IDIOPATHIC FIRST SEIZURE IN ADULT LIFE

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(Eén insult: toeval of niet?)

PROEFSCHRIFT

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Reliability of the diagnosis of a first seizure.
CA van Donselaar, AT Geerts, J Meulstee, JDF Habbema, A Staal
Neurology 1989; 39:267-271

Usefulness of an aura for the classification of a first generalized seizure.
CA van Donselaar, AT Geerts, RJ Schimsheimer
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EEG in patients with an idiopathic first seizure.
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CA van Donselaar, RJ Schimsheimer, AT Geerts, AC Declerck
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Idiopathic First Seizure in Adulthood. Who should be treated?
CA van Donselaar, AT Geerts, RJ Schimsheimer
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CONTENTS

LIST OF ABBREVIATIONS

ABNPAR	:	abnormalities non paroxysmal
ABPAR	:	abnormalities paroxysmal (non-epileptic)
AEDs	:	antiepileptic drugs
AVM	:	arterio-venous malformation
CI	:	confidence interval
CI diff	:	confidence interval of the difference
CT	:	computerised tomography
ECG	:	electrocardiogram
EEG	:	electroencephalogram
EPI	:	epileptic discharges
FED	:	focal epileptic discharges
FIRDA	:	focal intermittent rhythmic delta activity
GED	:	generalized epileptic discharges
k	:	kappa
kw	:	weighted kappa
NMR	:	nuclear magnetic resonance
NONEPI	:	non-epileptic abnormalities or normal EEG findings
NORM	:	normal (EEG findings)
OTH	:	non-epileptic abnormalities
se	:	standard error
STDEEG	:	standard electroencephalogram
SLPEEG	:	electroencephalogram after partial sleep deprivation
UTIR	:	unnecessarily treated to intractability ratio

CHAPTER 1

INTRODUCTION

The occurrence of a first epileptic seizure will in almost all cases constitute a major frightening event for the patient involved. Although he or she often cannot remember anything about the episode except for some vague preceding feelings, the patient infers from the reactions of his surroundings that something serious has happened.

Later on, the following questions emerge:

- What has happened, was it really an epileptic seizure?
- Why me? What does the future hold: do I have a brain disease; what was the cause?
- Will it recur?
- What can be done to prevent a next seizure; is medication necessary?
- Do I have to change my way of life and stick to certain rules?
- What are the social consequences?

A period of uncertainty and anxiety often ensues. In the beginning, the patient is afraid that a new attack will occur and is often frightened when he feels something strange. Driving privileges are withdrawn temporarily and sometimes the patient is not allowed to return to his job. Other members of the family are often very concerned and do not dare to leave the patient alone or are very worried if the patient does not turn up on time.

One estimates that 2% - 5.9% of the population will suffer one or more non-febrile convulsions during their life-time (Research Committee 1960, Annegers 1979, Goodridge 1983a, Juul-Jensen 1983). However, although the first seizure is a fairly common problem, it is quite difficult for the attending physician to give a sound answer to the questions above.

The diagnosis of a first seizure has to be based on an account of the episode by an eye-witness, since an objective test is lacking. The eye-witness, however, is often very frightened by the sight of the seizure and is busy with all sorts of things, except for a meticulous observation of what is happening. One cannot expect a very accurate description under these circumstances. Validated diagnostic criteria adapted to these conditions are lacking as are studies on the reliability and accuracy of the diagnosis of a first seizure. The International Classification of Seizures is not useful for

this purpose, since it is devised to classify a seizure once the diagnosis of a seizure has been made (ILAE 1981). So we can make a guess as to whether the patient indeed has suffered from a seizure, but we do not know how valid such a diagnosis will be.

Besides, it is quite possible that different doctors will have different opinions. For example: what should the diagnosis be in a healthy 45-years-old man who has seemingly suddenly lost consciousness. The last thing the patient remembers, is that he was walking along the beach with his dog. The next thing, that he was lying at the edge of the sea, initially rather confused but alert after 15 minutes with aching muscles, a headache and incontinence for urine. An eye-witness is lacking except for the dog. Has he indeed suffered from an epileptic seizure? Does the description contain sufficient leads upon which to make a diagnosis? What would have been the diagnosis if the patient had bitten his tongue?

In some patients, the seizure is clearly caused by an underlying disease such as a meningitis or subarachnoid haemorrhage. In others, the previous medical history provides aetiological clues like a cerebral infarction or a recent cranial trauma. Alcohol addiction may also have been a provocative factor. In a large proportion of the patients, however, an obvious explanation, why this particular patient has suffered an epileptic seizure, is lacking. Although this is reassuring for the physician, it will often lead initially to anxiety and disbelief in the patient.

One has to decide whether a computerised tomography scan (CT scan) or even a nuclear magnetic resonance scan (NMR scan) should be obtained in all patients to exclude underlying structural brain abnormalities. Opinions on the usefulness of such a policy are divided: some argue that the yield is too low to warrant this investigation (Hopkins 1988), others advise the opposite (Holmes 1988).

Studies on the prognosis after a first seizure have shown widely diverging results with recurrence rates varying from 20% to 80% (Thomas 1959, Johnson 1972, Saunders 1975, Cleland 1981, Hauser 1982, Goodridge 1983b, Elwes 1985, Hopkins 1988). Patient selection and study design might explain these differences. Studies assessing the long-term prognosis after a first seizure are lacking, since the first recurrence is an end-point in all these studies. However, we do know that about 75% of newly diagnosed epileptic patients can be treated adequately with antiepileptic drugs (Shorvon 1982, Goodridge 1983b, Ramsay 1983, Elwes 1984, Callaghan 1985, Mattson 1985, Turnbull 1985, Luhdorf 1986, Beghi 1988).

In some countries, like the United States, the majority of patients will be treated immediately with antiepileptic drugs to prevent recurrences. In other countries, such as the Netherlands, a more conservative approach is usual. In the United Kingdom, some argue that delaying treatment may

lead to worse treatment results in the long term and therefore suggest starting treatment immediately after the first seizure (Reynolds 1983, Reynolds 1987, Elwes 1988a). No trials, however, have been performed to support this hypothesis. Some advise treating those patients in whom the electroencephalogram (EEG) showed epileptic discharges (Holmes 1988). Studies on the predictive value of the EEG are contradictory. The finding of epileptic discharges was associated with an increased risk of recurrence in three studies (Cleland 1981, Hauser 1982, Annegers 1986). In the most recent study on 201 patients with a first seizure, however, the EEG findings did not correlate with the risk of recurrence (Hopkins 1988). These divergent findings may have been caused by different opinions on the interpretation of grapho-elements.

One commonly advises the patient to refrain from excessive lack of sleep, stress or excessive intake of alcohol to prevent a second seizure. We wondered whether there might be too much emphasis on these factors. Most patients (and their attending physicians) will look for a cause for the seizure and this may lead to too great an emphasis on these possibly provocative but not exceptional circumstances. This might lead to false reassurance.

One of the inconvenient consequences of a first seizure is the loss of driving privileges for a certain period of time. According to the official regulations in our country, one is not allowed to drive for one year. In my opinion this period is long since most recurrences will occur within six months. Anyway, I have no illusions that all patients indeed adhere to this ban. I asked 20 consecutive patients afterwards, whether they had indeed refrained from driving for a period of six months; 18 admitted that they had not done so for the entire period. A well-founded reasonable approach to this problem is clearly necessary for the patients as well as for the government agencies involved.

Seen the uncertainties above, we decided to carry out a prospective study of adults having a first seizure. We confined ourselves to those patients in whom an obvious cause, on clinical grounds, for the occurrence of the seizure was lacking (idiopathic seizures). We included patients in whom stress, exertion or lack of sleep might have provoked the seizure. None of the patients were treated with antiepileptic drugs unless a second seizure occurred.

The main purposes of the study may be described as follows:

- The first step was to develop criteria for the diagnosis of a first seizure suitable in research conditions. To assess the value of these criteria we studied the reliability (Chapter 2) and accuracy (Chapter 6) of these diagnostic criteria.

- Most patients who are referred to the hospital because of a first seizure, have suffered a generalized convulsion. These are commonly subclassified into partial seizures secondarily generalized or generalized from onset. The type of seizure may influence the choice of additional investigations and the selection of antiepileptic drugs. We studied the validity of such a classification (Chapter 3).
- An EEG will be made in almost all cases. We assessed the reliability of the visual EEG interpretation (Chapter 4) and the predictive value of the EEG (Chapter 5).
- Risk of recurrence, predictive factors, incidence of structural brain abnormalities and fate after the first recurrence are described in Chapter 6.
- We did not perform a trial comparing the efficacy of immediate versus delayed treatment to prevent early recurrences or intractibility in the long term. At the beginning of our study, we could not assess whether such a study would be justified at all, due to the lack of sound basic data like the recurrence rate after a first untreated seizure. This also made the proper design of such a trial impossible. Instead we made a decision analysis of this problem on the basis of current knowledge. Besides a possible practical advice, such an analysis might also give leads to guide future research (Chapter 7).
- Practical guidelines for the management of patients with a first seizure are presented in Chapter 8.

We confined ourselves initially to patients aged 15 years or over. In our opinion, epilepsy and the problems involved in the management of these patients are different from epilepsy in childhood. In the meantime, a comparable study on children with first seizures was started in 1989 (Southern-Holland Epilepsy in Childhood Study 1989).

The chapters of this thesis are based on separate articles, hence a certain overlap is inevitable.

CHAPTER 2

RELIABILITY OF THE DIAGNOSIS OF A FIRST SEIZURE

CA van Donselaar; AT Geerts; J Meulstee; JDF Habbema; A Staal

The diagnosis of a first epileptic seizure may have enormous consequences for patients, such as the loss of driving privileges, interference with their jobs and the starting of antiepileptic drugs. This diagnosis is generally based on the description of the episode and it is not possible to prove whether the episode was truly an epileptic seizure. Since it is difficult to improve the accuracy (validity) of the diagnosis, we should try at first to increase the reliability (precision, consistency) of the diagnosis by reducing the interrater variability (Wulff 1981, Sackett 1985, Longstreth 1987).

We assessed the interrater variability among three neurologists for 100 patients seen with a possible first seizure. We evaluated whether the use of diagnostic criteria formulated in simple descriptive terms could improve the reliability of the diagnosis. Furthermore, we determined whether the interrater variability could be reduced by having the neurologists discuss the patients among themselves.

PATIENTS AND METHODS

Definitions

For the purpose of this study, criteria for the diagnosis of a seizure were defined as listed in table 2.1. We excluded attacks that were (1) merely staring, (2) exclusively unconsciousness with or without incontinence for urine, and (3) solely disturbances of seeing, feeling or thinking. We made the diagnosis of a syncope with myoclonic jerks if there had been a clear cause for the syncope, the loss of consciousness had been of short duration, the patient looked pale during the attack and became alert immediately afterwards.

Table 2.1 Definition of a seizure

1. Unconsciousness with myoclonic jerks with or without tongue-bite or stiffening
2. Unconsciousness with tonic spasm, without myoclonic jerks, with or without tongue-bite
3. Unconsciousness with tongue-bite without myoclonic jerks or stiffening
4. Unconsciousness or staring with one of the following preceding symptoms perceived by the patient
   - a rising feeling from the stomach to the throat
   - smelling of odd scents
   - stiffening or convulsions in the face or limb(s)
   - turning the head to one side
5. Staring without reacting to external stimuli, with lip smacking, fumbling, blinking, making grimaces or making the same movements continuously, not remembered by the patient
6. Repetitive muscle jerks in the face or limb(s) without loss of consciousness

The diagnosis of a syncope with myoclonic jerks is made when there was a clear cause for the syncope, the loss of consciousness has been of short duration, the patient looked pale during the attack and became alert immediately afterwards

Note: incontinence for urine is not part of the criteria

Patients

All patients aged 15 years or more with a possible idiopathic first seizure and all patients with a possible first syncope with myoclonic jerks were studied prospectively in four teaching hospitals. We excluded patients who had suffered from a seizure in the past, with the exception of febrile convulsions. The attending neurologist made a description of the episode and completed an extensive questionnaire on the attack, the previous medical history, and the findings on neurological examination.

One-hundred patients were admitted during the period March 1986 to June 1987. There were 62 men and 38 women. The mean age in both groups was 40 years (range: 15-85 years). Fifty-two were seen within 24 hours after the first episode, 82 within 2 weeks, 92 within 1 month and all within 3 months. In 95 cases, an eye-witness report of at least a part of the attack could be obtained. In five episodes without an eye-witness, the diagnosis had to be based on the report of the patient himself of the circumstances and beginning of the attack, and on the occurrence of a tongue-bite.

Interrater variability study

The description of the episode by the attending neurologist, the previous medical history and the result of the neurological examination were

presented to three neurologists: a senior-consultant (A.S.), a registrar (C. van D.), and a neurologist with special interest in clinical neurophysiology (J.M.). They decided independently whether the description of the attack did or did not fulfil one of the criteria found in table 2.1. They also determined whether they would have diagnosed a seizure if they were the attending physicians irrespective of the criteria cited. Afterwards, the three neurologists discussed all patients.

Statistical methods

Since part of the observed agreement can be attributed to chance, we used kappa-statistics to assess the interrater variability (Cohen 1960, Sackett 1985, Longstreth 1987).

The kappa is the ratio of the observed agreement beyond chance to the maximal potential agreement beyond chance. A kappa of 0.0 indicates that the observed agreement can be attributed completely to chance. If the observed agreement is perfect, the kappa equals the maximal value of 1.0. A kappa of -1.0 is found in case the raters totally disagree.

$$\text{kappa} = \frac{\text{(observed agreement - chance agreement)}}{\text{(100 - chance agreement)}}$$

The observed agreement is calculated by adding the percentages in which both observers agree on the diagnosis of the patients studied. For example, in the following 2x2 table, the observed agreement is:

		observer 1 +	observer 1 -		
observer 2	+	40	20	60	observed agreement:
	-	10	30	40	40% + 30% = 70%
		50	50	100	

The chance agreement is calculated as follows: The same 2x2 table is used, but now only the marginal totals are printed. The chance agreements can be calculated by multiplying these marginal totals.

		observer 1 +	observer 1 -		
observer 2	+	A	B	60	chance agreement cell A: 50% x 60% = 30%
	-	C	D	40	chance agreement cell D: 50% x 40% = 20%
		50	50	100	

Table 2.2 Interrater variability of the diagnosis of a first seizure in 100 patients

A. diagnosis based on clinical judgment

1. Agreement before discussion

		neurologist 1 +		neurologist 1 -	
		neurologist 2 +	neurologist 2 -	neurologist 2 +	neurologist 2 -
neurologist 3	+	77	2	5	3
	-	1	2	3	7

pairing	P-obs	P-chance	kappa
1-2	0.88	0.73	0.56
1-3	0.89	0.74	0.58
2-3	0.91	0.77	0.62

group kappa: 0.58
(95% CI: 0.41 to 0.75)

2. Agreement after discussion

		neurologist 1 +		neurologist 1 -	
		neurologist 2 +	neurologist 2 -	neurologist 2 +	neurologist 2 -
neurologist 3	+	83	1	3	0
	-	0	1	0	12

pairing	P-obs	P-chance	kappa
1-2	0.95	0.75	0.80
1-3	0.96	0.76	0.83
2-3	0.99	0.77	0.96

group kappa: 0.86
(95% CI: 0.74 to 0.98)

+: episode is a seizure, -: episode is not a seizure

B. diagnosis based on diagnostic criteria as formulated in table 2.1

1. Agreement before discussion

		neurologist 1 +		neurologist 1 -	
		neurologist 2 +	neurologist 2 -	neurologist 2 +	neurologist 2 -
neurologist 3	+	75	2	5	1
	-	2	1	1	13

pairing	P-obs	P-chance	kappa
1-2	0.91	0.70	0.70
1-3	0.91	0.70	0.70
2-3	0.94	0.72	0.79

group kappa: 0.73
(95% CI: 0.58 to 0.88)

2. Agreement after discussion

		neurologist 1 +		neurologist 1 -	
		neurologist 2 +	neurologist 2 -	neurologist 2 +	neurologist 2 -
neurologist 3	+	80	0	2	0
	-	0	0	0	18

pairing	P-obs	P-chance	kappa
1-2	0.98	0.69	0.94
1-3	0.98	0.69	0.94
2-3	1.00	0.70	1.00

group kappa: 0.96
(95% CI: 0.90 to 1.00)

+: episode fulfils criteria, -: episode does not fulfil criteria

The total chance agreement is 30% (cell A) + 20% (cell D) = 50% and finally the kappa becomes:

kappa = (70% - 50%)/(100 - 50%) = 0.40

For a group of raters the mean kappa (group kappa), standard error and approximate confidence interval can be assessed (Schouten 1982). The group kappa is an approximate average of the kappas of each pair of raters. Since the same subjects were judged by the same group of neurologists, we used the standard jackknife technique to assess the 95% confidence interval of the difference between two group kappas (Schouten 1986).

RESULTS

Interrater variability, diagnosis based solely on clinical judgment

Table 2.2A presents the interrater variability, when the neurologists based the diagnoses solely on their clinical judgment without reference to the formulated criteria or to the results of the additional investigations. In 77 patients, all neurologists diagnosed a seizure, and in seven cases all three agreed that the episode had not been a seizure. In 16 patients, the opinions differed. The agreement rates, corrected for the agreement due to chance (kappa), were 0.56, 0.58 and 0.62 respectively for each pair of neurologists with a group kappa of 0.58 (95% confidence interval [CI], 0.41 to 0.75). After discussion, they reached consensus in 95 patients and the group kappa became 0.86 (95% CI, 0.74 to 0.98). The difference between these two kappa's was 0.28 (95% CI diff, 0.13 to 0.43).

Interrater variability, diagnosis based solely on diagnostic criteria

Table 2.2B presents the interrater variability, when the neurologists based the diagnoses on the criteria in table 2.1, irrespective of their clinical judgment and of the additional investigations (including EEGs). All three agreed that 75 patients did and 13 did not fulfil one of these criteria. In twelve patients the neurologists disagreed: five times on the distinction of a seizure from a syncope; three times on whether the patient actually had been unconscious; once on if there actually had been stiffening; once on whether the described movements were automatisms; once on a patient who fell, lost consciousness, and had signs of a tongue-bite without myoclonic jerks or tonic spasm; and once on a patient who became un-

conscious for a short period, but who noticed involuntary jerks in her arms and legs while recovering (an eye-witness report of the beginning of the attack was not available). The kappa statistics of each pair of neurologists were 0.70, 0.70 and 0.79 respectively with a group kappa of 0.73 (95% CI, 0.58 to 0.88).

After mutual consultation, agreement was reached in 98 patients, of whom 80 did and 18 did not meet one of the diagnostic criteria. In two patients, where no agreement was reached, one neurologist classified the attacks as a syncope with myoclonic jerks while the others made a diagnosis of a seizure. The group kappa became 0.96 (95% CI, 0.90 to 1.00). The difference between the kappa before discussion and the kappa after discussion was 0.23 (95% CI, 0.08 to 0.36).

Diagnosis based on clinical judgment compared with the results of using diagnostic criteria

After discussion, five patients did not fulfil one of the diagnostic criteria for a seizure whereas in two cases, two neurologists, and in the other three cases all three neurologists, would have diagnosed a seizure if they had been the attending physician. Of these five patients, four had been unconscious with incontinence for urine. One patient was found in bed unconscious, breathing heavily and noisily; she gradually recovered in 10 minutes and complained about aching muscles for the rest of the day. Since there was no eye-witness report of the beginning of her attack, the description did not fulfil any criteria for a seizure.

In no patients would a diagnosis of a seizure have been made on the basis of the criteria, when the participating neurologists concurred an alternative diagnosis based upon their clinical judgment.

The use of the diagnostic criteria provided better agreement rates than the diagnoses based on clinical judgment. The improvement of the kappa, if the diagnosis was based on diagnostic criteria instead of clinical judgment, equalled 0.15 before discussion (95% CI diff, 0.00 to 0.30). Similarly, the improvement after discussion (comparing diagnostic criteria versus clinical judgment) was 0.09 (95% CI diff, -0.01 to +0.19).

