Arq Neuropsiquiatr 1997;55(4):749-756

PROGNOSTIC FACTORS FOR RECURRENCE OF A FIRST SEIZURE DURING CHILDHOOD

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ABSTRACT - This study was designed with the objective of evaluating the chance of recurrence in our area and to answer questions regarding prognostic factors capable of helping in the management of the first seizure in childhood. One hundred and thirty six children from 1 month to 12 years of age seen at the Pediatric Emergency Division of Hospital de Clínicas de Porto Alegre because of a first seizure with or without triggering factors were included in the study. The follow-up included 121 children. We concluded that family history of seizures, presence of triggering factors at first event, seizure type, seizure duration and paroxysmal electroencephalographic abnormalities were predictive factors for seizure recurrence. The recurrence in this sample was 36.36% during the study. Cumulative recurrence risks were 14.88%, 23.14%, 28.93%, 33.06% and 35.54% to 3, 6, 9, 12 and 15 months, respectively.

KEY WORDS: seizures, child, prognoses, epilepsy.

Estudo dos fatores prognósticos na recorrência da primeira crise convulsiva na infância

RESUMO - Este estudo foi elaborado com a finalidade de avaliar a possibilidade de recorrência e de responder a questões referentes a fatores prognósticos capazes de auxiliar no manejo da primeira crise convulsiva na infância. Foram incluídas 136 crianças com idades entre 1 mês e 12 anos atendidas no Setor de Emergência Pediátrica do Hospital de Clínicas de Porto Alegre por ocasião da primeira crise convulsiva, com ou sem fator desencadeante. Foram seguidas 121 crianças por 24 meses, concluindo-se que história familiar de crise convulsiva, existência de fatores desencadeantes na primeira convulsão, tipo de crise, duração da crise e alterações paroxísticas no primeiro eletrencefalograma foram fatores preditivos para a recorrência de crise convulsiva. A recorrência foi de 36,36% no tempo em que durou o estudo. Os riscos acumulados para recorrência nesta amostra foram 14,88%, 23,14%, 28,93%, 33,06% e 35,54% para 3, 6, 9, 12 e 15 meses, respectivamente.

PALAVRAS -CHAVE: convulsões, criança, prognóstico, epilepsia.

Seizures are a common problem in pediatric neurology and it is estimated that approximately 4% of all children have a seizure during their first 15 years of life[9]. Authors who study the possibility of seizure recurrence during childhood, report it to be uncertain following a first event [5, 15, 17, 19, 25].

Several studies have been done with the objective of estimating the risk of recurrence following a first seizure, but with conflicting results. Livingston[20] reported seizure recurrence in 91% of untreated children. Blom et al.[7] observed that the result of the initial EEG had no value in predicting recurrence or in deciding about starting anticonvulsant treatment. They stressed the importance for other data

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such as history of pre, peri and post-natal anoxia; psychomotor development delay; family history of seizures, and seizure type. The decision to initiate treatment for a patient presenting with a first seizure has generated considerable debate[5, 15, 17, 19, 25]. In children, adverse effects of the antiepileptic drugs are common, and this should be considered when deciding about prolonged treatment[25]. Hart et al. [15] showed that the recurrence risk 12 months after the first seizure was 67% and after 36 months, 78%. Berg & Shinnar[5] found a variation of 23% to 71% in a two-year follow-up, since 80% of children who had recurrence, had it within two years. Verity & Golding[29] showed that the risk of developing epilepsy after a febrile seizure is smaller than previously reported and that brain damage following such events is rare. Koelfen et al. [17] found a recurrence risk of 68%, with 47% of these patients developing epilepsy. Eighty-five percent of recurrences happened in the first six months and 100% within two and a half years. Laubichler et al. [19] observed recurrence rates of 76% in the first semester and 18% in the second.

Conflicting results of different studies could be related to differences in the definition of first seizure: some authors consider it to be only one event; while others include several events happening in 24 hours and without history of previous episodes[5, 6, 15, 25]. Regarding study design, some were prospective[2, 15, 17, 19, 25, 28, 29], while others were retrospective[5, 24]. Also, Berg & Shinnar[5], Koelfen et al.[17] and Laubichler et al. [19], evaluated the interval between first seizure and recurrence, while Elwes et al. [10] observed the prognosis of untreated seizures. Another important factor in the recurrence of seizures during childhood is age. Gherpelli et al. [14], in a study of recurrence of neonatal seizures, demonstrated that 30% of the children had repeated events within nine months of follow-up, and that main risk factors were abnormalities in the neurologic exam, electroencephalogram (EEG) and head ultrasound.

