14. Gastaut H. Classification of the epilepsies. *Epilepsia* 1969;(suppl) 10:S14–21.
15. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;30:89–99.
16. Commission on Epidemiology and Prognosis of the International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. *Epilepsia* 1993;34:592–6.
17. Hauser WA, Anderson VE, Lowenson RB, McRoberts SM. Seizure recurrence after a first unprovoked seizure. *N Engl J Med* 1982;307:522–8.
18. Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. In: Gardner MJ, Altman DG, eds. *Statistics with confidence: confidence intervals and statistical guidelines.* London: British Medical Association, 1990:83–100.
19. Copas JB. Regression, prediction and shrinkage. *J R Stat Soc B* 1983;45:311–54.
20. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15: 361–87.
21. Carpay HA, Arts WFM, Geerts AT, Stroink H, Brouwer OF, Peters ACB, Van Donselaar CA. Epilepsy in childhood: an audit of clinical practice. *Arch Neurol* 1998;55:668–73.
22. Camfield CS, Camfield PR, Gordon K, Wirrell E, Dooley JM. Incidence of epilepsy in childhood and adolescence: a population-based study in Nova Scotia from 1977 to 1985. *Epilepsia* 1996; 37:19–23.
23. Sofijanow NG. Clinical evolution and prognosis of childhood epilepsies. *Epilepsia* 1982;23:61–9.