DISCUSSION

Interrater disagreement may be caused by the examiner, the examined, or the examination (Sackett 1985). For example, a patient or an eye-witness interviewed by two observers may give two dissimilar descriptions of the

same episode. Also, different questions may be asked or different opinions may be held. In our study, we investigated only a part of the possible sources of interrater variability regarding the diagnosis of a first seizure, since the descriptions of the episodes were identical for all neurologists.

We demonstrated that the diagnosis of an epileptic seizure is subject to interrater variability. When the three neurologists based the diagnosis solely on their clinical judgment, the observed agreement, corrected for the agreement due to chance (group kappa), was 0.58. This may seem rather low, but is similar to those for most clinical diagnoses (Wulff 1981, Sackett 1985, Koudstaal 1986). Discussion among the three neurologists improved the agreement.

We also evaluated whether the reliability could be increased by the use of explicit diagnostic criteria. These were formulated descriptively in simple terms to avoid differences in interpretation (Koudstaal 1986). The criteria provided better agreement rates. The kappa of 0.96, after mutual consultation, was excellent for diagnostic purposes. However, the improvement of the agreement rates by the use of these diagnostic criteria, compared with the agreement rates of clinical judgment alone, just did not reach a significant level. On the basis of the criteria, we excluded five patients in whom at least two of the neurologists would have made a diagnosis of a seizure, if they were the attending physician. All patients included on the basis of the diagnostic criteria were also diagnosed as having a seizure based upon clinical judgment.

These findings correspond to a former study from our department on the diagnosis of transient ischemic attacks, showing that the reliability of the diagnosis could be improved considerably by using criteria formulated descriptively and by offering the neurologists the opportunity of discussion among themselves (Koudstaal 1986).

Because the interval between the attack and the visit to the clinic might have influenced the quality of the descriptions, we analyzed the data to assess the effect of this factor on the interrater variability. The group kappas found for the 52 patients who visited the clinic within 24 hours did not differ significantly from the kappas of the 48 patients seen after 24 hours.

Our findings have applicability in the design of studies on seizure recurrence. A difference in patient selection probably partly explains the divergent findings in studies of patients with first seizures; for example, the risk of recurrence, in 3 years, varied from 27% (Hauser 1982) to 71% (Elwes 1985).

Reliable criteria should be used. Studies have not mentioned their diagnostic criteria (Thomas 1959, Johnson 1972, Saunders 1975, Camfield 1985, Elwes 1985, Hopkins 1988) or have used the International Classifica-

tion of Seizures (Hauser 1982, Annegers 1986). However, this widely used Classification (ILAE 1981) does not provide guidelines for the diagnosis of epileptic seizures; it only permits classification once the diagnosis is made. Therefore, for research purposes, we suggest simple and explicit diagnostic criteria that take into account the often limited information available on these patients. The criteria should be formulated in descriptive language with verified reliability.

We also suggest a committee approach for patient inclusion. One might argue that only those patients in whom all neurologists independently agreed on the diagnosis should be entered into the study. However, the exclusion of a patient where a single neurologist (among several) has doubt, might introduce bias toward the inclusion of only particularly severe seizures. Moreover, when the number of neurologists is large, the chance of divergent opinions will increase.

There is always the problem as to whether the first seizure was, in fact, "first". Unfortunately, there is no real solution for this problem other than a carefully taken medical history.

CHAPTER 3

USEFULNESS OF AN AURA FOR THE CLASSIFICATION OF A FIRST GENERALIZED SEIZURE

CA van Donselaar; AT Geerts; RJ Schimsheimer

Generalized seizures are commonly classified on clinical grounds into partial seizures secondarily generalized or generalized from the onset. EEG findings are also sometimes involved in such a categorization. In patients experiencing a first seizure, the type of seizure determines the risk of recurrence (Johnson 1972, Hauser 1982, Annegers, 1986) and might influence the decision to start antiepileptic drugs, the choice of medication, and the selection of additional investigations. The reliability (consistency, precision) of such a classification has been shown to be poor, however (Bodensteiner 1988), and data on its validity (accuracy) are lacking.

In the case of a first seizure, often only limited information is available and the occurrence of an aura may lead to the conclusion that it is of focal onset. An aura is defined as the part of the seizure preceding loss of consciousness for which memory is retained afterwards (ILAE 1981). Although the expression "aura" is widely used, it has not been clearly defined whether all kinds of sensations perceived by the patient immediately before loss of consciousness should be regarded as an aura or only some well-circumscribed feelings such as a rising feeling from the stomach to the throat.

In 67 of 149 patients with a generalized first seizure, the occurrence of some kind of sensation immediately preceding the loss of consciousness was the only clue that possibly indicated focal onset of the seizure. The descriptions of these feelings were presented to six neurologists for the purpose of assessing interobserver variation regarding diagnosis of an aura and classification of the seizure. In an attempt to determine the accuracy of such a classification, we obtained a standard EEG, an EEG after partial sleep deprivation, and a CT scan. We followed all patients for a period of 1 year to assess the nature of recurrences.

PATIENTS AND METHODS

Patients

This prospective study was restricted to patients aged 15 years or more, who were referred to one university and three teaching hospitals because of a first seizure. We excluded patients with a remote or acute symptomatic seizure according to the criteria outlined by Hauser (Hauser 1975), and included only patients in whom there was no apparent cause on clinical grounds for occurrence of the seizure (idiopathic seizure). The diagnosis of a seizure was based exclusively on the description of the episode according to prespecified simple descriptive criteria (table 2.1). In a former study, we described the reliability of these criteria (Chapter 2). Patients with a syncope with myoclonic jerks were excluded. To enhance the consistency of recruitment, all patients were discussed by three neurologists before entering the study.

After discussion, 165 consecutive patients fulfilled the criteria above. One patient with a simple partial seizure and two patients with complex partial seizures were excluded, leaving 162 patients with a generalized seizure. One patient was lost to follow-up, 1 month after his first seizure. In addition, we excluded 12 patients in whom the description of the episode indicated focal onset of the seizure: postictal paresis (3), march (2) and one-sided (3) or clearly asymmetrical myoclonic jerks (4).

The remaining 149 patients (89 males and 60 females) were the subject of this study. They had been unconscious with either repetitive myoclonic jerks (45), stiffening (7), tongue-biting (7) or a combination of these symptoms (90). The mean age was 38 years (range: 15 - 85 years); 76 were examined within 24 hours, 127 within one week, 143 within one month and all within three months of the seizure.

In 67 patients, the occurrence of some kind of sensation immediately preceding the loss of consciousness possibly indicated focal onset of the seizure. Eighty-two patients did not report any preceding feelings.

Interobserver study

The descriptions of the preceding feelings were recorded in the patient's own words on a questionnaire by the attending physician. They were presented to six experienced neurologists, three of whom are working in an epilepsy centre and three of whom are working in teaching hospitals. All decided independently whether they regarded the sensations described as an aura implicating a focal onset of the seizure or as a non-specific

symptom. They also classified the seizures on the basis of these preceding feelings according to the following scale:

- partial seizure secondarily generalized (certainty: >60%)
- undetermined (certainty more or less equal for both diagnoses)
- generalized from onset (certainty: >60%).

Accuracy study

All EEGs were recorded on 16- or 21-channel machines with both referential and bipolar recordings using the international 10 - 20 electrode placement system. Hyperventilation and photic stimulation were used in all patients. We obtained a standard EEG in 148 of the 149 patients. In one patient, no EEGs were made because the CT scan showed metastases (patient no. 6). Unless the first EEG showed spikes or spike-wave complexes (20 patients), a second EEG was recorded after partial sleep deprivation in 124 of the 128 eligible patients. This registration took place at the beginning of the afternoon, after five hours' sleep the preceding night. The patients were encouraged to sleep during the registration. Four patients refused a second EEG.

Only spikes or spike-wave complexes were considered epileptic discharges. One observer coded all EEGs blind using the following categories: normal (NORM), abnormalities consistent with generalized epileptic discharges (GED), abnormalities consistent with focal epileptic discharges with or without generalizing secondarily (FED) and other abnormalities (OTH). Details are described in Chapter 4.

A CT scan was performed in 146 patients. All patients were followed for 12 months to assess the nature of the recurrences. The patients were not treated with antiepileptic drugs after their first seizure except for one patient with a postictal fracture of a vertebra (no preceding feelings), and three patients in whom the CT scan showed structural abnormalities (2 without preceeding feelings and patient no. 6).

Statistics

To assess the interobserver variation, kappa-statistics were used to correct for the agreement due to chance (Cohen 1960, Sackett 1985, Longstreth 1987). See Chapter 2 for statistical methods. For the classification of the seizures, the weighted kappa was used to take into consideration the extent of disagreement (Cohen 1968). Quadratic observer weights were used.

RESULTS

Interobserver study

Descriptions of the sensations preceding loss of consciousness are shown in table 3.1, along with the opinion of the observers concerning the nature of these feelings and the classification of the seizures. Also, the findings of the EEGs, results of CT scans, and the nature of the recurrences can be found in this table. Table 3.2 presents the kappa-statistics.

There was total agreement between observers in only 14 cases with regard to the interpretation of the preceding feelings as either an aura (13) or a non-specific symptom (1). The group kappa was 0.26 (se: 0.05). One observer regarded preceding feelings in all but one case (patient no. 67) as an aura, holding a different but possibly not invalid view. Excluding this observer, a kappa of 0.37 (se: 0.07) was obtained.

In 16 patients, all observers agreed on the classification of the seizure as partial. They classified 23 patients as either partial or undetermined, three as partial or generalized from onset, and mentioned all three categories in the remaining 28 patients.

We found a weighted group kappa of 0.25 (se: 0.04) for the classification of the seizures. The observer mentioned above, who regarded nearly all preceding feelings as an aura, consequently diagnosed all seizures as partial secondarily generalized. If this observer was excluded, a weighted kappa of 0.40 (se: 0.07) was obtained.

Accuracy study

The EEG showed spikes or spike-wave complexes in 17 of the 67 (25%) patients with preceding feelings (table 3.1): 12 GED and 5 FED. The clinical classifications of the preceding feelings according to most of the observers contradicted the EEG findings in six (patients nos. 3, 5, 19, 22, 33 and 61) and were consistent in eight patients (patients nos. 18, 35, 38, 54, 59, 62, 63 and 64). In the nine patients with equally divided opinions concerning the nature of the preceding feelings, the EEG showed GED in two patients (patients nos. 42 and 46) and FED in one patient (patient no. 41). Of the 82 patients who did not report any preceding sensation, the EEG showed epileptic discharges in 20 patients (24%): 10 GED and 10 FED.

Table 3.1 Preceding feelings in 67 patients who had experienced a generalized first seizure; opinions of six observers regarding these feelings, results of additional investigations and follow-up.

Description of the preceding feelings	CLASSIFICATION aura #	p u g ###	EEG *	CT **	RECURRENCES type ***	preceding feelings and other details
1. Hearing sounds louder, feeling afraid.	6	6 0 0	NOR	N	-	
2. Suddenly feeling a spinning sensation in the head, without the head actually move.	6	6 0 0	OTH	N	GS	turning of the head.
3. Head turned to the right.	6	6 0 0	GED	N	GS	feels head turning to the left.
4. Light-headedness, as though not completely conscious, a feeling as though hearing a well-known tune.	6	6 0 0	NOR	N	GS	started to feel hot, all information was mixed up.
5. Head turning to one side.	6	6 0 0	GED	N	GS	
6. Had trouble speaking and felt twitches in right arm.	6	6 0 0	-	T	-	
7. Started to feel hot.	6	6 0 0	NOR	N	-	
8. Started to feel dizzy, felt as though he was turning to the right, called for help.	6	6 0 0	NOR	N	-	
9. Saw an illusion, felt anxious.	6	6 0 0	NOR	N	-	
10. Rising feeling from stomach/breast bone into throat.	6	6 0 0	NOR	N	-	
11. Saw a quivering spot in the right half of the field of vision, then saw all sorts of familiar things in a flash.	6	6 0 0	NOR	N	-	
12. Saw tobacco shop heading straight for him; it kept coming back and he wanted to push it away.	6	6 0 0	NOR	H	-	
13. Vision became blurred; he then saw all sorts of scenes from the past around him.	6	6 0 0	OTH	N	GS	sees certain scenes in front of him.
14. Unreal feeling; images staying still; feeling as though you don't belong.	5	5 1 0	OTH	N	-	
15. Sinking feeling in the stomach, a pain in the head, vision went white, sweating.	5	6 0 0	NOR	N	-	
16. Unwell, sparkling in front of the eyes.	5	5 1 0	OTH	N	-	
17. Feeling as though the mouth were being pulled open.	5	5 1 0	OTH	N	-	
18. Light of fluoroscope suddenly seemed bright and strange.	5	6 0 0	FED	N	-	
19. Strange sensation, felt withdrawn and clumsy; let something fall.	5	5 1 0	GED	N	GS	absences.

Table 3.1 Continued

Description of the preceding feelings	CLASSIFICATION aura #	p u g ###	EEG *	CT **	RECURRENCES type ***	preceding feelings and other details
20. A sudden unsteady feeling, as if he were turning.	5	5 1 0	NOR	N	-	
21. Feeling as if a haze was forming in front of the eyes and sick feeling in the stomach.	5	4 2 0	NOR	N	GS	asymmetrical muscle jerks.
22. Felt dizzy and giddy, saw blocks shooting back and forth.	5	5 1 0	GED	N	GS	blocks shooting back and forth.
23. The world moved to and fro, saw black balls in front of the eyes.	5	5 1 0	NOR	N	-	
24. Felt the world diminishing.	5	5 1 0	NOR	N	-	
25. Seeing the world spinning round from a distance.	4	4 1 1	NOR	N	-	
26. Dizzy, feeling sick.	4	6 0 0	NOR	N	-	
27. The light went on and off.	4	4 0 2	OTH	N	-	
28. TV image remained still.	4	4 0 2	OTH	N	-	
29. Seeing pavement slabs rising.	4	4 2 0	NOR	N	-	
30. Feeling miserable and sick.	4	4 2 0	NOR	N	-	
31. Queer feeling in the stomach, unsteady on the feet.	4	4 1 1	NOR	N	-	
32. Feeling cold.	4	4 2 0	NOR	N	GS	feeling queer.
33. Feeling sick, spinning sensation.	4	5 1 0	GED	-	CPS	
34. Became dizzy, saw people moving to and fro.	4	5 0 1	OTH	N	-	
35. Strange feeling in arms and legs, feeling of being hit on the head by a stone.	4	4 1 1	FED	N	GS	
36. Glittering in front of the eyes as if he was looking directly at the sun.	4	5 1 0	OTH	N	-	
37. Felt unwell for 5 min, funny feeling in the head.	4	4 1 1	OTH	N	CPS	funny feeling in the head.
38. Got a funny feeling.	4	4 1 1	FED	T	GS	
39. Dizzy, saw everything move, everything became misty.	4	4 2 0	NOR	N	-	
40. Shaky vision.	3	3 2 1	OTH	N	-	
41. Feeling of becoming ill.	3	3 3 0	FED	N	GS	
42. Sensation of eyes being pulled inward.	3	3 2 1	GED	N	CPS	
43. Double vision.	3	3 3 0	OTH	N	-	
44. Became anxious and had trouble breathing.	3	3 3 0	NOR	N	GS	
45. Suddenly felt himself getting heavier and uncertain.	3	3 2 1	NOR	N	-	
46. Got an anxious feeling.	3	3 2 1	GED	N	GS	becoming anxious.
47. Could not hear and felt himself slipping away.	3	3 2 1	OTH	N	-	

Table 3.1 Continued

Description of the preceding feelings	CLASSIFICATION aura #	p u g ###	EEG *	CT **	RECURRENCES type ***	preceding feelings and other details
48. Developed a strange, unpleasant feeling and felt a few slight jerks.	3	2 3 1	NOR	N	-	
49. Unsteady, everything went dark.	2	2 2 2	OTH	N	-	
50. Suddenly feeling unwell.	2	2 4 0	NOR	N	-	
51. Unsteady feeling, funny feeling in the head.	2	2 3 1	NOR	N	-	
52. Became dizzy.	2	2 3 1	OTH	N	-	
53. Sleepy, tired feeling.	2	2 3 1	NOR	-	-	
54. Felt giddy, "unwell".	2	2 3 1	GED	N	-	
55. Getting a dizzy feeling.	1	2 4 0	OTH	N	-	
56. Dizzy feeling.	1	2 4 0	OTH	N	GS	unilateral jerks, light-headed.
57. Light-headedness.	1	1 4 1	OTH	N	GS	
58. Floating sensation in the head, feeling as if he was going to faint.	1	1 4 1	NOR	N	-	
59. Black-out of vision.	1	1 3 2	GED	N	-	
60. Became anxious, dizzy, started to perspire, vision blacked out.	1	1 4 1	OTH	N	-	
61. Became light-headed, unwell.	1	1 4 1	FED	N	GS	
62. Black-out of vision.	1	1 4 1	GED	C	GS	
63. Light-headedness after getting up from a chair 30 seconds before the attack.	1	1 4 1	GED	I	CPS	
64. Felt he was becoming unwell.	1	1 4 1	GED	N	-	
65. Developed a giddy feeling.	1	1 5 0	NOR	N	-	
66. Suddenly became ill, everything went dark.	1	1 5 0	NOR	N	-	
67. Felt weak at the knees.	0	1 4 1	OTH	N	-	

CLASSIFICATION p: partial seizure secondarily generalized
u: undetermined
g: generalized from onset

* EEG NOR : normal EEG
GED : generalized epileptic discharges
FED : focal epileptic discharges with or without secondary generalization
OTH : other abnormalities

** CT scan C: cyst
H: hygroma
I: infarction
N: normal
T: tumour

*** Type CPS : complex partial seizure
GS : generalized seizure
SP : simple partial seizure

#: number of observers

Table 3.2 Observer variation between 6 neurologists interpreting the feelings preceding a generalized first seizure and the classification of the seizure in 67 patients.

Diagnosis of an aura or non-specific symptom		chance agreement	observed agreement	group kappa	standard error
6 observers	:	51 %	64 %	0.26	0.05
5 observers *	:	50 %	68 %	0.37	0.07
Classification of the seizure		chance agreement	observed agreement	weighted group kappa	standard error
6 observers	:	56 %	67 %	0.25	0.04
5 observers *	:	52 %	72 %	0.40	0.07

* excluding one observer who diagnosed nearly all preceding feelings as an aura and hence all seizures as partial secondarily generalized.

The CT scan showed (unexpectedly) focal abnormalities in five patients (8%) of the group with preceding feelings: two tumours (patients nos. 6 and 38), one cyst (patient no. 62), one infarction (patient no. 63) and one thin hygroma (patient no. 12). In the other group, the CT scan showed 10 (12%) structural abnormalities: three tumours, one arterio-venous malformation, and six local atrophies.

We followed all patients for one year. In 22 of the 67 patients with preceding feelings (33%), seizures recurred. In 11 patients, the description of at least one of the recurrences was indicative of a partial onset: in four patients the type of recurrence was complex partial (patients nos. 33, 37, 42, and 63); four had an identical preceding feeling (patients nos. 3, 13, 22, and 46) and in two patients the myoclonic jerks were one-sided (patient no. 56) or clearly asymmetrical (patient no. 21); in one patient (patient no 2), the second seizure started with turning the head. Of these 11 patients, the original EEG showed GED in 6 patients (patients nos. 3, 22, 33, 42, 46, and 63). Of the 82 patients who did not report any preceding feeling, 33 suffered one or more recurrences (40%); in three of these, this seizure was complex partial. Three patients reported a preceding feeling in at least one of the recurrences.

DISCUSSION

In patients with a generalized first seizure, the occurrence of some kind of sensation immediately preceding the loss of consciousness is often the only clinical clue that possibly indicates focal onset of the seizure. This prospective study shows that the interpretation of these preceding feelings, and hence the subclassification of generalized first seizures, is subject to substantial interobserver variation. The interobserver agreement rates are below the usual level for most components of clinical examination (Sackett 1985, Longstreth 1987), but correspond to a former study of the interobserver variability of the ILAE classification of seizures (Bodensteiner 1988).

All observers based their judgment on the same written information to exclude variation caused by the patient or eye-witness. As a result, only some of the possible sources of interobserver variation were studied. The wide interobserver variation may be ascribed partly to different opinions held by the observers. One neurologist regarded nearly all preceding feelings as an aura, and consequently diagnosed all seizures as partial. Because a gold standard is lacking, it is not possible to prove whether this is a valid or invalid view; however, even when this observer was excluded, the agreement rates remained rather low.