Studies predicting the risk of recurrence of childhood seizures are important tools for decisions regarding starting treatment, choice of medication, duration of treatment, detection of adverse reactions and observation of elements to prevent new events. This study intends to evaluate the recurrence of childhood seizures in our area. Specific objectives were to identify acute triggering factors as well as remote factors related to seizure recurrence; to study the incidence of recurrent seizures in childhood, and to correlate type of seizure and EEG findings with recurrence risk.

PATIENTS AND METHODS

One hundred and thirty-six children, one month to 12-years old, who were seen in the pediatric emergency of *Hospital de Clínicas de Porto Alegre* with a first seizure between July 1993 and October 1994, were included. Study design was a contemporary cohort, observational, individual, to identify prognostic factors with the endpoint being seizure recurrence.

Data were collected according to a predetermined model of risk factors tracking. It included personal and socio-cultural data; neuropsychomotor development; pre, peri and post-natal complications; neuropsychiatric family history; history of the event, and neurologic examination. Children were followed for 24 months, being seen at the time of first event and then at time of recurrence or at 3, 6, 12, 18 and 24 months. Consent was given by a legal guardian. This study was classified as at minimum risk, according to Resolution # 01/88 of the *Conselho Nacional de Saúde* and was approved by the hospital medical ethics committee.

Awake and asleep EEGs with photo stimulation and hyperventilation were obtained after the first seizure and recurrence. Exams were classified as normal or having nonspecific abnormalities, focal paroxysms, generalized paroxysms or focal paroxysms with secondary generalization. Other tests were ordered as needed in a case-by-case manner.

Univariate and multivariate (logistic regression) analyses were used to correlate study variables with the endpoint (recurrence). Chi-square, exact Fisher's test and odds ratio were used when appropriate. Kaplan-Meyer survival analysis was used to estimate the risk of recurrence. Results were considered statistically significant for a level of significance of 5% ($p<0.05$).

RESULTS

One hundred and twenty-one children were followed for 24 months, with a mean follow-up of 17 months and 11 days and standard error (SE) of 26 days. Subjects were divided in two groups; Group I, children with a single seizure (n=77); Group II, children with recurrent seizures (n=44).

Seventy-three (60.33%) children were male and 48 (39.67%) female. Ages ranged from one to 149 months, mean of 29 months and 20 days and standard deviation (SD) of 30 months and 10 days. Median was 20 months and mode was in the interval between 11 and 32 months. In both groups there was a predominance of children between one and 48 months of age. No statistically significant difference was found between the two groups regarding age, race, and sex. In Group I there was a predominance of boys ($p<0.005$).

We verified that parental education was predominantly of incomplete elementary school in both groups, with a small incidence of illiteracy. It was correlated with recurrence with a tendency for statistical significance ($p=0.073$ and $p=0.045$).

Regarding prenatal complications, 40 children (33.06%) had positive history. Threatened abortion occurred in 13 (32.50%) of the cases, premature labor in 7 (17.50%), maternal infection in 5 (12.50%), drug use in 4 (10.00 %), maternal hypertension in 9 (22.50 %), placenta previa in one (2.50%) and abruptio placentae in one (2.50%) case. There was no association between history of prenatal maternal complications and seizure recurrence ($p=0.826$). In the perinatal period there was also no statistically significant difference of recurrence when type of delivery, Apgar score, birth weight / gestational age were considered; except for a trend for the Apgar score ($p=0.740$, $p=0.078$ and $p=0.773$ respectively). In the immediate post-natal period events were reported in 31 (25.62%) children. Among these, prematurity occurred in 10 (32.36 %), jaundice in 9 (29.03 %), infections in 6 (19.35 %), tremors in 2 (6.45 %) and metabolic disturbances in 4 (12.90 %), without an association between this events and seizure recurrence ($p=0.325$).

Our study revealed that 12 (9.92%) children had developmental delay, with no statistically significant difference between the groups with single and recurrent seizures ($p=0.543$, Fisher's exact test).