A second cause for the interobserver variation could have been the nature of the described feelings. In accordance with former studies (Lennox 1933, van Buren 1963, Taylor 1987), the reported sensations in our study were rather diverse and sometimes vague. Moreover "classic" auras, like a rising feeling from the stomach to the throat, were few in number. After several seizures, the patient may sometimes give a more precise description of the feeling and the recurrence of identical preceding feelings may favour their interpretation as an aura. This is not helpful in patients experiencing a first seizure, however. In our study, four patients reported identical preceding feelings, but the EEG showed GED in three.

In studies of first epileptic seizures, the grounds on which generalized seizures were subclassified have not been clearly defined. The category undetermined is often not used (Johnson 1972, Hauser 1982). Differences in classification might explain the divergent findings on the correlation between the type of seizure and risk of recurrence (Johnson 1972, Annegers 1986, Hopkins 1988) and might also explain the different distribution of seizure types.

It is unfortunate that a gold standard for the classification is lacking. Indirectly, EEG findings, results of CT scanning, and nature of the recurrences may give some indication of the validity of the original clinical classification. In accordance with a former study, however, results of the

additional investigations and the follow-up were often inconsistent with the original clinical classification (Rodin 1987). The EEG showed GED relatively more often in the group of patients with preceding feelings, even in patients in whom most of the observers diagnosed an aura. The incidence of structural CT scan abnormalities was higher in the group without preceding feelings. In several patients, the type of recurrence was not consistent with the original clinical classification or the EEG findings. However, the description of the recurrences pointed to a focal onset in a higher proportion of patients with preceding feelings as compared to patients without them. Apart from this, in most patients the EEG will not show epileptic discharges, and in most epidemiologic studies the classification is based exclusively on clinical grounds (Sander 1987).

We conclude that for the present time, the classification of a first generalized seizure on clinical grounds into partial seizure secondarily generalized or generalized from onset, is too unreliable and probably too invalid as well to be useful in clinical practice or epidemiological research.

To enhance the consistency of such a classification, one must develop explicit criteria in plain language about the kind of preceding feelings that should be considered as a focal epileptic discharge. This would open the way for studies of the validity of such a classification. Differences in seizure type may represent a continuum rather than a true dichotomy, however (Rodin 1987).

Note:
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CHAPTER 4

RELIABILITY OF THE EEG

CA van Donselaar; RJ Schimsheimer; AT Geerts; AC Declerck

EEG findings may be of value in predicting the risk of recurrence in patients who have experienced a first epileptic seizure (Cleland 1981, Hauser 1982, Annegers 1986), and may influence the highly debated decision to initiate or delay treatment with antiepileptic drugs (Holmes 1988). The type of epileptic discharges may guide the physician in his choice of drugs.

The usefulness of such a diagnostic tool depends on its reliability (interobserver variation, consistency, precision) and on its validity (accuracy) (Sackett 1985). Studies on the predictive value of the EEG in patients who have experienced a first seizure, are contradictory (Cleland 1981, Hauser 1982, Annegers 1986, Hopkins 1988). Investigations of the consistency of visual interpretation of the EEG have usually concentrated on items that are not relevant to the management of patients with a first seizure (Blum 1954, Houfek 1959, Woody 1968, Rose 1973, Struve 1975, Spencer 1985).

We performed a prospective multi-centre study of the natural history of an idiopathic first seizure. This part concerns the reliability of visual interpretation of EEG findings. Four neurologists independently read 50 EEGs of patients with a first epileptic seizure. Half of the EEGs were made after partial sleep deprivation. We used a fixed protocol to classify the EEGs. The predictive value of the EEG regarding the risk of recurrence within two years in 157 patients with an idiopathic first seizure is described in Chapter 5. None of the patients received antiepileptic drugs unless they suffered a second seizure.

METHODS

The EEGs were obtained from patients aged 15 years or over who were admitted to a prospective multi-centre study of the natural history of an idiopathic first seizure. In Chapter 5 we shall describe detailed features of these patients.

All EEGs were recorded on 16 to 21 channel machines with both referential and bipolar recordings using the international 10 - 20 electrode placement system. In all patients a standard EEG (STDEEG) was made with hyperventilation for three minutes and intermittent photic stimulation. We also obtained an EEG after partial sleep deprivation (SLPEEG). This latter registration took place early in the afternoon after a maximum of five hours' sleep the night before. The patient was encouraged to sleep during the registration. If the first EEG showed epileptic discharges, the attending physician was allowed to cancel the second EEG to prevent provocation of a second seizure.

The observers coded the EEGs without access to the clinical data according to a fixed protocol describing and classifying the main grapho-elements with emphasis on the occurrence of (poly) spikes or (poly) spike wave-complexes (Appendix). These last grapho-elements were sub-classified as generalized epileptic discharges (GED) or as focal epileptic discharges with or without secondary generalization (FED). Other paroxysmal diffuse or focal events like FIRDA or focal delta or theta paroxysms were classified as "paroxysmal abnormalities otherwise" (ABPAR). Persistent diffuse or focal abnormalities were classified as non-paroxysmal abnormalities (ABNPAR). The observers scored sleep stages as superficial (sleep stage I and II) or deep (sleep stage III and IV).

The observers reached the following final conclusions on each EEG:

- normal (NORM), yes / no,

If abnormal:

- epileptic discharges (EPI), yes / no,
- abnormalities otherwise paroxysmal (ABPAR), yes / no,
- abnormalities non-paroxysmal (ABNPAR), yes / no.

The observers also classified each conclusion according to the following scale: certain (>80%), probable (51-80%), possible (20-50%) or improbable (<20%). Percentages between brackets indicate the observer's degree of certainty of a particular conclusion.

First of all, one observer coded all EEGs. We divided them into three categories: 1. normal, 2. epileptic with or without other abnormalities and 3. abnormal non-epileptic. We took a stratified sample of 25 STDEEGs and 25 SLPEEGs at random: 18 from the first category, 13 from the second and 19 from the last category. It turned out that this included both EEGs from ten patients.

Three other neurologists read these EEGs independently using the same protocol. The protocol and the definitions were discussed briefly in

advance. The observers were not aware of the stratification policy. Two of the participating neurologists are working in the same epilepsy-centre and two in the same University Hospital. All observers are experienced clinical neurophysiologists.

Statistics

To assess the interobserver variation, kappa statistics were used to correct for chance agreement (Sackett 1985, Cohen 1960, Longstreth 1987). See Chapter 2, statistical methods, for details. To take into account the extent of disagreement (certain, probable, possible, improbable) we also assessed the weighted kappa for the end-conclusions (Cohen 1968). Quadratic observer weights were used.

RESULTS

Table 4.1 shows how often the observers agreed on each final conclusion.

Table 4.1 Agreement on the classification of each end-conclusion using the dichotomous scale.

	4 observers		3 observers		2 observers	TOTAL
	yes	no	yes	no	yes/no	
NORM	10	16	4	12	8	50
EPI	6	25	5	7	7	50
ABPAR	7	14	5	13	11	50
ABNPAR	4	29	2	9	6	50

NORM : normal EEG
EPI : epileptic discharges
ABPAR : abnormalities otherwise paroxysmal
ABNPAR : abnormalities non-paroxysmal

The range of kappa values for each pair of observers, the observed agreement rates, chance agreement rates and the values for the group-kappa are presented in table 4.2. We also calculated the outcomes of the weighted group kappa statistics using the four-point scale (certain, probable, possible, improbable) to take the extent of disagreement into account.

Table 4.2 Results of the final conclusions of the standard EEG and EEG after partial sleep deprivation using the dichotomous scale (yes, no) and the four-point scale (certain, probable, possible, improbable).

		dichotomous scale					four-point scale	
		po	pc	k	se	range	kw	se
NORM	STDEEG	0.73	0.50	0.47	0.12		0.59	0.10
	SLPEEG	0.73	0.54	0.42	0.13		0.58	0.10
	50 EEGs	0.73	0.52	**0.45**	0.09	0.24-0.63	**0.59**	0.07
EPI	STDEEG	0.84	0.61	0.59	0.13		0.68	0.12
	SLPEEG	0.73	0.55	0.41	0.13		0.43	0.12
	50 EEGs	0.79	0.58	**0.50**	0.09	0.27-0.62	**0.56**	0.08
ABPAR	STDEEG	0.67	0.57	0.23	0.13		0.25	0.10
	SLPEEG	0.69	0.50	0.38	0.12		0.46	0.09
	50 EEGs	0.68	0.52	**0.33**	0.08	0.27-0.44	**0.38**	0.07
ABNPAR	STDEEG	0.75	0.60	0.38	0.17		0.41	0.14
	SLPEEG	0.87	0.73	0.51	0.17		0.45	0.15
	50 EEGs	0.81	0.66	**0.44**	0.11	0.30-0.63	**0.43**	0.10

po : observed agreement
pc : chance agreement
k : kappa
se : standard error
range : range of kappa values for pairs of observers
kw : weighted kappa

NORM : normal EEG
EPI : epileptic discharges
ABPAR : abnormalities otherwise paroxysmal
ABNPAR : abnormalities non-paroxysmal

STDEEG : standard EEG
SLPEEG : EEG after partial sleep deprivation

With regard to the question whether the 50 EEGs were normal or abnormal, a group-kappa 0.45 was found. A slightly better result was found for the presence or absence of epileptic discharges (group-kappa 0.50). The agreement rate for paroxysmal abnormalities was lower with a group-kappa of 0.33. For the presence or absence of non-paroxysmal abnormalities a group-kappa of 0.44 was obtained.

The agreement rates on the presence of epileptic discharges were higher for the STDEEG compared to the SLPEEG (group-kappa 0.59 versus 0.41). The kappa values for the presence or absence of non-epileptic abnormalities were lower for the STDEEG compared to the SLPEEG (ABPAR 0.23 versus 0.38; ABNPAR 0.38 versus 0.51). The use of the four-point scale (certain, probable, possible, improbable) instead of the dichotomous scale (yes, no) resulted in higher group-kappa values for three of the four categories (table 4.2).

Disagreement on the presence or absence of epileptic discharges was caused by the following points: distinction between spikes and fast sharp beta-activity or sharp transients (6); interpretation of bursts of focal theta or delta activity mixed with sharp beta or alpha transients (5); distinction of isolated spikes from artefacts (4). The observers disagreed on three occasions about the interpretation of sharp activity on the vertex during drowsiness and once on the interpretation of spikes as epileptic discharges or drowsiness-phenomena. On one occasion one observer, contrary to the others, came to a final conclusion of epileptic discharges on the basis of one single spike.

The distinction of paroxysmal from non-paroxysmal abnormalities proved to be another reason for disagreement. For example, should focal delta activity during 80% of the registration be interpreted as a paroxysmal or non-paroxysmal abnormality? Also, differentiation of normal from abnormal caused disagreement, e.g. interpreting fast activity due to medication as normal (for a patient using medication) or abnormal.

In 8 STDEEGs and in 10 SLPEEGs, at least two observers diagnosed epileptic discharges, leading to 58 duplicate observations of epileptic discharges. They agreed 35 times (23 GED, 12 FED) and disagreed 23 times about the type of epileptic discharges. One observer classified epileptic discharges far more often as generalized, and caused 18 of the 23 disagreements.

In 19 of the 25 SLPEEGs, at least one of the observers disagreed on the deepest sleep stage reached during the registration. This was caused eleven times by one observer, who classified sleep stages as more superficial compared to the others.

DISCUSSION

This study shows that visual interpretation of the EEG in patients with a first epileptic seizure is subject to substantial interobserver variation. We deliberately discussed the protocol and definitions only roughly in advance.

Discussing every possible difficulty and extensive training of the observers might have resulted in better agreement rates. Our study merely reflects differences in visual interpretation of EEGs in everyday practice. We restricted the items studied to 'crude' final conclusions, as these might be used as a basis for deciding to initiate antiepileptic drugs.

Differences in interpretation could not be resolved into one item on which opinions differed repeatedly. Better arrangements about distinction of sharp fast beta-activity or sharp transients from spikes, about the significance of finding a single spike and about interpretation of medication induced changes, might reduce interobserver disagreement. Disagreement on sleep stages and on classification of epileptic discharges as focal or generalized were mainly caused by one observer who held a different but possibly not invalid opinion compared to the other observers.

In retrospect, we believe that using the categories paroxysmal and non-paroxysmal for classifying non-epileptic abnormalities was an unfortunate choice. In our opinion, it is difficult to define these categories unambiguously.

There are no fixed criteria but only rough indications for the clinical significance of a given kappa (Sackett 1985, Longstreth 1987). Moreover, one should realise that prevalence of a disease or positive test-result influences the kappa. The kappa values found in our study may seem rather poor. However, they were better than the interpretation of exercise ECGs (kappa 0.31) (Blackburn 1968) or ambulatory EEG-cassettes (kappa 0.21) (Wroe 1989). In a previous study, a kappa of 0.58 was found for the agreement on the clinical diagnosis of a seizure (Chapter 2); interpretation of supratentorial CT scan lesions resulted in kappa values of 0.47 to 0.50 (Heimans 1990). The values are lower in comparison with the diagnosis of 50% or more stenosis on Duplex scan of the carotid artery (kappa 0.92) (Kohler 1985).

Former studies on the reliability of the EEG assessment usually concerned EEGs made in psychiatric patients for screening purposes. Values of the kappa-statistics varied from 0.54 (Rose 1973) to 0.73 (Houfek 1959) on a normal-abnormal dichotomy and from 0.78 to 0.86 on a trichotomy of normal, paroxysmal abnormal or non-paroxysmal abnormal (Struve 1975). These investigations however, concerned populations not comparable to ours.

If the EEG should play a part in the clinical management of patients with a first seizure, interpretation of the EEG should result in reliable and "simple" statements. This study shows that in everyday practice, the reliability of the diagnosis of epileptic discharges on the basis of visual EEG interpretation is moderate and requires improvement. This is of

particular importance, since far-reaching decisions are often based upon EEG findings. Holmes, for example, advised treating those patients immediately with antiepileptic drugs, in whom the EEG showed epileptic discharges (Holmes 1988). Analysis and discussion of different ways of interpretation are clearly necessary.

Note:
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CHAPTER 5

PREDICTIVE VALUE OF THE EEG

CA van Donselaar; RJ Schimsheimer; AT Geerts

Treatment of patients who have experienced an idiopathic first seizure, is a controversial issue. EEG findings may be of value in predicting the risk of recurrence (Cleland 1981, Hauser 1982, Annegers 1986) and some physicians use the EEG to select those patients who should immediately receive treatment with antiepileptic drugs (Holmes 1988). Studies on the predictive value of the EEG in patients with a first seizure are contradictory, however (Cleland 1981, Hauser 1982, Annegers 1986, Hopkins 1988).

We studied prospectively 165 patients aged 15 years or over, who had suffered an idiopathic first seizure. Diagnosis was based exclusively on the description of the episode without reference to results of additional investigations (Chapter 2). None of the patients were treated with antiepileptic drugs unless they experienced a second seizure. A standard EEG was made in all patients. Unless the first EEG showed epileptic discharges, we also obtained an EEG after partial sleep deprivation. All EEGs were read by one neurologist, who had no access to clinical data of the patients. In Chapter 4 we have shown that reliability of visual interpretation of EEGs is only moderate. In this part we present data on the predictive value of the EEG regarding the risk of recurrence within two years after an untreated idiopathic first seizure.

METHODS

Patients

We studied prospectively 165 consecutive patients aged 15 years or over with an idiopathic first seizure, who were referred to four teaching hospitals. We excluded patients with remote or acute symptomatic seizures according to criteria outlined by Hauser (Hauser 1975) and only included patients in whom there was no obvious cause, on clinical grounds, for the occurrence of the seizure ("idiopathic" seizures). Diagnosis of a seizure was

based exclusively on the description of the episode according to prespecified simple descriptive criteria without reference to results of additional investigations (table 2.1). We have shown in a previous study that the reliability of these diagnostic criteria is good (Chapter 2). With a view to enhancing the consistency of recruitment, all patients were discussed by three neurologists before recruitment.

Of the 165 patients, 97 were male and 68 female; mean age was 38 years (range 15 - 85 years). Mean interval between the first seizure and visit to the hospital was 6.7 days, median interval was one day. Fifty-three percent of the patients were seen within 24 hours, 70% within one week, 83% within two weeks, 94% within one month and all within three months. Length of follow-up was determined by the moment of admission into the study for each patient. All were followed for two years or until the end of the study was encountered with a minimum of twelve months. One patient was lost to follow-up after one month and one after twenty months. Nine patients died of causes unrelated to epilepsy: four brain tumours, cerebral metastases, cardiac arrhythmia, myocardial infarction, lungcancer without cerebral metastases and leukaemia. We obtained a CT scan in 162 patients. Findings of structural abnormalities was in itself not a reason for exclusion.

We excluded the following eight patients from the analysis:

- One patient in whom no EEGs were made because the CT scan showed metastases. Medication was started immediately.
- Three additional patients who were treated immediately: one because of focal CT scan abnormalities (local atrophy due to a contusio cerebri 10 years earlier), one patient who suffered a fracture of a vertebra due to the seizure (CT scan local atrophy) and one patient in whom the CT scan revealed an arterio-venous malformation.
- Four patients who experienced a recurrence within 24 hours after their first seizure; CT scan revealed a tumour in one and a transient hypodensity ("vanishing tumour") in another patient,

None of the 157 remaining patients were treated with antiepileptic drugs unless they suffered a second seizure. We classified 154 of the 157 seizures as "generalized". These patients had been unconscious with either repetitive myoclonic jerks (49), stiffening (7), tongue-biting (7) or a combination of these symptoms (91). One patient suffered a simple partial seizure and two complex partial seizures. We did not subclassify generalized seizures, since we showed in a former study that the reliability and accuracy of such a categorization is too poor to be clinically useful (Chapter 3).

EEGs

Detailed features of techniques of EEG recordings and of the way the EEG findings were classified, are described in Chapter 4. A standard EEG (STDEEG) was made in all patients. Unless the STDEEG showed spikes or spike-wave complexes (19 patients), a second EEG was recorded after partial sleep deprivation (SLPEEG) in 134 of the 138 eligible patients. Three patients refused a SLPEEG. In one patient, the second EEG was omitted because a tumour was found on CT scan. If the first EEG showed epileptic discharges, the attending physician was allowed to refrain from the second EEG to avoid provoking a second seizure. Nevertheless, in 11 patients a SLPEEG was made, although the STDEEG showed epileptic discharges.

One neurologist (RJS) who was not aware of the clinical data, classified all EEGs according to the protocol mentioned above (Appendix). The following end-conclusions were reached:

- normal yes / no,

If abnormal:
- epileptic discharges yes / no,
- abnormalities otherwise paroxysmal yes / no,
- abnormalities non-paroxysmal yes / no.

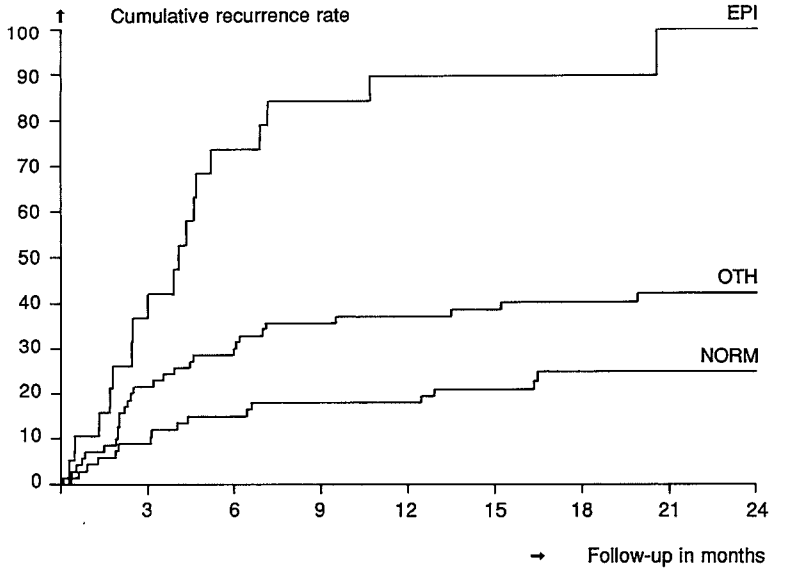
Statistics

Survival analysis techniques were used (Kaplan-Meier) for calculation of cumulative recurrence rates (BMDP 1981). We used Mantel-Cox test for comparison of survival curves. EEGs showing epileptic discharges together with other abnormalities (paroxysmal and/or non-paroxysmal) were combined (EPI) with those having only epileptic discharges. Also, EEGs with paroxysmal abnormalities, non-paroxysmal abnormalities or a combination of these two were taken together (OTH).

RESULTS

Cumulative recurrence rates for the STDEEG and SLPEEG are presented in figure 5.1 and 5.2. Mantel-Cox statistics and approximate 95% confidence intervals of the differences between the recurrence rates at two years are presented in table 5.1.

Figure 5.1: Cumulative recurrence rates based on the findings of the standard EEG of 157 patients with an idiopathic first seizure.



months	0	6	12	18	24
EPI (1)					
cum. recurr. rate	0	74%	89%	89%	100%
95% CI	-	54-94%	76-100%	76-100%	74-100%
patients at risk	19	5	2	1	0
recurr./censored		14/0	3/0	0/1	1/0
OTH (1)					
cum. recurr. rate	0	30%	37%	40%	42%
95% CI	-	19-41%	26-48%	29-52%	30-54%
patients at risk	70	49	44	36	22
recurr./censored		21/0	5/0	2/6	1/13
NORM (2)					
cum. recurr. rate	0	15%	18%	25%	25%
95% CI	-	6-23%	9-27%	14-35%	14-35%
patients at risk	68	57	55	37	17
recurr./censored		10/1	2/0	4/14	0/20

EPI : epileptic discharges
OTH : non-epileptic abnormalities
NORM : no abnormalities

(1) : one or both EEGs
(2) : both EEGs

The STDEEG showed epileptic discharges (EPI) in 19 patients, 18 of whom experienced a recurrence within two years. In 17, the recurrence was within 12 months. One patient was censored after 18 months (as scheduled at entry into the study), resulting in a cumulative recurrence rate at two years of 100% (approximate 95% CI 74 to 100%). The STDEEG showed non-epileptic abnormalities (OTH) in 70 patients, 29 of whom experienced a second seizure within two years (cum. rate 42%, 95% CI 30 to 54%), and was normal (NORM) in 68 patients, 16 of whom experienced a recurrence (cum. rate 25%, 95% CI 14 to 35%). The differences in recurrence rates were statistically significant (table 5.1).

Table 5.1 Pairwise comparison of EEG findings. Recurrence rates at two years after an idiopathic first seizure.

Mantel-Cox statistics

	STDEEG		SLPEEG		combined EEGs	
	T	p	T	p	T	p
EPI - OTH	20.7	<0.01	2.3	=0.13	14.6	<0.01
EPI - NORM	46.5	<0.01	14.6	<0.01	45.0	<0.01
OTH - NORM	4.8	<0.05	5.1	<0.05	11.2	<0.01

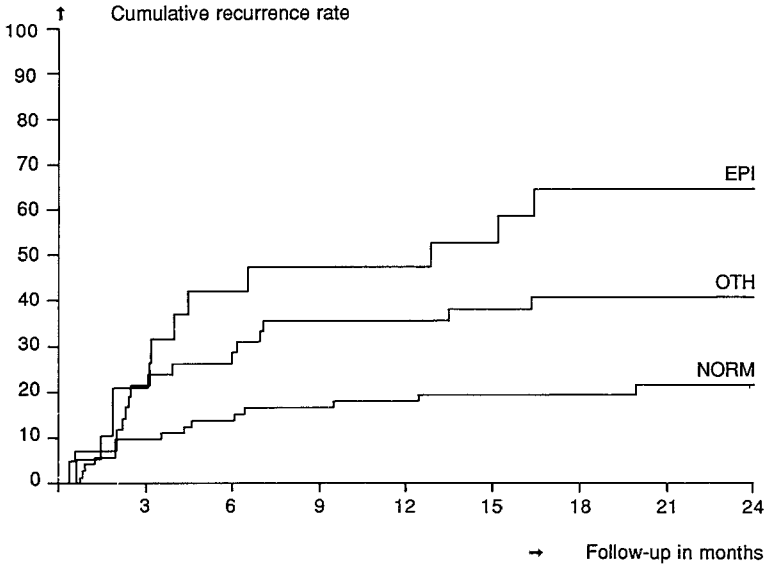
Differences with 95% confidence intervals

	STDEEG	SLPEEG	combined EEGs
EPI - OTH	58% (46 to 69%)	23% (-2 to 50%)	42% (25 to 59%)
EPI - NORM	75% (65 to 86%)	42% (19 to 66%)	71% (56 to 86%)
OTH - NORM	17% (2 to 33%)	19% (1 to 37%)	29% (15 to 44%)

EPI : epileptic discharges
OTH : non-epileptic abnormalities
NORM : no abnormalities
STDEEG : standard EEG
SLPEEG : EEG after partial sleep deprivation
T : Mantel-Cox statistics
p : p value

The CT scan unexpectedly showed clinically relevant structural abnormalities in an additional four patients (three tumours and one arachnoid cyst). Exclusion of these patients did not influence the recurrence rates since they were few in number (STDEEG: 100%, 40% and 25% respectively).

Figure 5.2: Cumulative recurrence rates based on the findings of the EEG after partial sleepdeprivation of 134 patients with an idiopathic first seizure. The standard EEG did not show epileptic discharges.

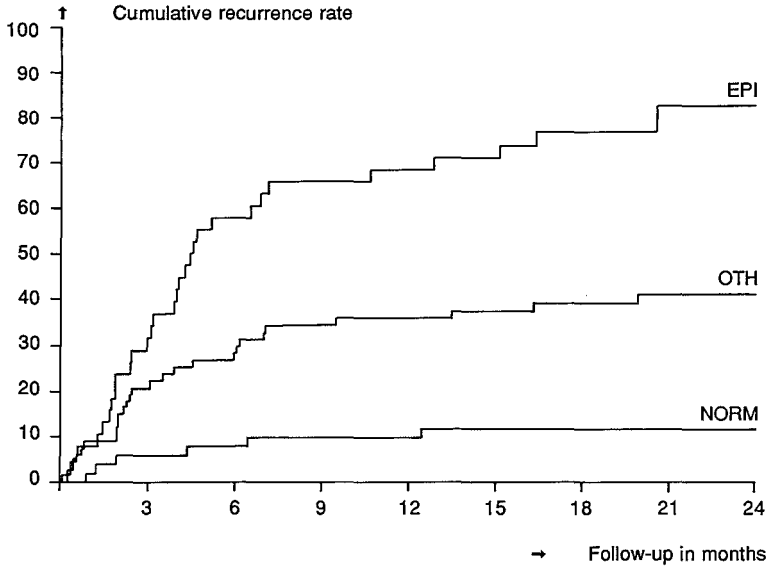


months	0	6	12	18	24
EPI (1)					
cum. recurr. rate	0	42%	47%	64%	64%
95% CI	-	20-64%	25-70%	42-87%	42-87%
patients at risk	19	11	10	6	2
recurr./censored		8/0	1/0	3/1	0/4
OTH (1)					
cum. recurr. rate	0	29%	36%	41%	41%
95% CI	-	15-42%	21-50%	26-56%	26-56%
patients at risk	42	30	27	23	14
recurr./censored		12/0	3/0	2/2	0/9
NORM (2)					
cum. recurr. rate	0	14%	18%	19%	22%
95% CI	-	6-22%	9-27%	10-29%	12-32%
patients at risk	73	62	59	44	23
recurr./censored		10/1	3/0	1/14	1/20

EPI : epileptic discharges
OTH : non-epileptic abnormalities
NORM : no abnormalities

(1) : one or both EEGs
(2) : both EEGs

Figure 5.3: Cumulative recurrence rates based on the combined findings of the standard EEG and the EEG after partial sleep deprivation of 157 patients with an idiopathic first seizure.



months	0	6	12	18	24
EPI (1)					
cum. recurr. rate	0	58%	68%	77%	83%
95% CI	-	42-74%	54-83%	64-91%	69-97%
patients at risk	38	16	12	7	2
recurr./censored	22/0	4/0	3/2	1/4	
OTH (1)					
cum. recurr. rate	0	28%	36%	39%	41%
95% CI	-	18-39%	24-47%	27-51%	29-53%
patients at risk	67	48	43	35	23
recurr./censored	19/0	5/0	2/6	1/11	
NORM (2)					
cum. recurr. rate	0	8%	10%	12%	12%
95% CI	-	1-15%	2-18%	3-21%	3-21%
patients at risk	52	47	46	32	14
recurr./censored	4/1	1/0	1/13	0/18	

EPI : epileptic discharges
OTH : non-epileptic abnormalities
NORM : no abnormalities

(1) : one or both EEGs
(2) : both EEGs

A SLPEEG was made in 134 of the 138 patients in whom the STDEEG did not show EPI. Three of these patients did not sleep during the registration, 98 reached superficial sleep (sleep stage I or II) and 33 deep sleep (sleep stage III or IV). This second registration identified 19 additional patients with EPI, 12 of whom suffered a recurrence within two years (figure 5.2, cum. rate 64%, 95% CI 42 to 87%). In 11 of the 19 patients in whom the STDEEG showed EPI, a SLPEEG was made, again showing epileptic discharges in 10 patients.

Combination of the two registrations gave the following results (figure 5.3). If both EEGs were normal (52 patients) the recurrence rate at two years was 12% (95% CI 3 to 21%), rising to 83% (95% CI 69 to 97%) if one or both EEGs showed EPI (38 patients). Presence of non-epileptic abnormalities in one or both registrations was associated with a risk of recurrence of 41% (95% CI 29 to 53%). Differences between these recurrence rates were highly significant (table 5.1). Recurrence rate in case of focal epileptic discharges (15 patients) tended to be higher, compared to generalized epileptic discharges (23 patients): 87% versus 78% respectively (95% CI -15 to 33%).

The standard EEG showing EPI, identified 18 of 63 recurrences (sensitivity 29%, 95% CI 17 to 40%) and the combined EEGs nearly half of the patients who experienced a second seizure (sensitivity 48%, 95% CI 35 to 60%). In 93 of the 94 seizure-free patients, the STDEEG did not show epileptic discharges (specificity 99%, 95% CI 94 to 100%). The specificity of the combined EEGs was 91% (95% CI 86 to 97%).

All EEGs were read by one observer (RJS). In Chapter 4 we investigated the interobserver agreement on visual interpretation of EEGs. Three other neurologists coded 50 EEGs from the present study, which makes it possible to compare the "success-rate" for each observer. The single observer who read all EEGs that were used in the present study, diagnosed epileptic discharges in 13 of these 50 EEGs. All these patients suffered from a second seizure. The other three raters diagnosed epileptic discharges in 10, 17 and 20 EEGs with recurrence rates of 90%, 82% and 75% respectively, sensitivities were 50% (RJS), 35%, 54% and 58% respectively.

DISCUSSION

If the EEG could predict accurately whether a patient with an idiopathic first seizure has a high or low risk of recurrence, it could play an important role in the decision to initiate or delay treatment with antiepileptic drugs. We found that the presence of epileptic discharges in a standard EEG was

associated with a highly increased risk of recurrence within two years (100%) compared to the overall recurrence rate (41%). Normal EEG findings were associated with a decreased risk of recurrence (25%). Sensitivity proved to be 29%, specificity 99%.

We also obtained an EEG after partial sleep deprivation. We cannot assess whether it might be sufficient to obtain solely a SLPEEG instead of a STDEEG. For ethical reasons, we did not obtain a SLPEEG in all patients in whom the STDEEG showed epileptic discharges. However, the finding of epileptic discharges in 11 STDEEGs was duplicated 10 times in the SLPEEG. The SLPEEG identified an additional number of patients with epileptic discharges above the standard EEG. The significance of these findings was hampered by a number of "false-positives", meaning that about one third of these patients did not suffer a second seizure within two years. Whether these facts indeed justify obtaining also a SLPEEG or replacing the STDEEG by the SLPEEG is a rather subjective choice. In addition, one should bear in mind that interobserver variation of visual interpretation of SLPEEGs is larger than that for STDEEGs (Chapter 4).

Our findings are better than those of Hauser and Annegers, who found that the risk of recurrence was almost doubled if the EEG showed epileptic discharges as opposed to normal findings (Hauser 1982, Annegers 1986). In both studies, the majority of patients were treated with anti-epileptic drugs, which might have suppressed recurrence rates. Conversely, Hopkins did not find any relationship between EEG findings and risk of recurrence (Hopkins 1988). In the last study, incidence of epileptic discharges was much higher compared to our study (27% versus 12% on the STDEEG), whereas overall recurrence rates were quite similar (45% versus 41% resp. at two years). This suggests that a more liberal definition of epileptic discharges was used and might explain these diverging results.

The clinical significance of our findings depends on the policy that one has towards treatment of a first seizure. In our country, standard policy is "to wait and see", thus avoiding unnecessary treatment. Our results indicate, however, that it might be worthwhile to consider treating those patients in whom standard EEG, or EEG after partial sleep deprivation, or both show epileptic discharges. As the recurrence rate in this group of patients is very high, immediate treatment would mean that none or only a small minority of patients would subsequently be treated unnecessarily. Whether immediate treatment is indeed warranted, will depend also on other considerations, like appraisal of risks and benefits of early treatment.

In other countries like the U.S.A., the majority of patients will receive treatment with antiepileptic drugs immediately. Our study showed that the risk of recurrence was only 12% if both EEGs were normal and 25% if only the standard EEG was normal. One must consider whether the

possible (and not proven) advantages of treating this group of patients immediately (Reynolds 1983), counterbalance the "losses" consisting of treating the large majority of patients unnecessarily, who would not experience a second seizure even without treatment. In our view, risk of recurrence in this group of patients is too low to warrant immediate treatment irrespective of possible advantages of this policy.

One should bear in mind that the scarce studies on the predictive value of the EEG are contradictory. The moderate reliability of visual interpretation of EEGs certainly requires improvement and makes extrapolation of our findings hazardous. However, the excellent predictive value in spite of the considerable interobserver variation, illustrates that the EEG is a potential accurate instrument to predict the risk of recurrence. One might argue that this high predictive value might have been caused by selection of a very accurate observer. Comparison with the other three observers who also scored 50 EEGs, does not support this hypothesis. Value of computerised analysis of the EEG might be promising, but its reliability and accuracy still have to be proven (Hachinski 1989, Hopkins Duffy 1989, Nuwer, 1989).

CHAPTER 6

IDIOPATHIC FIRST SEIZURE IN ADULTHOOD

CA van Donselaar; AT Geerts; RJ Schimsheimer

Opinions differ on treatment of patients with an idiopathic first seizure (Hachinski 1986, Hart 1986, Hauser 1986). In the U.S.A., the majority of patients will be treated immediately with antiepileptic drugs (AEDs), whereas in other countries, like ours, a more conservative approach is usual (Hauser 1982, Annegers 1986, Hopkins 1988). Treating all patients immediately after their first seizure might reduce the number of recurrences and some argue that early treatment reduces the number of intractable patients in the long run (Reynolds 1983, Reynolds 1987). Not all patients suffer a second seizure, however, and treating all patients immediately would imply that a considerable number of patients would be treated "unnecessarily".

Data required to solve this dilemma are either lacking or a matter of dispute. Diagnosis of a first seizure is often difficult and its reliability and accuracy are hardly known (Johnson 1972, Chapter 2). Investigations of the recurrence rate after a first seizure or predictive value of the EEG have shown widely diverging results (Johnson 1972, Saunders 1975, Blom 1978, Cleland 1981, Hauser 1982, Elwes 1985, Annegers 1986, Hopkins 1988). Differences in treatment policies, study design and selection of patients might explain these disagreements. The first recurrence is an end-point in all these studies, and hence the fate after the first recurrence is not known. The supposed superiority of immediate treatment has not yet been proven. Also necessity to obtain an electroencephalogram (EEG), or a computerised tomography (CT) scan, or both in all patients has recently been challenged (Holmes 1988, Hopkins 1988).

Considering the many uncertainties mentioned above, we conducted a prospective investigation of 161 patients aged 15 years or more with an untreated first seizure. Only patients in whom there was no clear cause for the occurrence of the seizure (idiopathic seizures) were included. Primary aim was to assess the recurrence rate, predictive factors and yields of additional investigations, consisting of a CT scan, standard EEG

(STDEEG) and an EEG after partial sleep deprivation (SLPEEG). In addition, we evaluated the accuracy of the diagnosis of a first seizure that was based on a description of the episode. All patients were followed up for one to two years. Patients who suffered recurrences were followed up for an additional year since the first year of treatment is crucial for the long-term prognosis (Shorvon 1982, Shorvon 1984, Elwes 1984, Luhdorf 1986).

In former studies, we described the interobserver agreement of the diagnostic criteria (Chapter 2) and the reliability and accuracy of the EEG as predictor of the risk of recurrence (Chapters 4 and 5).

METHODS

Patients

We studied prospectively all patients aged 15 years or more with a presumed idiopathic first seizure, who were referred to three teaching hospitals and one university hospital during the period of March 1986 to March 1988.

Patients who had suffered a seizure in the past, regardless of supposed aetiology with exception of febrile convulsions, were excluded, as were patients presenting with status epilepticus or with a seizure lasting more than 30 minutes. We admitted only those patients for whom there was no obvious cause on clinical grounds for the occurrence of the seizure (idiopathic seizures). We excluded patients with remote or acute symptomatic seizures according to the criteria outlined by Hauser et al. (1975). For example, patients with abnormal neurological examinations were classified as acute symptomatic as were patients known to have a recent malignancy that might have caused intracerebral metastases. Seizures possibly induced by sleep deprivation or stress were classified as idiopathic except for very extreme conditions like not sleeping for several days.

The clinical diagnosis of a presumed idiopathic seizure was based on the description of the episode according to prespecified diagnostic criteria (table 2.1) and on the results of previous medical history and neurological examination without reference to results of additional investigations. Three neurologists first independently judged whether the description of the episodes fulfilled the criteria above. In a former study, we showed that the reliability of these criteria was good (kappa 0.73) in the first 100 consecutive patients (Chapter 2). They also classified the seizures according to aetiology. All patients were discussed afterwards by the three participating neurologists before admission. Majority ruled in case of disagreement.

The four centres referred 226 patients, four of whom were excluded immediately as they did not keep appointments for additional investigations (table 6.1 summarizes all in- and excluded patients). Twenty-four episodes were classified as remote or acute symptomatic seizures and in two patients another diagnosis was made: hyperventilation and migraine.

Table 6.1 Summary of in- and excluded patients

Total number of patients referred:	226
Excluded:	
- did not show up for additional investigations	4
- other diagnosis	2
- acute or remote symptomatic seizures	24
- syncope with myoclonic jerks	7
- episode did not fulfil criteria	24
Included: clinically presumed idiopathic seizure	165 [1)]
- CT scan major abnormalities	9
- treated immediately	2
- recurrence within 24 hours	3
Isolated, idiopathic (confirmed by CT scan), untreated first seizure	151 [2)]

ad 1. Patients studied to determine the accuracy of the clinical diagnosis of an idiopathic first seizure.

ad 2. Possible predictive factors and fate after first recurrence are studied in this group of patients.

We made a diagnosis of syncope with myoclonic jerks in seven patients. Twenty-four patients were not admitted since the description of the episode did not fulfil one of our diagnostic criteria whereas no other diagnosis could be made. These last two groups of patients were followed for one year except for one patient, who was lost to follow-up after 5.5 months.

We diagnosed a presumed idiopathic seizure on clinical grounds in 165 patients: 97 were male and 68 female. Mean age was 38 years (range 15 to 85 years). They had been unconscious with either repetitive myoclonic jerks (52), stiffening (8), tongue-biting (7) or a combination of these symptoms (95). One patient suffered from a simple partial and two from complex partial seizures. We did not subclassify the generalized seizures since the reliability and probably also the accuracy of such a categorization

has been proven to be too poor to be clinically useful (Bodensteiner 1988, Chapter 3).

Fifty-three percent of the patients were seen within 24 hours of the seizure, 70% within one week, 83% within two weeks, 94% within one month and all within three months. Mean interval between seizure and visit to the hospital was 6.7 days, median interval was one day.