Of the 121 children evaluated, 84 (69.42%) had a positive family history: 76/84 (90.48%) had relatives with history of seizures, 7/84 (8.33%) of psychiatric disorders and 1/84 (1.19%) of neurologic disease. These data shows an association with recurrence that tended toward statistic significance ($p=-0,067$). Table 1 shows the distribution of children about family history of seizures and psychiatric disease. The risk seizure recurrence of a child with family history of seizures was 2.37 times higher ($OR=2.37$, $0.98<OR<5.84$).

Table 2 shows the seizure characteristics.

Table 1. Familiar history.

	Group I		Group II		p
	n	%	n	%	
Seizures					
Yes	43	56	33	75	
No	34	44	11	25	0.035*
Psychiatric disease					
Yes	6	8	1	2	
No	71	92	43	98	0.203

OR= 2.37 0.98<OR<5.84

Table 2. Seizure characteristics.

	Group I		Group II		p
	n	%	n	%	
Triggering factors					
Yes	64	83	28	64	
No	13	17	16	36	0.015*
Seizure Type					
Partial	3	4	8	18	
Generalized	74	96	36	82	0.011*
Duration					
5'	39	51	28	64	
5' - 20'	32	41	9	20	
more than 20'	6	8	7	16	0.043*
State					
Awake	44	64	32	74	
Sleep	25	36	11	26	0.240

Seizure triggering factors were reported in 92 (76.03%) children. In 67 (72.83%) was reported hyperthermia and in 23 (25%) infection without hyperthermia. The risk of recurrence for a child who had a triggering factor was 0.36 folds, with a statistically significance difference between the two groups (p=0.015).

Regarding seizure type, generalized predominated over partials, respectively 110 (90.91%) and 11 (9.09%), with a higher risk of recurrence when the first seizure was partial (p=0.011, Fisher's exact test). Duration of first seizure was of up to 5 minutes in 67 (55.37%) cases, of 5 to 20 minutes in 41 (33.88%) and of more than 20 minutes in 13 (11.76%). Risk of recurrence was higher when the first episode was of short duration (p=0.043). Regarding characteristics of the moment of the seizure episode and the child's state of sleep/awakening, we found no statistic significance.

One hundred and two initial EEGs were obtained, of which 48 (47.06%) were normal, 10 (9.80%) had nonspecific abnormalities, 30 (29.41%) had focal paroxysms, 5 (4.90%) had generalized paroxysms and 9 (8.82%) had focal paroxysms with secondary generalization. Data were stratified in normal and with paroxysms (Fig 1). The risk of recurrence for a child with paroxysmal EEG was 3.45 times higher and there was a statistic significant difference between the groups (p=0.002, OR=3.45, 1.39<OR<8.65). When focal paroxysms were compared with all other EEG findings, the recurrence risk was three times higher (OR=3.00, 1.21<OR<7.51), being statistically significant

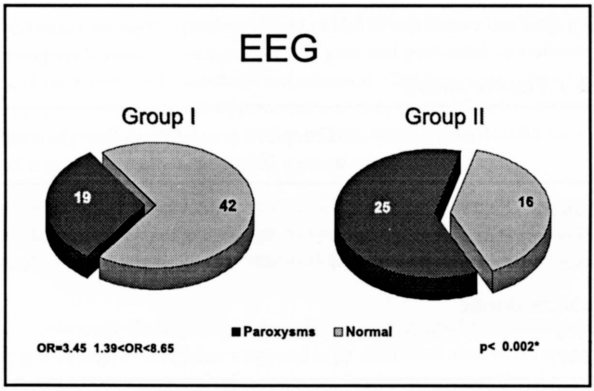

Fig 1. EEG distribution.

Table 3. EEG abnormalities and recurrence.

	Group I		Group II		p
	n	%	n	%	
Focal paroxisms	17	28	22	54	
Another EEG	44	72	19	46	0.008*
Generalized paroxisms	2	3	3	7	
Another EEG	59	97	38	93	0.317

OR = 3.00 1.21<OR<7.51

Table 4. Classification of recurrent seizures.

Epilepsies	n	%
Localized	8	18.18
Idiopathic CT+	4	9.09
Symptomatic T++	4	9.09
Generalized	36	81.82
Idiopathic FH+***	5	11.36
Symptomatic MF****	1	2.27
Without specific etiology	6	13.64
Ocasional	16*	36.36
Febrile	8	18.18
Total	44	100.00

CT+, centre-temporal; T++, temporal; FH+***, positive familiar history; MF****, central nervous system malformation. *p <0,05.