ECG and blood samples were obtained as a matter of routine. In 162 of the 165 patients, a CT scan was made. If the native scan was abnormal, intravenous contrast was administered. Results of CT scanning made the clinical diagnosis of a presumed idiopathic seizure inaccurate in nine patients (see results for details). In none of the three patients in whom the CT scan was omitted, did signs or symptoms point to a focal structural abnormality during the follow-up period.

For analysis of the recurrence rates, we excluded the nine patients above with major CT scan abnormalities and three patients who suffered a second seizure within 24 hours. In addition, we excluded two patients who were treated immediately with AEDs. In one of these, local atrophy was found on the CT scan, which we regarded as clinically irrelevant. Inquiry revealed that the patient had suffered a cranial trauma seven years previously. The attending physician initiated medication. The other patient suffered a fracture of a vertebra as a result of the seizure and was also treated with AEDs.

A standard EEG (STDEEG) was made in all remaining 151 patients. Unless the first EEG showed spikes or spikewave complexes, an EEG after partial sleep deprivation (SLPEEG) was also made. Three of the eligible patients refused a second EEG. All EEGs were read by one neurologist (RJS), who had no access to the clinical information. The EEGs were coded as follows:

- normal yes / no,

if abnormal:
- epileptic discharges yes / no,
- abnormalities otherwise paroxysmal yes / no,
- abnormalities non-paroxysmal yes / no.

In former studies we described details of the registration of the EEGs and of the protocol used for the visual EEG-interpretation (Appendix). The interobserver variation proved considerable (kappa 0.50 for the classification epileptic versus non-epileptic, Chapter 4).

Diagnosis of a recurrence was made by one of the authors (CAvD) based on the description of the episode.

Length of follow-up was determined by time of admission to the study with a minimum of one and a maximum of two years. One patient was lost to follow-up after one month since he moved to another part of the country. Another patient, who was scheduled to be followed up for two years, was lost after 20 months. Patients who suffered one or more recurrences were followed up for an additional year either after initiating treatment, or after the first recurrence in the case of treatment being withheld.

Statistics

Survival analysis techniques were used (Kaplan-Meyer) for calculation of cumulative recurrence rates (BMDP 1981). We included the two patients who were lost to follow-up. Although it is more likely that they did not suffer recurrences, the number is too small to have any possible influence on the results. EEGs showing epileptic discharges together with other abnormalities were combined with those having only epileptic discharges and were labelled as EPI. EEGs with paroxysmal abnormalities, or non-paroxysmal abnormalities, or both, were also combined (OTH).

RESULTS

Accuracy of the clinical diagnosis of a presumed idiopathic seizure

Patients excluded from the study. Sixty-one of 226 referred patients were excluded. In two patients the following diagnoses were made: hyperventilation and migraine. Follow-up for one year did not throw any doubts on these diagnoses. In 24 patients, the episodes were classified as acute or remote symptomatic seizures. Half of these were supposed to be due to alcoholism; four to intracerebral metastases or primary brain tumours, since these patients were known to have a recent malignancy or since focal abnormalities were found on neurological examination; other aetiological conditions were: dialysis, use of medication (salbutamol), subarachnoid haemorrhage, cranial trauma twice, cerebral infarction in the previous medical history and two patients with a craniotomy in the past because of a tumour. Additional investigations like CT scans or liver function tests in patients suspected of alcoholism, confirmed the diagnoses as far as possible in all but one patient, in whom the CT scan did not show the expected metastases.

A diagnosis of a syncope with myoclonic jerks was made seven times. EEGs did not reveal epileptic abnormalities. One patient suffered a second episode (this time without myoclonic jerks) during a follow-up period of one year which was again regarded as a syncope.

Twenty-four patients were excluded since the description of the episode did not fulfil one of our criteria, whereas no other diagnoses could be made. One or both EEGs showed epileptic discharges in five patients. In one patient, cardiac arrhythmias were found which might have provoked the first episode. Three suffered more episodes but a firm diagnosis of epilepsy could not be made in any.

Patients admitted to the study. The CT scan made the initial clinical diagnosis of an idiopathic seizure inaccurate in nine patients (5.5%, 95% CI 2 to 9%): one arterio-venous malformation, one time metastases, four brain tumours, one arachnoidal cyst and two infarctions. We found focal atrophies in six patients, which we regarded as clinically irrelevant. The CT scan showed a transient hypodensity ("vanishing tumour") in one patient who was admitted because of a focal seizure recurring within 24 hours.

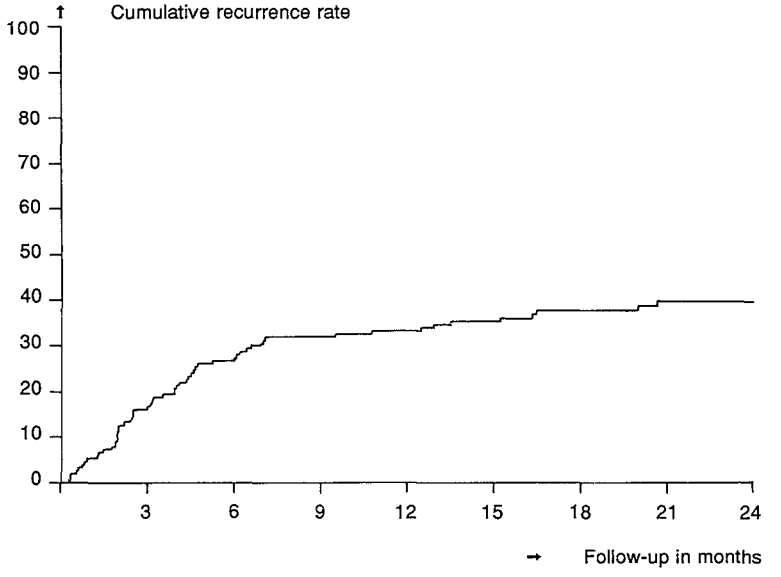
One patient developed a psychogenic hemiplegia shortly after her first seizure, which raised doubts about the first episode. Three additional patients suffered a combination of pseudo-seizures and epileptic seizures requiring hospitalization in all. Four patients, (including the patient with the AVM mentioned above) raised a suspicion of alcohol addiction during follow-up, and it was discovered afterwards, that one patient had discontinued prolonged use of minor tranquilizers two days prior to the seizure. One patient with a seizure accompanied by a "postictal paresis" and an initial normal CT scan, appeared retrospectively to have suffered an infarction on the basis of a subsequent CT scan, which was repeated after a second identical episode. Three patients turned out to have cardiac arrhythmias which might have caused the "seizures". One additional patient aged 17 years, who was admitted because of a nocturnal generalized seizure, suddenly died 12 months later. After her first seizure she complained a few times about episodes of feeling dizzy without clear provocative conditions. A few weeks prior to her death, she nearly fainted on two occasions after an unexpected sound. In retrospect, the initial ECG showed a prolonged QT-interval, indicating she probably suffered from a prolonged QT-syndrome. It is possible that the first nocturnal episode was caused by this cardiac abnormality, but this cannot be proven. Her family history was negative for the prolonged QT syndrome but positive for epilepsy. The STDEEG had shown non-epileptic abnormalities, the SLPEEG was normal.

Summarizing, in 19 of the 165 recruited patients (12%, 95% CI 7 to 16%), results of additional investigations or follow-up period questioned the initial clinical diagnosis of an idiopathic seizure.

Risk of recurrence, predictive factors

The CT scan revealed the major abnormalities mentioned above in nine patients, two of whom received AEDs immediately. Seven suffered a second seizure. One patient with metastases, who was treated immediately with AEDs, and one patient with an infarction, who did not receive AEDs, remained seizure free. All patients with brain tumours or metastases died.

Figure 6.1: Cumulative recurrence rate of 151 patients with an idiopathic first seizure.



months	0	6	12	18	24
cum. recurr. rate	0	27%	33%	38%	40%
95% CI	-	20-34%	26-41%	30-46%	32-48%
patients at risk	151	109	100	73	38
recurr./censored		41/1	9/0	6/21	2/33

The overall recurrence rate for the 151 patients with an idiopathic (confirmed by CT scan), untreated, isolated seizure was 27% at six months, 33% at one year and 40% at two years (figure 6.1). Three patients presented with a status epilepticus as "second" seizure. None of the second seizure caused serious morbidity. Four patients died: cardiac arrhythmia, myocardial infarction, lung cancer without intracerebral metastases and leukaemia.

We studied the following "a priori" selected possible predictive factors in these 151 patients (table 6.2). Positive family history or provocative circumstances had no statistically significant influence on the risk of recurrences. The association of the risk of recurrence with the interval between first seizure and first visit to the hospital, was inconsistent. Thirty-three patients experienced their first seizure during sleep or awakening. The cumulative rate for these patients was significantly higher compared to the 118 patients whose fit occurred during daytime (72% versus 32%, 95% CI diff. 23 to 58%). Tendency to recurrence was higher in the younger age group (15 - 24 years: 50%, 25 - 44 years: 39%, 45 - 85 years: 29%).

The STDEEG showed epileptic discharges in 16 patients of whom 15 experienced a second seizure within two years (one patient remained seizure free during the scheduled follow-up period of 16 months, cumulative risk of recurrence at two years 100%, approximate 95% CI 70 to 100%). The cumulative recurrence rate at two years was 40% (95% CI 29 to 52%) in 68 patients in whom the STDEEG showed other abnormalities and 25% (95% CI 15 to 35%) in 67 patients with a normal STDEEG. The SLPEEG identified 19 additional patients with epileptic discharges, 12 of whom relapsed. Combination of the two registrations gave the following results (figure 6.2). If both EEGs were normal, the risk of recurrence after two years was 12% (95% CI 3 to 21%), rising to 81% (95% CI 66 to 97%) if one or both EEGs showed epileptic discharges. If one or both EEGs showed non-epileptic abnormalities, the recurrence rate was found to be 39% (95% CI 27 to 51%).

Twenty-seven of the 58 patients who suffered a second seizure could be identified by the combined EEGs (sensitivity 47%, 95% CI 34 to 59%). Specificity proved to be 91% (95% CI 86 to 97%).

In analyzing the data "a posteriori" we found that tongue-biting in 70 patients was associated with a higher risk of recurrence (55% versus 27%, 95% CI difference 13 to 44%).

Table 6.2. Possible predictive factors for the risk of recurrence (151 patients)

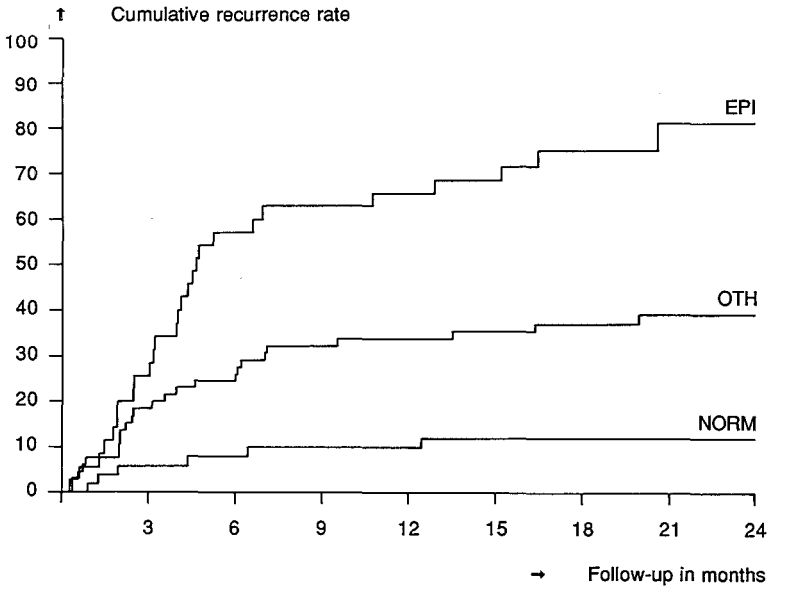
predictive factor	number of patients	rec. rate at one yr	rec. rate at two yrs
Age			
15 to 24 yrs	50	46%	50%
25 to 44 yrs	52	27%	39%
45 to 85 yrs	49	27%	29%
Family history			
negative	133	33%	40%
positive	16	44%	44%
Interval between first seizure and first visit **			
< 24 hours	77	25%	31%
1-14 days	54	44%	53%
> 14 days	20	35%	35%
Time of day *			
during daytime	118	26%	32%
asleep/awakening	33	58%	72%
Provocative circumstances			
absent	100	36%	44%
present	51	28%	32%
Standard EEG ***			
EPI	16	87%	100%
OTH	68	35%	40%
NORM	67	18%	25%
Combined EEGs *			
EPI	35	66%	81%
OTH	65	34%	39%
NORM	51	10%	12%
Tongue-bite *			
absent	81	24%	27%
present	70	44%	55%
Sex			
male	91	31%	35%
female	60	37%	47%

* difference significant ($p < 0.05$)

** recurrence rate for the patients seen within 24 hours significantly lower compared to patients seen within 1 - 14 days

*** recurrence rate in case of EPI significantly higher compared to NORM or OTH

Figure 6.2: Cumulative recurrence rates based on the combined findings of the standard EEG and the EEG after partial sleep deprivation of 151 patients with an idiopathic first seizure.



months	0	6	12	18	24
EPI (1)					
cum. recurr. rate	0	57%	66%	75%	81%
95% CI	-	41-74%	50-81%	61-90%	66-97%
patients at risk	35	15	12	7	2
recurr./censored		20/0	3/0	3/2	1/4
OTH (1)					
cum. recurr. rate	0	26%	34%	37%	39%
95% CI	-	16-37%	22-45%	25-49%	27-51%
patients at risk	65	48	43	35	23
recurr./censored		17/0	5/0	2/6	1/11
NORM (2)					
cum. recurr. rate	0	8%	10%	12%	12%
95% CI	-	1-15%	2-18%	3-21%	3-21%
patients at risk	51	46	45	31	13
recurr./censored		4/1	1/0	1/13	0/18

EPI : epileptic discharges
OTH : non-epileptic abnormalities
NORM : no abnormalities

(1) : one or both EEGs
(2) : both EEGs

Course

For analysis of the course after 58 first recurrences in the 151 patients mentioned above, we excluded one patient who refused medication despite several recurrences. Forty (70%) of the 57 patients became seizure free, 8 (14%) suffered sporadic seizures (one or two during twelve months after a titration period of two months) and 9 (16%) did not become seizure free despite medication during a follow-up period of one year. The combined EEGs had shown epileptic discharges in 10 out of these 17 non-seizure-free patients, other abnormalities in six, and both had been normal in one patient.

Twenty-five patients were put on medication immediately after the first recurrence ("early" treatment group). Three of these had suffered a status epilepticus as a second seizure. In 32 patients, treatment was postponed until more recurrences had occurred (26 patients) or not initiated at all (6 patients, none suffered from more recurrences). Some patients initially refused medication and in some the long interval between first and second seizure led to abstain from treatment. Retrospectively, the decision to start or postpone treatment after the first recurrence seemed to have been made at random in the majority of patients. Mean interval between first seizure and first recurrence was equal in both groups. Results in the early treatment group were better compared to results if treatment was postponed: seizure free 86% versus 54% (95% CI diff 9 to 57%); sporadic seizures 5% versus 27% (95% CI diff 3 to 42%); "intractable" 9% versus 19% (95% CI diff -9 to 30%).

DISCUSSION

Diagnosis of a first seizure is often difficult. Little attention has been paid to this problem in the past. Former studies on first seizures did not even mention the diagnostic criteria (Thomas 1959, Johnson 1972, Saunders 1975, Cleland 1981, Elwes 1985, Hopkins 1988) or used the International Classification of Seizures (Hauser 1982, Annegers 1986). This widely used Classification, however, only provides guidelines for classification of seizures, once the diagnosis has been made. Differences in patient selection might explain partly the diverging findings.

To enhance the consistency of recruitment, we used simple descriptive diagnostic criteria. In a former study we showed that the reliability of these criteria was good (Chapter 2). Moreover, all patients were discussed by three neurologists prior to recruitment.

The CT scan falsified the initial clinical diagnosis in 5.5% of the patients. This is in accordance with a former study from a non-tropical area (Hopkins 1988). Whether this indeed warrants making a CT scan in all patients, will also depend on other factors which lie outside the scope of this study. In our opinion, this yield is sufficiently high to warrant this additional investigation, but we do realize that we are living in a prosperous country.

Follow-up threw doubts on the initial clinical diagnosis in an additional 6%. This does not mean that all other admitted patients had indeed suffered an idiopathic seizure, since an objective test is lacking. Strikingly, none of the former studies, with exception of Johnson et al. (1972), who studied navy personnel with an unexplained loss of consciousness, mentioned any patient in whom the initial diagnosis proved to be wrong.

Twenty-four patients were excluded since the description of the episode did not fulfil our criteria and no other diagnosis could be made. In none could a firm diagnosis of epilepsy be made, but doubts remained in three.

We classified seizures which were possibly provoked by sleep deprivation or stress, as being idiopathic. We hold the opinion that most patients will look for an explanation for their seizure leading to overestimation of possible provocative conditions. The presence of such circumstances was associated with a merely slightly lowered risk of recurrence. One should be reluctant to blame the occurrence of a first seizure solely on provocative circumstances, since this might lead to false reassurance.

Distinction of an epileptic seizure from a syncope with myoclonic jerks may cause interobserver disagreement. We made this last diagnosis seven times. Results of follow-up did not question this diagnosis in any patient.

In our opinion, the diagnosis according to the criteria above, provided that the CT scan does not show abnormalities and the medical history or the ECG does not point to cardiac arrhythmias, proved to be sufficiently reliable and accurate to allow far-reaching decisions to be made, such as initiation of antiepileptic drug therapy. One should bear in mind that we did not investigate the accuracy of the diagnosis in general practice but in hospital conditions which may have led to referral bias.

Our prospective hospital based study shows that the cumulative recurrence rate after an idiopathic, isolated first seizure is 33% at one year and 40% at two years. These results are in agreement with the study of Hopkins et al. (1988), who found a recurrence rate of 45% at two years (including 4% patients with CT scan abnormalities). Lower recurrence rates were found

in studies from the U.S.A., in whom the majority of patients were treated immediately with AEDs (Hauser 1982, Annegers 1986). Unfortunately, intervals between the first seizure and admission into these studies were not stated. The longer the waiting list, the higher the chance that patients had already suffered a relapse (Reynolds 1987). This may have led to bias towards inclusion of patients with a more favourable prognosis. We did not find a consistent correlation between this interval and the recurrence rate, but this may be due to the relatively short interval in our study.

Elwes et al. (1985) found a much higher recurrence rate of 69% at two years. The design of their study may have led to bias towards inclusion of patients with a poor prognosis. Their study proved to be partly pro- and partly retrospective (Elwes 1988b). Patients were seen within a median time of 24 hours after their first seizure, which is comparable to our study. Mean interval is not given. Moreover, idiopathic, remote symptomatic and acute symptomatic seizures were recruited. Patients with seizures recurring within 24 hours were included. In our opinion, these patients should not be taken into account, since immediate treatment will not prevent these very early recurrences.

The results of our study seems to be of importance in assessing the pros and cons of immediate treatment. Considering the present knowledge, we conclude that the risk of recurrence after an idiopathic first seizure is about 40% at two years. In our study, 30% of the 57 patients suffering a second seizure (11% of the original 151 patients with an idiopathic first seizure) did not become completely seizure free within one year. This is in accordance with former studies on the prognosis of newly treated patients with epilepsy (Shorvon 1982, Ramsay 1983, Elwes 1984, Callaghan 1985, Mattson 1985, Turnbull 1985).

Treating all patients immediately might prevent a number of second seizures (Camfield 1989) and might possibly prevent development of intractability in some patients in the long run. This last hypothesis emerged from the observation that intervals between untreated seizures decreased successively and that the number of seizures before treatment was started, correlated to treatment results (Elwes 1984 and 1988a). Delaying treatment until more than one recurrence had occurred, resulted in poorer treatment results in our study too. The number of patients was small, however, and the patients were not randomised.

But even if immediate treatment of all patients would halve the number of eventually non-seizure-free patients, which seems to us rather optimistic, one would still have to balance the unnecessary treatment of those patients who would not experience a second seizure even without medication (60% of the study population) against the possible halving of

the number of non-seizure-free patients (from 11 to 5.5%). Besides, a trial designed to study such a hypothesis would require recruitment of about 1300 patients (Pocock 1983).