(p=0.008). The same did not happen with generalized paroxysms (Table 3). When clinical-electrographic correlation was performed, no significant associations were found (p=0.470 for Group I and p=0.314 for Group II).

General recurrence risk was 36.36 %. Seizure recurrence happened from 30 hours to 14 months after the first crisis, average of four months and 24 days and SD of three months and 20 days. Median was four months and mode was of up to six months following the first seizure. Recurrent events were similar to the first seizures. On Table 4, recurrent seizure events were grouped according

Table 5. Logistic regression.

Items	Constant ß	p	OR	CI
FH+ seizures	1.0917	0.0335*	2.9794	1.089 - 8.151
Duration - 5'	0.5365	0.0478*	1.7100	1.030 - 3.850
Duration - 5-20'	-0.0737	0.9194	0:9290	0.223 - 3.867
Duration - +20'	1.2693	0.1215	3.5584	0.714 - 17.740
1st partial seizure	2.1103	0.0186*	8.2507	1.424 - 47.810
1st parox ++EEG	1.1800	0.0123*	3.2545	1.291 - 8.203
Constant	-7.2630	0.0010*		

FH+, positive familiar history; parox++., paroxystic; OR, odds ratio; CI, confidence interval; *statistically significant.

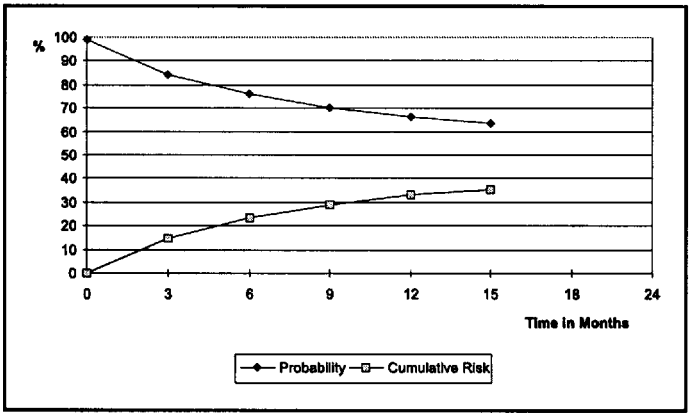

Fig 2. Cumulative risks and probability of recurrent seizures.

to the 1989 International Classification of Epilepsy and Epileptic Syndromes of the International League Against Epilepsy (ILAE).

Drug treatment was given to 38 of the children with recurrent seizures and the most frequently used drug was phenobarbital (21 children, 55.26 %) for both events associated or not with hyperthermia.

No significant complications were observed in the two years of follow-up of children with single or repetitive seizure. Regarding EEG follow-up, it was done more often in Group II and with a higher incidence of positive findings.

Multivariate analysis showed that family history of seizure, short duration of first event, partial seizure as a first event and paroxysms in the first EEG were statistically significant when adjusting for other variables (Table 5).

Figure 2 shows the probability of recurrence in up to 14 months of 63.64% with cumulative risk of 14.88% for 3 months (EP=3.30); 23,14% for 6 months (EP=3.88); 28.39% for 9 months (EP=4.16); 33.06% for 12 months (EP=4.30), and 35.54% for 15 months (EP=4.37).

DISCUSSION

There are population-based studies in the literature finding a predominance of seizures, with or without fever, among white boys, with the first event between one and 38 months of age[8,12,16,22,23,30]. This present study, although made on clinical basis, is in agreement with these informations.

Regarding our results about pre, peri and postnatal complications, they are controversial, and agree with other studies like Berg et al.[4], Forsgren et al.[13], Monetti et al.[21] and Silva[27].

Children with repeated seizures may have delayed neuropsychomotor development, which is variable according to the underlying cause[1]. However, we cannot say that the developmental delay has independent influence on seizure recurrence, but that the same etiology is responsible for both. This study showed 9% of children with developmental delay, without relationship with recurrent seizures.