An alternative approach is to take into account the EEG findings. In our study, occurrence of epileptic discharges was associated with a highly increased risk of recurrence. Immediate treatment of these patients would implicate that only a small number of patients would be treated unnecessarily. Moreover, the combined EEGs had shown epileptic discharges in 10 of the 17 patients who eventually did not become seizure free despite medication.

Risk of recurrence if both EEGs were normal, was rather low. Only one patient from this group of 51 patients ended with sporadic seizures despite medication, whereas all others who eventually suffered recurrences, became seizure free. In our opinion it is certainly unwise to initiate treatment in these patients immediately. Also, the 39% risk of recurrence in case of non-epileptic abnormalities seems to be too low, in our opinion, to warrant immediate treatment.

For the time being, it seems unwise to initiate AEDs in every patient with an idiopathic first seizure. On grounds of our findings, we come to the conclusion that initiating AEDs in those patients in whom a STDEEG, or a SLPEEG, or both show epileptic discharges, and delaying treatment in the remaining patients until the first recurrence, seems to be the most sensible option. One should bear in mind, however, that the reliability of visual interpretation of EEGs is moderate (Chapter 4). On the other hand, all former studies but one (Hopkins 1988) showed an increased risk of recurrence in case of EEG abnormalities (Cleland 1981, Hauser 1982, Annegers 1986).

CHAPTER 7

DILEMMAS IN THE TREATMENT OF AN IDIOPATHIC FIRST SEIZURE IN ADULTHOOD. A DECISION-ANALYTICAL APPROACH

CA van Donselaar; AT Geerts; JDF Habbema

The occurrence of a first seizure confronts both the patient and physician with the choice to initiate treatment with antiepileptic drugs (AEDs) immediately or to delay treatment until further possible recurrences. Opinions on this subject differ worldwide (Hachinski 1986, Hart 1986, Hauser 1986).

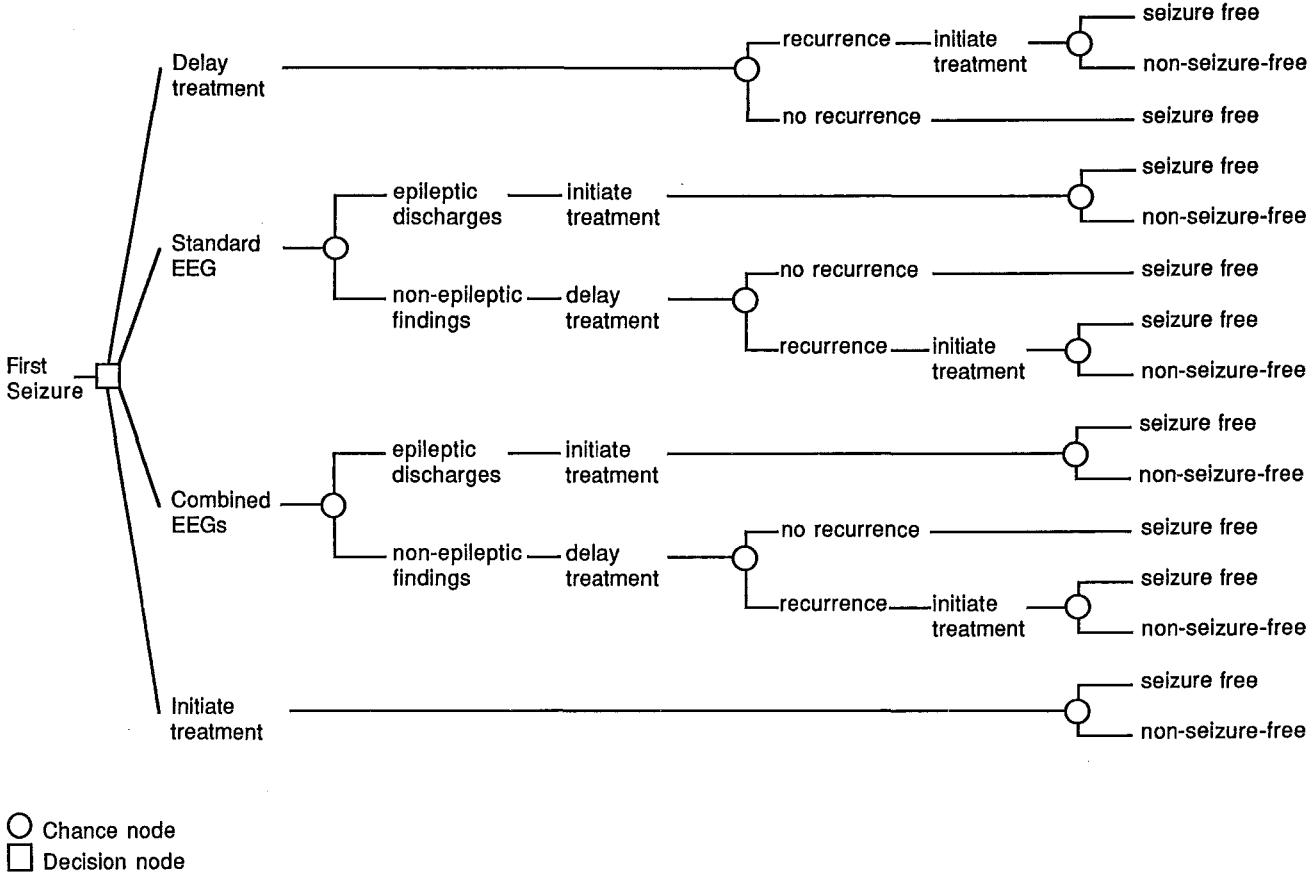
In this dilemma, one has to balance issues that are hardly comparable. Not all patients suffer a second seizure and treating all patients immediately would implicate that a number will be treated "unnecessarily". Withholding treatment will probably lead to a greater number of second seizures. Moreover, some argue that delaying treatment may result in a greater number of intractable patients in the long term (Reynolds 1983, Elwes 1984, Reynolds 1987, Elwes 1988a, Chapter 6).

Theoretically, decision analysis might be helpful in such a dilemma by rational weighing of the pros and cons of the different treatment strategies. It might result in an advice on the best treatment policy (Weinstein 1980).

We performed a decision analysis of this problem with the purpose to assess whether such an approach indeed might be of some use in the solution of this everyday clinical problem.

We restrict ourselves to a hypothetical (but not uncommon) patient aged 40 years, who is referred to the hospital within 24 hours after a first generalized epileptic seizure. The patient has always been in good health and clear provocative circumstances are absent. Neurological examination is normal, CT scan and ECG show no abnormalities. A diagnosis of an idiopathic seizure is made. Seizures do not recur within 24 hours.

Figure 7.1 Decision tree; different treatment strategies in a patient with an idiopathic first seizure.



PROBLEM

The large majority of patients who are referred to the hospital because of a first seizure, have suffered a generalized convulsion. We do not subclassify these seizures into partial seizures secondarily generalized or generalized from onset, since the reliability and probably also the accuracy of such a classification is very poor (Bodensteiner 1988, Chapter 3).

The different management strategies are depicted in figure 7.1 in the form of a condensed decision-tree. A decision node denotes that one can choose between several alternative courses and is depicted as a square. A chance node (depicted as a circle) denotes that several events may take place beyond control of the physician or patient (Weinstein 1980).

First step should be to make a diagnosis of a seizure on the basis of the description of the episode. Next decision is to initiate or delay treatment with AEDs. The first option is delaying treatment in all patients. Some will relapse and subsequently be put on medication. The second option is to obtain a standard EEG (STDEEG) and initiate treatment in case of epileptic discharges. The third option is to obtain an EEG after partial sleep deprivation (SLPEEG) in those patients in whom the STDEEG did not show epileptic discharges, and initiate treatment in the case of epileptic discharges (Holmes 1988). The fourth option is to initiate treatment in all patients immediately.

Ideally, one would like to compare long-term outcomes for each strategy, taking into account all kinds of possible future events. Such an approach, however, would lead to a rather complicated decision analysis and necessary data are lacking. We confine ourselves to the outcomes at two years. The following assumptions are made:

- If the patient remains seizure free during the first year of treatment, seizures will not recur.
- If treatment is delayed and the patient does not suffer a recurrence within one year, he will remain seizure free.
- If the patient suffers a recurrence despite medication (after a titration period) he will not become seizure free.

Apparently, this is a simplified approach to a complicated problem. However, more than 80% of the recurrences after a first untreated seizure will occur within one year (Hauser 1982, Hopkins 1988, Chapter 6) and the first year of treatment is crucial for the long-term prognosis (Shorvon 1982, Elwes 1984, Shorvon 1984, Luhdorf 1986).

Doubt on the diagnosis is not considered just as the possibility that the original diagnosis of an idiopathic seizure proves to be wrong during follow-up. We classify EEGs as epileptic or non-epileptic and do not take

into consideration a more detailed categorization. For the sake of clarity, we have left out the possibility to withhold treatment until the third or perhaps even the fourth recurrence, as well as problems involved in selection of AEDs.

Treatment with AEDs exposes the patient to possible side-effects both in the short and long term. Moreover, treatment may have psychological and social consequences. Patients experiencing one or more recurrences, are subject to the risks involved with a seizure. Only the EEG may be considered as a rather harmless experience. We did not append separate branches for these possibilities.

We disregard problems and consequences of discontinuing treatment after a certain seizure free period.

NECESSARY KNOWLEDGE

To "fill out" the tree and estimate the value of the different outcomes, the following data are required:

1. Reliability and accuracy of the diagnosis of a first seizure.
2. Recurrence rate within one year after an idiopathic first seizure if medication is withheld in all patients.
3. Sensitivity and specificity of the STDEEG and the combination of the STDEEG and the SLPEEG regarding recurrences.
4. Efficacy of treatment:
   - initiated immediately
   - initiated after the first recurrence
   - initiated immediately in patients with "epileptic" EEG findings
   - initiated after the first recurrence in patients with non-epileptic EEG findings
5. Morbidity and mortality of treatment with AEDs.
6. Morbidity and mortality of a first recurrence.

If all these data would be known with certainty, it would be possible to assess how often every strategy would result in one of the different outcomes. The next step is to evaluate these outcomes by "utility-analysis". The "profits" and "losses" of the different strategies can then be compared.

ASSUMPTIONS

1. Reliability and accuracy of the diagnosis of a first seizure.

If agreement on what should be labeled a seizure is very poor, advice on treatment policies would be useless. The same applies if the diagnosis of a first seizure often proves to be wrong. In absence of an objective test, one has to rely on the description of the episode by an eyewitness who is often shocked by seeing an epileptic seizure. We showed in a former study that use of simple descriptive criteria (table 2.1) considerably increased the reliability and accuracy of the diagnosis, provided that the CT scan did not show abnormalities (Chapters 2 and 6). One should be aware, however, of cardiac arrhythmias masquerading as epileptic seizures (Schott 1977, Luxon 1980, Pritchett 1980, Braham 1981). In our opinion, diagnosis of an idiopathic first seizure according to the criteria above, proved to be sufficiently reliable and accurate on which to base far-reaching decisions, such as initiating AEDs.

2. The recurrence rate after an idiopathic untreated first seizure within one year

In the scope of this study, recurrences after more than one year are disregarded, as are recurrences within 24 hours, since immediate oral treatment will not prevent these very early recurrences.

The lowest recurrence rates at one year were reported in the U.S.A. (Hauser 1982, Annegers 1986) of 13% and 26% respectively. In these studies the majority of patients were treated immediately with antiepileptic drugs and intervals between first seizure and admission into the study were not stated. The longer the wait for consultation, the higher the chance that patients already suffered a relapse (Reynolds 1987). This may have led to bias towards a low recurrence rate. Elwes et al. (1985) reported a much higher recurrence rate of 60% at one year. This study, however, proved to be partly pro- and partly retrospective (Elwes 1988b). Moreover, idiopathic, remote symptomatic and acute symptomatic seizures were taken together, as were seizures recurring within 24 hours. This may have led to bias towards the inclusion of patients with a poor prognosis.

In two recent prospective European studies of idiopathic first seizures in adulthood, recurrence rates at one year of 37% and 33% respectively were found (Hopkins 1988, Chapter 6). In the first study 12% of the 201 patients were treated with AEDs; in the second none of the 151.

In our opinion, it seems likely that the recurrence rate after an untreated idiopathic first seizure in adulthood is 35% at one year, with a plausible range of 30 to 40%.

3. Sensitivity and specificity of the EEG

Visual interpretation of EEGs is subject to interobserver disagreement (Chapter 3) and will depend on definitions used and experience of the EEG readers. Presence of abnormalities was associated with a highly increased risk of recurrence in four studies (Cleland 1981, Hauser 1982, Annegers 1986, Chapters 5 and 6), whereas no correlation was found in the study of Hopkins et al. (1988). In this study, the STDEEG showed epileptic discharges in a large proportion of patients compared to our study (27% versus 12%). Overall recurrence rates were similar, suggesting that a more liberal definition of epileptic discharges was used.

In our study of 157 patients with a clinically presumed idiopathic first seizure, the sensitivity of the STDEEG at one year proved to be 31% (Chapter 5). We found a very good specificity of 98%. Unfortunately, neither sensitivity nor specificity are discussed in any of the other studies. To be on the safe side for our analysis, we assume the sensitivity to be 30% and the specificity 93% (lower limit of the 95% confidence interval; Chapter 5).

Sensitivity of the combination of a STDEEG and a SLPEEG proved to be 47%, specificity 88%. Since data from other studies are lacking we use these figures in our analysis.

4. Efficacy of treatment.

In our study, 17 of the 57 patients (30%) who suffered a recurrence after an untreated idiopathic first seizure, did not become completely seizure free despite medication (Chapter 6). Eight patients suffered sporadic seizures (one or two fits in the first year of treatment after a titration period of two months) and nine suffered more seizures.

Several studies have been published on prognosis of newly diagnosed epileptic patients (Shorvon 1982, Goodridge 1983b, Ramsay 1983, Turnbull 1983, Elwes 1984, Callaghan 1985, Luhdorf 1986, Beghi 1988). Unfortunately, criteria for success or failure are not standardized (Chadwick 1985). Seizures were not controlled completely in 13 - 37% of the patients. We assume the failure rate of delaying treatment (including sporadic seizures) to be 30% and the range to be 13 to 37%. The same applies if the EEG(s) are decisive to delay treatment.

Only one controlled trial on efficacy of early treatment in children on the short-term outcome has been published (Camfield 1989). Prevention of first recurrences in the treated group was counterbalanced by side-effects of the AEDs.

Some argue that initiating treatment immediately after the first seizure might give better results in the long term. This hypothesis emerged following the observation that the number of seizures before treatment was started correlated with long-term results and that intervals between untreated seizures successively decreased (Reynolds 1983, Elwes 1984, Reynolds 1987, Elwes 1988a).

In absence of adequate studies, it is difficult to assess whether treating immediately would indeed reduce the number of eventually non-seizure-free patients compared to delaying treatment. In our opinion, it is unlikely that initiating treatment immediately after the first seizure would reduce the number of eventually non-seizure-free patients with more than 50% compared to initiating treatment after the first recurrence. Compliance might be lower. Moreover, (non randomized) initiation treatment immediately after the first seizure in a number of patients in two studies, did not reduce recurrence rates (Hauser 1982, Hopkins 1988).

For our analysis we assume that immediate treatment reduces the failure rate with 25%. We value the upper limit to be 50% and the lower limit to be 0%; the same assumptions are used in case EEG findings are decisive to initiate or delay treatment.

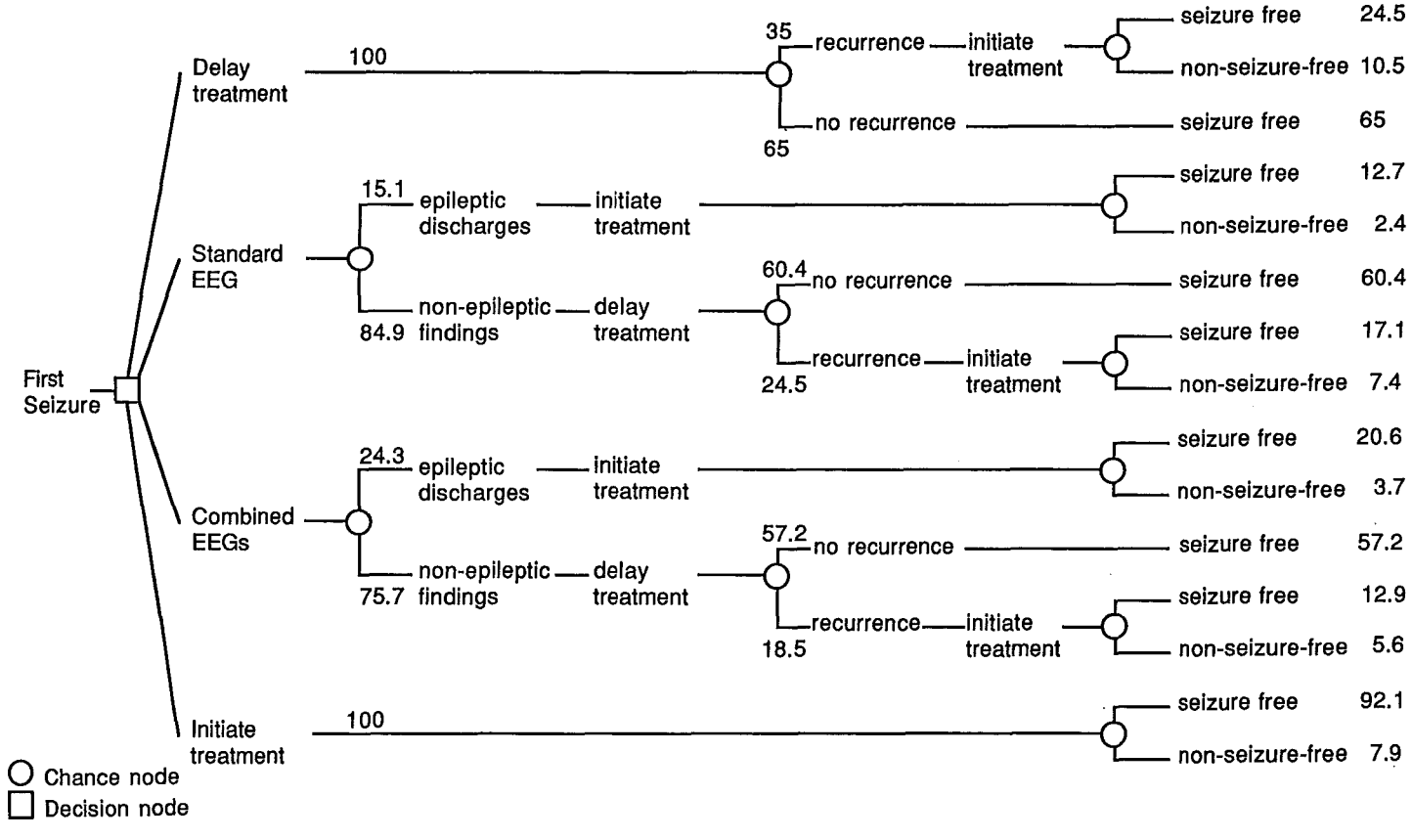
Table 7.1 Assumptions

1.	The diagnosis of a first seizure is sufficiently reliable and accurate on which to base decisions such as initiation of treatment with AEDs.
2.	The recurrence rate after an idiopathic first untreated seizure within one year: 35% (30-40%)
3.	Sensitivity STDEEG 30%, specificity 93%. For the combination of a STDEEG and a SLPEEG: sensitivity 47%, specificity 88%.
4.	If treatment is initiated after a first recurrence, 30% will not become seizure free (13 - 37%). Treating immediately after the first seizure leads to a reduction of "intractability" of 25% (0 - 50%) compared to the results of delaying treatment until the first recurrence. The same applies if the EEG is decisive.