Several authors comment on the association between positive family history of seizures and development of epilepsy[3,4,11,21,27]. Our results agree with these studies. Regarding family history of psychiatric disorders, we did not find association with seizure recurrence (p=0.203) as in Aicardi[1]. Our observations could reflect the sample characteristics or size, not a real disagreement. We would suggest a specifically study to verify association between recurrent seizures and family history of psychiatric diseases.

Triggering factors have been exhaustively studied and appear like a protective factor, consequently, if there is a triggering factor, the risk of recurrence is low[4,18]. On the present study the results are similar.

We found a predominance of generalized over partial first seizures, emphasizing studies in which low ages are involved. The high risk of recurrence in partial seizures observed on our study is in agreement with Camfield et al.[8] and Offringa et al.[23].

We observed that short duration of first crisis elevates the risk of recurrence. This association is controversial in the literature and the different results may be due to differences in methods[23,27].

Regarding characteristics of the moment of seizure episode and the child's state of sleep/ awakening, we found no statistic significance. This results agree with the observations of many authors[8,25-27].

Shinnar et al. [26] and Silva[27] observed the relationship between paroxystic EEG and recurrent seizures: the risk of recurrence was higher in this circumstance. Our study is in agreement with their results. No similar data about the comparison between focal paroxysms and high risk of recurrence was found in the literature.

Camfield et al.[8] and Silva[27] founded recurrent seizures in a medium time about 5 and 12 months, similar to our results. This study showed a clear predominance of generalized over localized forms ($p<0.005$), in agreement with the literature when the predominant age (between one to 48 months) is studied[8]. Regarding EEG follow-up, which was done more often in Group II, this fact demonstrates the relationship between compliance and disease perspective, as seen in the literature[30].

When we consider the multivariate analysis, our results are in agreement with Forsgren et al.[13], who did not found association between pre and perinatal factors and recurrent seizures and with Berg et al.[4], who compared family history of seizures and recurrence.

Kaplan-Meyer survey is an available method to detect the risk of recurrence after a first seizure, used for many authors. Our results are similar to the findings of Berg et al.[2], who have studied febrile recurrence risk, and of Silva[27], who has studied unprovoked recurrence risk.

CONCLUSIONS

It was possible to conclude that:

the incidence of recurrent seizures was 36.36% during the study duration;

predictive factors for recurrent seizures in childhood were maternal low education, family history of seizures, existence of a triggering factor, type of seizure, seizure duration and paroxysms on EEG;

acute triggering factors, hyperthermia and infection were protective against recurrence;

remote triggering factors had no influence on seizure recurrence;

when variables were adjusted in a logistic regression model, maternal low education and existence of triggering factors showed only tendency toward statistic significance;

when the first seizure was partial, the recurrence risk increased six folds;

when focal paroxysms were seen in the first EEG, the recurrence risk was three times higher;

cumulative recurrence risks were of 14.88 % for 3 months, 23.14% for 6 months, 28.39 % for 9 months, 33.06% for 12 months and 35.54% for 15 months;

although not statistically significant, there was a strong tendency for association of seizure recurrence and paternal low education, low Apgar score, positive family history of neuro-psychiatric disease and abnormalities on initial exam.

Acknowledgments - The authors thank Francisco T. Rotta, MD for valuable suggestions to this manuscript.