5. Morbidity and mortality due to AEDs

Different AEDs may cause a spectrum of adverse side-effects varying from aplastic anemia to Stevens-Johnson syndrome, lethargy, ataxia, rashes, liver problems, impotence, subtle impairment of mental function, teratogenicity etc (Reynolds 1985, Lesser 1986, Wallace 1986, Brodie 1987, Dreifuss 1987a and 1987b, Vining 1987, Meador 1990). Very severe side-effects leading to death or severe morbidity are very rare (Mattson 1985, Dreifuss

Figure 7.2 Decision tree; different treatment strategies for patients with an idiopathic first seizure. Outcomes based on assumptions as stated in table 7.1, see table 7.2 for calculations, n = 100.



1988, Herranz 1988, Collaborative group 1989, Davidson 1989). Estimated incidence of aplastic anemia caused by carbamazepine is 0.5 per 100.000 patients per year (Ramsay 1986). Incidence of minor side-effects has been reported to be 50% (Ramsay 1983, Mattson 1985); moreover, AEDs may interact with other medication (Kutt 1984).

We did not append separate branches for mortality or severe morbidity due to medication, since the estimated incidence is very low. Similarly, no separate branches for patients suffering milder side-effects are appended; these effects, however, will influence the estimation of the values of the different outcomes.

6. Morbidity and mortality of a second seizure

Delaying treatment probably exposes a greater number of patients to a second seizure. Little is known about the risks involved with a second fit, but accidents leading to death or severe morbidity certainly occur, although rarely (Russell Jones 1989). Recurrent seizures may lead to cardiac arrhythmias (Gilchrist 1985, Kiok 1986, Smaje 1987, Howell 1989) or to status epilepticus (Dasheiff 1986, Chapter 6). Studies on large groups of patients with a first recurrence are lacking and we cannot assess the magnitude of this problem. Therefore, we do not append separate branches for these possible complications. In the evaluation of the different treatment strategies, however, we will have to take this factor into account for those patients in whom treatment is delayed.

RESULTS

The tree can now be filled according to the data above (figure 7.2, see table 7.2 for the calculations and table 7.3 for the results). Assuming a population of 100 patients with an idiopathic first seizure (as our hypothetical patient), delaying treatment would lead to a 35% risk of a second seizure and a 10.5% risk of not becoming seizure free.

The STDEEG would reveal epileptic discharges in 15.1 patients of whom 10.5 (true positives) would relapse if medication was withheld. Immediate treatment of these patients would reduce the number of patients suffering a second seizure from 10.5 to 2.4 (from 70% to 16%). Moreover, the number of patients not becoming seizure free, would be reduced with 25%, from 3.2 to 2.4 (21% to 16%). Theoretically, 4.6 (false positives, 19%) of these patients would have been treated unnecessarily.

The STDEEG would be normal or reveal non-epileptic findings in 84.9 patients. Delaying treatment would result in 24.5 second seizures (false negatives 29%) and 7.4 (9%) patients not becoming seizure free.

Table 7.2 Formulas decision analysis

Variables	
Recurrence rate	: RR (35%)
Failure Delayed Treatment	: FDT (30%)
Reduction Immediate Treatment	: RIT (25%)
Failure Immediate Treatment	: FIT = FDT x (100 - RIT) (22.5%)
Sensitivity EEG	: sens (STDEEG 30%, combined EEGs 47%)
Specificity EEG	: spec (STDEEG 93%, combined EEGs 88%)
EEG true positives	: sens x RR
EEG false positives	: (1 - spec) x (1 - RR)
EEG true negatives	: spec x (1 - RR)
EEG false negatives	: (1- sens) x RR
Delaying treatment:	
- Second seizures	: RR
- Seizure free without medication	: 100 - RR
- Non-seizure-free	: RR x FDT
EEG based strategies:	
Number of epileptic EEGs	: true positives + false positives
Treating immediately:	
- Recurrences	: true pos. x FIT
- Non-seizure-free	: true pos. x FIT
- Seizure free on medication	: false pos. + true pos. x (100 - FIT)
- Unnecessarily treated	: false pos.
Number of non-epileptic EEGs	: true neg. + false neg.
Delaying treatment:	
- Recurrences	: false neg.
- Non-seizure-free	: false neg x FDT
- Seizure free without medication	: true negatives
- Seizure free on medication	: false neg x (100 - FDT)
Treating immediately:	
- Non-seizure-free	: RR x FIT
- Seizure free on medication	: RR x (100 - FIT)
- Unnecessarily treated compared to delaying treatment	: 100 - RR
- Unnecessarily treated compared to EEG based strategy	: (100 - RR) - false positive EEGs

The combined EEGs would reveal epileptic discharges in 24.3 patients of whom 16.5 (true positives) would relapse if medication is withheld. Treating these patients immediately would result in a reduction of the number of second seizures from 16.5 (68%) to 3.7 (15%). The number of non-seizure-free patients would be reduced from 5 (20%) to 3.7 (15%), whereas one might say that 7.8 (false positives, 32%) patients would be treated unnecessarily.

The combined EEGs would have shown non-epileptic discharges in 75.7 patients. Untreated, 18.5 (false negatives 24%) would relapse and 5.6 patients (7%) would not become seizure free.

Immediate treatment of all patients would reduce the risk of a second seizure from 35% to 7.9% and diminish the risk of eventually not becoming seizure free from 10.5% to 7.9%. However, there would be a 65% chance of unnecessary medication.

Table 7.3 Outcomes decision analysis (n = 100 patients)

	Recurrences	Seizure free without medication	Seizure free on medication	Non-seizure-free
Delaying treatment	35	65	24.5	10.5
STDEEG				
EPI(15.1)	2.4	0	12.7	2.4
NONEPI (84.9)	24.5	60.4	17.1	7.4
Total	27.7	60.4	29.8	9.8
Combined EEGs				
EPI (24.3)	3.7	0	20.6	3.7
NONEPI (75.7)	18.5	57.2	12.9	5.6
Total	22.2	57.2	33.5	9.3
Treating all patients immediately	7.9	0	92.1	7.9

CONSIDERATIONS

Treating immediately all patients or those patients in whom the EEG shows epileptic discharges, reduces the risk of recurrence and decreases the chance of eventually not becoming seizure free. However, a risk of being treated unnecessarily is implicated.

Most patients and physicians will favour initiating treatment if the risk of recurrence is very high. There is no consensus, however, as to how high the recurrence rate should be to warrant treating immediately. Undoubtedly, this balance will vary between individual patients and physicians. We estimate that the threshold rate for most patients will be a risk of recurrence between 50 and 70% at one year.

From this point of view, the EEG based strategy seems to be the most sensible. Presence of epileptic abnormalities is associated with a risk of recurrence of 70% for the STDEEG and 68% for the combined EEGs, which will be reduced to 16% and 15% respectively, by treating with AEDs. Absence of epileptic discharges is associated with a risk of recurrence of merely 29% and 24% respectively, and thus delaying treatment in these patients seems to be appropriate. Differences between the two EEG based strategies seems to be marginal from this point of view. Treating all patients immediately should not be approved, since it would reduce the risk of recurrence from merely 35% to 8%.

Treating immediately might decrease the number of patients that would not become seizure free in the long term, so from this point of view, treating all patients immediately would have to be the preferred choice. Compared with delaying treatment, this policy would reduce the number of eventually non-seizure-free patients from 10.5 to 7.9. The chance of being treated unnecessarily, however, would be 65%. In other words, 65 patients would be treated unnecessarily, whereas only 2.6 extra patients would become completely seizure free (Unnecessarily Treated to Intractability Ratio = UTIR 65 / 2.6 = 25). Standards as to whether or not this is a reasonable option are lacking. In our opinion, the pros do not counterbalance the cons and hence we disapprove this policy. We estimate that the maximum UTIR acceptable to most patients and physicians will be between 10 and 20.

The EEG based strategies would also lead to a decrease in the number of non-seizure-free patients. The STDEEG based strategy would result in 9.8 patients who would not become seizure free (reduction compared to delaying treatment 0.7), whereas only 4.6 patients would be treated unnecessarily (UTIR: 4.6 / 0.7 = 7). The combined EEGs option

would reduce the number of non-seizure-free patients from 10.5 to 9.3, whereas 7.8 patients would be treated unnecessarily (UTIR: 7). The combined EEGs strategy would decrease the number of non-seizure-free patients, compared to the STDEEG based strategy, from 9.8 to 9.3 whereas 3.2 (7.8 minus 4.6) extra patients would be treated unnecessarily (UTIR: 6). From this point of view, the combined EEG based strategy seems to be the most rational choice.

We conclude that the decision to treat or delay treatment based on the combined EEG findings seems to be the most sensible choice. This policy identifies those patients with a high risk of recurrence, eventually decreases the number of non-seizure-free patients, whereas the number of patients treated unnecessarily will be relatively low.

SENSITIVITY ANALYSIS

This decision analysis was based on a number of assumptions. Next step is to vary these assumptions within the indicated plausible ranges, in order to assess under which conditions the conclusion above might be refuted.

The diagnosis of a first epileptic seizure is based on a description of the episode, since no gold standard exists. The possibility of a "false" diagnosis of an epileptic seizure certainly speaks against treating immediately. Chances of a false diagnosis may be rather low if the EEG shows epileptic discharges; this, however, has not been investigated.

Treating those patients immediately in whom the STDEEG or SLPEEG showed epileptic discharges would reduce the risk of recurrence from 68% to 15% and diminish the chances of not becoming seizure free from 20 to 15%; 32% of the patients, however, would have been treated unnecessarily (UTIR: 6).

Changes of the recurrence rate within the plausible ranges will not lead to a different conclusion. If the overall recurrence rate would be 30%, treating immediately the 22.5 patients with epileptic EEGs, would decrease the number of recurrences from 14.1 (63%) to 3.2 (14%). The number of non-seizure-free patients would decrease from 4.2 to 3.2, whereas 8.4 patients (false positives) would be treated unnecessarily (UTIR: 8).

The balance might change, if the failure rate of delaying treatment would be much lower than the assumed 30%. In case the failure rate would be 13%, treating in case of epileptic EEG findings would reduce the risk of recurrence from 68% to 7%; the number of non-seizure-free patients would be reduced from 2.2 (9%) to 1.6 (7%, UTIR: 13). In our opinion, treating this subgroup of patients under these conditions is an acceptable option.

We assumed that immediate treatment would reduce the number of eventually non-seizure-free patients with 25% compared to delaying treatment. If the reduction would be nil, the EEG based strategy would still reduce the risk of recurrence from 68% to 15% but would not reduce the number of eventually non-seizure-free patients, whereas 7.8 patients (32%) would be treated unnecessarily.

We advise delaying treatment in case of non-epileptic discharges since the number of second seizures in this group of patients is only 24%. Moreover, treating all these patients immediately would decrease the number of non-seizure-free patients from 7% to 6% but would also implicate that 76% of the patients would be treated unnecessarily (UTIR: 41).

If the failure rate of delaying treatment would be 37%, treating the patients with non-epileptic EEG findings immediately would decrease the number of eventually non-seizure-free patients from 6.9 to 5.1; 57.2 patients (true negatives) would be treated unnecessarily (UTIR: 32). This will not challenge our conclusion above.

If treating immediately would reduce the number of non-seizure-free patients with 50% compared to delaying treatment, the balance might change. Treating immediately all patients with non-epileptic EEGs would reduce the risk of recurrence from 24% to 4%; the number of non-seizure-free patients would fall from 5.6 (7%) to 2.8 (4%), whereas 57.2 patients (true negatives) would be treated unnecessarily (UTIR: 20). For some, the balance might then shift towards immediate treatment of all patients.

DISCUSSION

This analysis leads us to conclude that the decision to initiate or delay treatment with AEDs depending on the occurrence of epileptic discharges in a STDEEG or a SLPEEG, is the most sensible option. The finding of epileptic discharges is associated with a high risk of recurrence and treating immediately might lead to better treatment results in the long term.

Absence of epileptic discharges is associated with a low risk of recurrence. Therefore, delaying treatment in these patients seems appropriate. Immediate treatment might result in better treatment results in some of these patients in the long term. This does not counterbalance, in our opinion, the disadvantages of treating the large majority of these patients unnecessarily.

We confined ourselves to compare the main outcomes for each strategy and assessed whether these outcomes were considered (by us) to

be within an acceptable range. We did not perform an extended utility analysis, comparing the different outcomes qualitatively and quantitatively. The weighing of these outcomes is rather subjective (Payer 1988) and formal analysis of this subjective weighing is still in infancy (Fischoff 1981, Struyker Boudier 1985, Hopkins 1989, Redelmeier 1990).

This evaluation was based on a number of assumptions, some of which are subjective estimations. Varying our assumptions independently within the plausible ranges did not challenge our conclusion. A combination of deviations of our assumptions, however, might lead to a different conclusion. In addition, the balance might shift if treating patients with non-epileptic EEG findings immediately, would reduce the number of eventually non- seizure-free patients with at least 50%.

In our opinion, the onus of proof rests now upon the advocates of this policy to prove that treating these patients immediately, is indeed so successful. A randomized trial would require the recruitment of about 2100 patients (see footnote). In our opinion, it seems more promising to direct future research upon standardization of the EEG interpretation to improve the accuracy and reliability of the EEG.

Clearly, such a decision-analytical approach will not resolve the dilemmas facing patients and physicians and it might seem to be "juggling with figures on quicksand". The assumed ranges may seem rather arbitrary. Moreover, such an analysis has to be based on a simplified model. One might argue that such an approach is useless, because of the many uncertainties involved. For instance, what is meant by "non-seizure-free" and what exactly are the consequences and risks of postponing treatment or of unnecessary treatment with AEDs? However, faced with a patient who has suffered a first seizure, a decision has to be made whether to initiate or delay treatment on the basis of current knowledge.

Such an approach will, however, elucidate the pros and cons of the different treatment strategies and the possible consequences for the patients involved. It will also compel the physicians involved to make more explicit their subjective weighing and provides a more systematic and formal framework for discussion. Such an analysis illustrates the interrelationship between the different strategies. Variation of the assumptions influences distinct treatment strategies in the same or opposite directions. In addition, it identifies missing knowledge and provides guidelines for future research.

Note:

Size of a trial to study the efficacy of immediate treatment to halve the number of eventually non-seizure-free patients compared to delaying treatment in patients with non-epileptic EEG findings (Pocock 1983).

- failure rate standard therapy: $p_1 = 7\%$
- failure rate treating immediately which one desires to detect as being different from p_1 $p_2 = 3.5\%$
- alpha 0.05, beta 0.05 $f = 13.0$

$$n = \frac{p_1 \times (100 - p_1) + p_2 \times (100 - p_2)}{(p_2 - p_1)^2} \times f = \text{1049 patients on each treatment}$$

CHAPTER 8

PRACTICAL GUIDELINES

Based on our findings, we suggest the following guidelines for the management of adult patients who have been referred because of an idiopathic first seizure:

1. Diagnosis

   The diagnosis of a seizure has to be based on the description of the episode irrespective of the additional investigations. (See no. 3 of this Chapter for the aetiological classification.)
   The criteria mentioned above, proved to be useful (Chapters 2 and 6). In the case of a generalized seizure, the description should contain the following elements: loss of consciousness with either myoclonic jerks, tongue-bite, stiffening or a combination of these symptoms. If the episode only consists of loss of consciousness with or without incontinence, simply wait and see what develops, seems to be the preferred choice.

2. Classification

   Subclassification of generalized seizures into partial seizures secondarily generalized or generalized from onset, proved to be unreliable and probably also inaccurate (Bodensteiner 1988, Chapter 3). Therefore, it seems to be irrational to take into account such a classification in choice of additional investigations or selection of antiepileptic drugs.

3. Differential diagnoses

   The CT scan will reveal major structural abnormalities in about 6% of the patients in whom a clinically presumed diagnosis of an idiopathic seizure is made. One should be aware that hypodensities on the CT scan sometimes spontaneously disappear after a certain period of time ("vanishing tumours") (Sethi 1985, Bansal 1989, Chapter 6).
   Cardiac arrhythmias may lead to seizures also in younger patients

(Schott 1977, Chapter 6). Clues from the previous medical history, physical examination, abnormalities on the ECG, provocation of the attack by an unexpected sound or frightening experience (prolonged QT-syndrome), unexplained syncopes or dizzy spells may all point to underlying cardiac abnormalities.
The incidence of pseudoseizures proved to be very low in our study (1 out of 165 patients, Chapter 6). An objective test, however, is lacking. Three additional patients were thought to suffer pseudoseizures as well as epileptic seizures.

4. Additional investigations

On ground of our findings, it seems to be reasonable, in our opinion, to obtain a CT scan, ECG and EEG in all patients, irrespective of the age of the patient. Obtaining an EEG after partial sleep deprivation, unless the first EEG showed epileptic abnormalities, seems to be sensible (Chapter 6). Whether it might be sufficient to obtain solely a SLPEEG has not been investigated. The yield of blood tests is low, but occasionally reveals hypoglycaemia, hypocalcaemia or disturbed liver function tests pointing to alcohol addiction.
The yield of an NMR will probably be too low to warrant this investigation in all patients. Undoubtedly, the NMR sometimes reveals structural abnormalities in patients with normal CT scans (Duncan 1990), but the incidence in case of a first seizure can be expected to be very low.

5. Recurrence rate, medication.

The overall recurrence rate proved to be 33% at one year and 40% at two years. The first six months after the first seizure is the critical period for a second one: 68% of the second seizures will fall within this period (Chapter 6).
The finding of epileptic discharges in a standard EEG or combination of standard EEG and EEG after partial sleep deprivation is associated with a recurrence rate of at least 80% at two years (Chapters 4 and 6). Initiating treatment in these patients seems to be a reasonable choice and we favour to discuss with the patient the pros and cons of immediate treatment under these circumstances. Delaying treatment might result in a higher chance of eventually not becoming seizure free (Reynolds 1983, Elwes 1984, Reynolds 1987, Elwes 1988a, Chapter 6).
In the case of non-epileptic abnormalities or normal EEG findings (recurrence rates at two years 39% and 12% resp.), postponing the

beginning of treatment until a second seizure, seems to be the most rational choice (Chapter 7). If seizures recur within one year, further delay of treatment might lead to worse treatment results in the long term (Reynolds 1983, Elwes 1984, Reynolds 1987, Elwes 1988a, Chapter 6) and hence, initiating treatment in these patients seems to be the best option.

6. Long-term prognosis.

If seizures recur, antiepileptic drugs will suppress them completely in 70% of the patients (Chapter 6). Initiating treatment immediately after the first seizure in those patients with epileptic EEG findings, might lead to better treatment results, but this has not been investigated.
The chances of a false-negative CT scan are very low. We do not think it is useful to discuss this possibility with the patient. However, one should consider a second CT or NMR in a case of intractability.

7. Rules of life

Refraining from driving for a six-month period seems to be a reasonable period of time, whether the patient receives medication or not. Most recurrences will fall within this period. Moreover, such a period might be acceptable to the patient and this increases the chances that he / she will indeed refrain from driving. One should realise that driving privileges should have to be withdrawn for one year according to the official regulations in our country. However, the attending physician is allowed to deviate from these rules.
In addition, it seems to be a sound advice, not to swim for the first six months and then only to swim accompanied for the next year and a half.
The avoidance of possibly provocative circumstances is not a perfect safeguard against new seizures (Chapter 6).

8. How long should AEDs be continued if seizures do not recur?

We did not address this subject in our study and studies on this particular group of patients are lacking. For the time being, one might expect that about 20 - 66% of the patients will relapse if medication is discontinued after two years (Chadwick 1983, Overweg 1985). One should realise, however, that continuation of treatment will not prevent recurrences in all patients (Overweg 1985). Whether or not medication should be indeed discontinued is a subjective choice.

SUMMARY

The occurrence of a first seizure confronts both the patient and physician with the choice to initiate treatment with antiepileptic drugs immediately, or to delay treatment until further possible recurrences. Opinions on this subject differ worldwide. Treating immediately reduces the risk of a second seizure and might decrease the number of intractable patients in the long term. Immediate treatment of all patients would, however, also implicate that a number of patients will be treated unnecessarily.

Opinions also differ on the question as to which additional investigations might be useful.

This thesis is based on a prospective investigation of 226 patients aged 15 years and older, who were referred to one of the participating hospitals due to a possible idiopathic first seizure. Only those patients were admitted to the study in whom an obvious cause on clinical grounds for the occurrence of the seizure was lacking. A standard EEG, an EEG after partial sleep deprivation and a computerised tomography scan (CT scan) were obtained in all patients. None of the patients were treated with antiepileptic drugs, unless a second seizure occurred. Follow-up in all patients was 1 - 2 years.