REFERENCES

1. Aicardi J. Epilepsy in children. Ed 2. New York: Raven Press 1994:1-543.
2. Berg AT, Shinnar S, Hauser WA, et al. A prospective study of recurrent febrile seizures. N Engl J Med 1992;327:1122-1127.
3. Berg AT, Shinnar S, Hauser WA, Leventhal JM. Predictors of recurrent febrile seizures: a metaanalytic review. J Pediatrics 1990;116:329-337.
4. Berg AT, Shinnar S, Shapiro ED, Salomon ME, Crain EF, Hauser WA. Risk factors for a first febrile seizure: a matched case-control study. Epilepsia 1995;36:334-341.
5. Berg AT, Shinnar S. The risk of seizure recurrence following a first unprovoked seizure: a quantitative review. Neurology 1991;41:965-972.
6. Berg AT, Testa FM, Levy SR, Shinnar S. The epidemiology of epilepsy: past, present and future. In Riggs J (ed) Neurologic clinics neuroepidemiology 1996;14:383-398.
7. Blom S, Heijbel J, Bergfors PG. Incidence of epilepsy in children: a follow-up study three years after the first seizure. Epilepsia 1978;19:343-350.
8. Camfield P, Camfield C, Gordon K, Dooley J. What types of epilepsy are preceded by febrile seizures? a population - based study of children. Dev Med Child Neurol 1994;36:887-892.
9. Dodson E, Pellock JM. Epileptic syndromes. In Pediatric epilepsy: diagnosis and therapy. Ed 2. New York: Demos 1993:78-94.
10. Elwes RDC, Johnson AI, Reynolds EH. The course of untreated epilepsy. Br Med J 1988;297:948-950.
11. Esch A van, Steyerberg EW, Berger MY, Offringa M, Derksen-Lubsen G, Habbema JD. Family history and recurrence of febrile seizures. Arch Dis Child 1994;70:395-399.
12. Farwell JR, Blackner G, Sulzbacher S, Adelman L, Voeller M. First febrile seizures: characteristics of the child, the seizure, and the illness. Clin Pediatr 1994:263-267.
13. Forsgren L, Sidenvall R, Blomquist HK son, Heijbel J, Nyström L. Pre and perinatal factors in febrile convulsions. Acta Paed Scand 1991;80:218-225.
14. Gherpelli JLD, Paz JA, Leone CR, Ramos JLA, Diament AJ. Seizure recurrence in infants with neonatal convulsions. Arq Neuropsiquiatr 1992;50:31-36.
15. Hart YM, Sander JW, Johnson AL, Shorvon SD. National general practice study of epilepsy: recurrence after a first seizure. Lancet 1990;336:1271-1274.
16. Hauser WA. The prevalence and incidence of convulsive disorders in children. Epilepsia 1994;35:S1-S6.
17. Koelfen W, Maser P, Korinthenberg R. Risk of recurrent seizures after the first afebrile grand mal seizure in childhood. Monats Kinderheilkd 1991;139:639-642.
18. Komori H, Wada M, Eto M, Oki H, Ainda K, Fujimoto T. Benign convulsions with mild gastroenteritis: a report of 10 recent cases detailing clinical varieties. Brain & Dev 1995;17:334-337.
19. Laubichler W, Ortner J, Plochl E, Wenger E. The status of afebrile infantile convulsions within the epilepsy spectrum: a follow-up of 55 patients. Nervenarzt 1992;63:741-745.
20. Livingston S. Comprehensive management of epilepsy in infancy, childhood and adolescence. Springfield: Charles Thomas, 1972.
21. Monetti VC, Granieri E, Casetta I et al. Risk factors for idiopathic generalized seizures: a population-based case control study in Copparo, Italy. Epilepsia 1995;36:224-229.
22. Murphy CC, Trevathan E, Yeargin-Allsopp M. Prevalence of epilepsy and epileptic seizures in 10-year-old children: results from the Metropolitan Atlanta developmental disabilities study. Epilepsia 1995;36:866-872.
23. Offringa M, Bossuyt PMM, Lubsen J et al. Risk factor for seizure recurrence in children with febrile seizures: a pooled analysis of individual patient data from five studies. J Pediatrics 1994;124:574-584.
24. Plöchl E, Laubichler W. Retrospektive Studie bei 160 Kindern mit Fieberkrämpfen. Klin Pädiatr 1992;204:16-20.
25. Shinnar S, Berg AT, Moshé S et al. Risk of recurrence following a first unprovoked seizure in childhood: a prospective study. Pediatrics 1990;85:1076-1085.
26. Shinnar S, Kang H, Berg AT, Goldensohn ES, Hauser WA, Moshé SL. EEG abnormalities in children with a first unprovoked seizure. Epilepsia 1994;35:471-476.
27. Silva CA da. Estudo prospectivo sobre o prognóstico de crises epilépticas recentes não provocadas ocorridas em crianças atendidas em um hospital universitário. Dissertação de Mestrado, Universidade Federal do Paraná. Curitiba, 1995.
28. Tsuboi T, Endo S, Iida N. Long-term follow-up of a febrile convulsion cohort. Acta Neurol Scand 1991;84:369-373.
29. Verity CM, Golding J. Risk of epilepsy after febrile convulsions: a national cohort study. Br Med J 1991;303:1373-1376.
30. Watts AE. The natural history of untreated epilepsy in a rural community in Africa. Epilepsia 1992;33:464-468.