Diagnosis of a seizure has to be made on the description of the episode since an objective test is lacking. We developed criteria for the diagnosis of a first seizure suitable for research conditions. In Chapter 2 we investigated the interobserver variability between three neurologists on the diagnosis of a seizure in the first 100 referred patients. Use of the criteria improved the agreement rates compared with the agreement rates of clinical judgment alone (observed agreement corrected for the agreement due to chance = kappa : 0.73 versus 0.58).

The three neurologists discussed all patients before admission into the study. In 165 patients, a diagnosis of a presumed idiopathic seizure was made. Results of additional investigations and follow-up questioned the initial diagnosis in 19 patients (12%, Chapter 6). The CT scan unexpectedly revealed structural brain abnormalities in 9 patients (5.5%). Four additional patients proved to have cardiac arrhythmias which might have caused the "seizure". In one patient a diagnosis of a pseudo-seizure was established retrospectively.

Sixty-one patients were excluded: 37 patients because a different diagnosis was made; 24 patients because the description of the seizure did not fulfil our criteria whereas no other diagnosis could be made. Additional investigations were obtained in all 61 patients; the latter 24 patients were followed for one year. One patient proved to be excluded inaccurately and in three other patients doubts on the diagnosis remained.

We conclude that the diagnosis of an idiopathic first seizure based on our criteria is sufficiently reliable and accurate.

The large majority of patients who are referred due to a first seizure, have suffered a generalized convulsion. These are commonly classified into partial seizures secondarily generalized or generalized from onset. Type of seizure may influence the selection of additional investigations or choice of medication. In Chapter 3 we studied the validity of such a classification in 149 patients with a generalized seizure. Almost half of these patients perceived some kind of sensation immediately preceding loss of consciousness, and this was the only clue indicating a possible focal onset of the seizure. Descriptions of these feelings were presented to three epileptologists and three neurologists. The interobserver agreement on classification of these seizures proved to be poor (weighted kappa: 0.25). Moreover, results of additional investigations and the nature of recurrences were often inconsistent with the initial clinical classification.

In our opinion, such a classification is too unreliable and possibly too inaccurate to be useful in clinical practice or epidemiological research.

All EEGs were rated by one clinical neurophysiologist according to a fixed protocol. Three other neurologists independently scored 50 EEGs according to the same protocol (Chapter 4). Agreement proved to be moderate (corrected observed agreement on the occurrence of epileptic discharges = kappa: 0.50).

To assess the risk of recurrence, we excluded 14 patients: 9 patients with focal structural CT scan abnormalities; 3 patients in whom seizures recurred within 24 hours and 2 patients in whom medication was started immediately after the first seizure (Chapters 5 and 6).

The risk of recurrence proved to be 33% at one year and 40% (95% CI 32 to 48%) at two years. The occurrence of a tongue-bite and occurrence of a seizure during the night or at awakening was associated with a high risk of recurrence. The standard EEG showed epileptic discharges in 16 patients. Cumulative risk of recurrence proved to be 100% (95% CI 70 to 100%) at two years. Normal EEG findings were associated with a risk of recurrence of 25%, increasing to 40% in case of non-epileptic abnormali-

ties. EEGs after partial sleep deprivation identified an additional 19 patients with epileptic discharges of whom 12 eventually suffered a second seizure. Combination of the two registrations gave the following results: if both EEGs were normal, risk of recurrence after two years was 12% (95% CI 3 to 21%), increasing to 81% (95% CI 66 to 97%) if one or both EEGs showed epileptic discharges; if one or both EEGs showed non-epileptic abnormalities, the recurrence rate was 39% (95% CI 27 to 51%). The sensitivity proved to be 47% and the specificity 91%.

Fifty-seven patients suffered a second seizure; 40 patients (70%) became completely seizure free after initiation of medication; 8 patients (14%) suffered sporadic seizures (one or two during the first year of treatment) and 9 patients (16%) did not become seizure free, despite medication. Treatment results were better for those patients in whom medication was initiated after the first recurrence compared to those patients in whom initiation of treatment was further delayed (Chapter 6).

In Chapter 7 a decision analysis was performed to assess which treatment strategy is preferable. Assumptions for this analysis were partly based on previous studies and partly on our own study. We confined ourselves to compare the main outcomes of each strategy and did not perform an extended utility analysis, since weighing of these outcomes is rather subjective.

This analysis led us to conclude that the decision to initiate or delay treatment depending on the EEG findings is the most sensible option. If both EEGs are normal or show non-epileptic abnormalities, the possibility of a recurrence is very low and, in our opinion, the possible advantages of immediate treatment do not counterbalance the disadvantages. If one or both EEGs show epileptic discharges, however, the possibility of a second seizure is high and further delay of treatment might result in a greater number of intractable patients in the long term.

The balance might change, however, if treating all patients with normal or non-epileptic EEG findings would reduce the number of non-seizure-free patients with 50% or more in the long term.

In Chapter 8 practical guidelines for the management of patients with an idiopathic first seizure are presented.

SAMENVATTING

Wanneer iemand voor de eerste keer een epileptische aanval krijgt, staat men voor de keuze: direct behandelen met anti-epileptica of wachten tot een eventuele volgende aanval. Wereldwijd wordt hierover nogal verschillend gedacht. Direct behandelen vermindert de kans op een tweede aanval en maakt de uiteindelijke kans op succes van de therapie mogelijk groter. Aan de andere kant betekent direct behandelen dat een deel van de patiënten onnodig medicijnen krijgt.

Daarnaast bestaat onenigheid over de vraag welke aanvullende onderzoeken na een eerste aanval zinvol zijn.

Dit proefschrift is gebaseerd op een prospectief onderzoek bij 226 patiënten van 15 jaar of ouder, die verwezen werden naar één van de deelnemende ziekenhuizen, omdat ze mogelijk een eerste epileptische aanval hadden doorgemaakt. Alleen die patiënten werden in het onderzoek opgenomen, bij wie op het eerste gezicht geen duidelijke oorzaak voor de aanval kon worden aangewezen. Bij alle patiënten werd een standaard electroencephalogram (EEG), een EEG na partiële slaapdeprivatie en een Computer Tomogram (CT scan) gemaakt. De patiënten werden niet behandeld met anti-epileptica en allen werden 1 tot 2 jaar gevolgd.

De diagnose "insult" werd gesteld op grond van de beschrijving van de aanval, omdat een objectieve test ontbreekt. Voor dit onderzoek werden een aantal descriptieve diagnostische criteria opgesteld. In Hoofdstuk 2 wordt een onderzoek beschreven naar de overeenstemming tussen drie neurologen over de diagnose bij de eerste 100 aangemelde patiënten. Gebruik van deze criteria leidde tot een betere overeenstemming dan de "klinische blik" (gevonden overeenstemming gecorrigeerd voor het toeval = kappa: 0.73 resp. 0.58).

De drie bovengenoemde neurologen bespraken alle patiënten alvorens ze in het onderzoek werden opgenomen. Bij 165 patiënten werd op klinische gronden de diagnose idiopathisch insult gesteld. Uit de resultaten van het aanvullende onderzoek en de follow-up bleek dat deze diagnose bij 19 (12%) patiënten waarschijnlijk onjuist is geweest (Hoofdstuk 6). Op de CT scan werden onverwachts bij 9 (5.5%) patiënten structurele afwijkingen gevonden. Daarnaast bleken onder andere vier patiënten uiteindelijk aan

hartritme stoornissen te lijden die waarschijnlijk de eerste aanval hebben veroorzaakt; bij één patiënt is achteraf sprake geweest van een psychogene aanval.

In totaal werden 61 patiënten niet in het onderzoek opgenomen, omdat of een andere diagnose werd gesteld (37) of de beschrijving van de aanval niet aan de criteria voldeed, terwijl geen andere diagnose kon worden gesteld (24). Ook bij al deze patiënten werd uitgebreid aanvullend onderzoek gedaan en de laatste groep patiënten is nog één jaar gevolgd. Achteraf bleek 1 patiënt ten onrechte uitgesloten te zijn, terwijl bij 3 andere patiënten twijfels over de juiste diagnose zijn blijven bestaan.

Op grond van deze onderzoeken concluderen we dat de diagnose "idiopathisch insult" met voldoende consistentie en accuraatheid kan worden gesteld.

Verreweg de meeste patiënten die naar het ziekenhuis worden verwezen vanwege een eerste epileptische aanval, hebben een gegeneraliseerd insult (grote aanval) doorgemaakt. Gewoontegetrouw worden deze aanvallen ingedeeld in aanvallen die direct gegeneraliseerd zijn en aanvallen die focaal beginnen en daarna generaliseren. Sommige artsen laten het type aanval meewegen bij de keuze van het aanvullende onderzoek of van de eventueel voor te schrijven medicatie.

In Hoofdstuk 3 wordt een onderzoek beschreven naar de waarde van een dergelijke classificatie bij 149 patiënten uit ons onderzoek met een gegeneraliseerd insult. Bijna de helft van de patiënten voelde de aanval aankomen en dit was het enige aanknopingspunt voor een mogelijk focaal begin. De beschrijving van deze voorgevoelens werd voorgelegd aan drie epileptologen en drie neurologen. Deze bleken het erg vaak oneens te zijn over de classificatie (gewogen gecorrigeerde overeenstemming = gewogen kappa: 0.25). Bovendien waren de resultaten van het aanvullende onderzoek en de aard van de recidieven vaak in tegenspraak met de klinische classificatie. Bij deze groep patiënten is een dergelijke classificatie voor de dagelijkse praktijk of epidemiologisch onderzoek ons inziens dan ook zinloos.

Bij alle patiënten werden een of meerdere EEG's gemaakt. Al deze EEG's werden door een klinisch neurofysioloog gescoord volgens een vast protocol. Drie andere klinisch neurofysiologen scoorden 50 EEG's onafhankelijk van elkaar volgens hetzelfde protocol (Hoofdstuk 4). De mate van overeenstemming bleek slechts matig te zijn (gecorrigeerde overeenstemming voor de vraag epilepsie ja/nee = kappa: 0.50).

Voor het bepalen van de recidiefkans werden 14 patiënten uitgesloten: 9 patiënten bij wie structurele afwijkingen op de CT scan werden gevonden; 3 patiënten die binnen 24 uur recidiveerden en 2 patiënten die direct op medicatie werden ingesteld (Hoofdstuk 5 en 6).

De recidiefkans bedroeg 33% na een jaar en 40% (95% CI 32 tot 48%) na twee jaar. Het voorkomen van een tongbeet en het optreden van het insult gedurende de nacht of bij het ontwaken correleerde met een hogere recidiefkans. Het standaard EEG toonde bij 16 patiënten afwijkingen passend bij epilepsie; de cumulatieve recidiefkans was 100% (95% CI 70 tot 100%) na 2 jaar. Het voorkomen van andersoortige afwijkingen was geassocieerd met een recidiefkans van 40%, terwijl de recidiefkans 25% bedroeg wanneer het standaard EEG normaal was. Het tweede EEG, gemaakt na partiële slaapdeprivatie, toonde bij nog eens 19 patiënten afwijkingen passend bij epilepsie; 12 recidiveerden. Wanneer beide EEG's normaal waren, bedroeg de recidiefkans slechts 12% (95% CI 3 tot 21%); het voorkomen van epileptische afwijkingen in een of beide EEG's was geassocieerd met een recidiefkans van 81% (95% CI 66 tot 97%); bij niet-epileptische afwijkingen in een of beide EEG's bedroeg de recidiefkans 39% (95% CI 27 tot 51%). De sensitiviteit van de gecombineerde EEG's was 47%, de specificiteit bedroeg 91%.

Van de 57 patiënten die een recidief kregen, werden 40 (70%) aanvalsvrij na starten van de medicatie; 8 patiënten (14%) maakte een of twee aanvallen door gedurende de eerste twaalf maanden van de behandeling; 9 patiënten (16%) werden niet aanvalsvrij ondanks medicatie. De behandelingsresultaten waren beter wanneer direct na het eerste recidief met medicamenteuze therapie werd begonnen dan wanneer nog langer werd gewacht met het starten van de medicatie (Hoofdstuk 6).

Hoofdstuk 7 beschrijft een besliskundige analyse van de vraag wat de beste behandelingsstrategie is. Deze analyse werd gebaseerd op een aantal aannames, die deels gebaseerd waren op ons eigen onderzoek, deels ontleend werden aan de literatuur. We beperkten ons hierbij tot het tegenover elkaar zetten van de belangrijkste uitkomsten van de verschillende behandelingsstrategieën. Een uitgebreide quantitatieve en qualitatieve "utility-analysis" was ons inziens niet zinvol gezien de subjectieve factoren die hierbij een rol spelen.

Op grond van deze analyse concluderen wij dat het zinvol is om de EEG bevindingen mee te laten wegen bij de keuze wel of niet behandelen. Wanneer beide EEG's normaal zijn of niet-epileptische afwijkingen laten zien, is de recidiefkans zo laag dat ons inziens de voordelen van direct behandelen zeker niet opwegen tegen de nadelen. Wanneer echter epi-

leptische afwijkingen op een of beide EEG's worden gevonden is de recidiefkans dermate hoog dat direct behandelen zinvol is, temeer daar vroeg behandelen mogelijk leidt tot betere behandelingsresultaten op de langere termijn.

Slechts wanneer direct behandelen van alle patiënten met niet-epileptische EEG bevindingen leidt tot een reductie van het aantal uiteindelijk niet-aanvalsvrije patiënten met 50% of meer, valt te overwegen ook deze patiënten direct op medicatie in te stellen.

In Hoofdstuk 8 worden een aantal praktische richtlijnen gegeven voor de diagnose en behandeling van patiënten met een éénmalig idiopathisch insult.

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CURRICULUM VITAE

De auteur van dit proefschrift werd op 16 juni 1953 geboren te Utrecht. Na het behalen van het gymnasium-β diploma (Utrechts Stedelijk Gymnasium) begon hij in 1971 met de studie geneeskunde aan de Rijks-Universiteit te Groningen. In deze periode is hij werkzaam geweest als student-assistent op de afdelingen Medische Fysica en Neurologie. In 1979 werd hij tot arts bevorderd.

Na 6 maanden gewerkt te hebben als arts-assistent op de afdeling Neurologie van de Deventer Ziekenhuizen, begon hij in 1980 aan zijn specialisatie tot neuroloog met de stage psychiatrie in het Psychiatrisch Ziekenhuis Veldwijk te Ermelo (opleider Drs. E. Boerman). Begin 1982 was hij drie maanden werkzaam op de afdeling Interne Geneeskunde van het ziekenhuis van de "University of the West-Indies" te Kingston, Jamaica (opleider Prof. R. Richards). In 1982 vervolgde hij zijn opleiding op de afdeling Neurologie van het Academisch Ziekenhuis Dijkzigt te Rotterdam (opleider Prof.Dr. A. Staal). In juli 1985 werd hij ingeschreven in het specialisten register "zenuw en zielsziekten".

Van juli 1985 tot december 1987 werkte hij als junior specialist op de afdeling Neurologie van het Dijkzigt Ziekenhuis waar de basis voor dit proefschrift werd gelegd (TNO Cleo project A-57). Van december 1987 tot december 1988 verbleef hij op de afdeling Klinische Neurofysiologie (opleider Dr. K. Mechelse).

Sinds januari 1989 is hij als staflid verbonden aan het St. Clara Ziekenhuis te Rotterdam. Daarnaast bleef hij verbonden aan het Dijkzigt Ziekenhuis als coördinator van het Zuid-Hollandse Kinderepilepsie Onderzoek: een samenwerkingsverband van de kinderneurologische afdelingen van de Academische Ziekenhuizen van Leiden en Rotterdam, het Westeinde Ziekenhuis en Juliana Kinder-Ziekenhuis te Den Haag en de afdeling Maatschappelijke Gezondheidszorg van de Erasmus Universiteit te Rotterdam (TNO Cleo project A-72).

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APPENDIX

ond nr: .....

FIRST FIT ONDERZOEK

BEOORDELINGS-FORMULIER EEG

ACADEMISCH ZIEKENHUIS ROTTERDAM-DIJKZIGT

afd. NEUROLOGIE

ALGEMENE GEGEVENS

Patiënt : ..... geb. dat.:...../..../....

EEG nr.: ..... dat. reg.:...../..../....

EEG: routine / na slaapdeprivatie Maudsley electrodes: ja / nee

Beoordeeld door: ..... dat. beoord.:...../..../....

Medicatie: nee / ja :.....

BESCHRIJVING GRAFO-ELEMENTEN EEG

Omcirkelen wat van toepassing is, meerdere antwoorden mogelijk

A. Waak-fase

1. normaal
2. specifieke afwijkingen passend bij epilepsie
   a. pieken
   b. polypieken
   c. piekgolfcomplexen: laag freq. (<2,5 per sec)
   d. freq (2,5-4 per sec)
   e. FSW (4 -6 per sec)
   f. polypiekgolfcomplexen laag freq. (<2,5 per sec)
   g. freq (2,5-4 per sec)
   h. FSW (4 -6 per sec)
   i. sharp wave complexen
3. aspecifieke irritatieve afwijkingen
4. non-irritatieve afwijkingen, niet paroxysmaal,
   - veroorzaakt door medicatie: ja / nee
5. non-irritatieve afwijkingen, paroxysmaal

B. Tijdens hyperventilatie

1. normaal
2. specifieke afwijkingen passend bij epilepsie
   a. pieken
   b. polypieken
   c. piekgolfcomplexen: laag freq. (<2,5 per sec)
   d. freq (2,5-4 per sec)
   e. FSW (4 -6 per sec)
   f. polypiekgolfcomplexen laag freq. (<2,5 per sec)
   g. freq (2,5-4 per sec)
   h. FSW (4 -6 per sec)
   i. sharp wave complexen
3. aspecifieke irritatieve afwijkingen
4. non-irritatieve afwijkingen, niet paroxysmaal,
   - veroorzaakt door medicatie: ja / nee
5. non-irritatieve afwijkingen, paroxysmaal
6. niet van toepassing, geen hyperventilatie gedaan

C. Tijdens lichtflitsprikkeling

1. normaal
2. specifieke afwijkingen passend bij epilepsie
   a. pieken
   b. polypieken
   c. piekgolfcomplexen: laag freq. (<2,5 per sec)
   d. freq (2,5-4 per sec)
   e. FSW (4 -6 per sec)
   f. polypiekgolfcomplexen laag freq. (<2,5 per sec)
   g. freq (2,5-4 per sec)
   h. FSW (4 -6 per sec)
   i. sharp wave complexen
3. aspecifieke irritatieve afwijkingen
4. non-irritatieve afwijkingen, niet paroxysmaal,
   - veroorzaakt door medicatie: ja / nee
5. non-irritatieve afwijkingen, paroxysmaal
6. niet van toepassing, geen lichtflitsprikkeling gedaan

D. Slaap-fase

1. patiënt bereikt non-Rem slaap:
   a. nee
   b. oppervlakkige slaap (stadium 1 en 2)
   c. diepe slaap (stadium 3 en 4)
2. patiënt bereikt REM slaap
   a. nee
   b. ja

E. Tijdens slaap

1. normaal
2. specifieke afwijkingen passend bij epilepsie
   a. pieken
   b. polypieken
   c. piekgolfcomplexen: laag freq. (<2,5 per sec)
   d. freq (2,5-4 per sec)
   e. FSW (4 -6 per sec)
   f. polypiekgolfcomplexen laag freq. (<2,5 per sec)
   g. freq (2,5-4 per sec)
   h. FSW (4 -6 per sec)
   i. sharp wave complexen
3. aspecifieke irritatieve afwijkingen
4. non-irritatieve afwijkingen, niet paroxysmaal,
   - veroorzaakt door medicatie: ja / nee
5. non-irritatieve afwijkingen, paroxysmaal
6. niet van toepassing, niet geslapen

F. Indien tijdens slaap afwijkingen werden gevonden, dan graag aangeven in welk stadium van de slaap. Gebruik hiervoor de letters en cijfers uit de vorige vraag.

1. oppervlakkige slaap afw: .....
2. diepe slaap afw: .....
3. niet van toepassing

G. Waar zijn de epileptische afwijkingen voornamelijk gelocaliseerd?

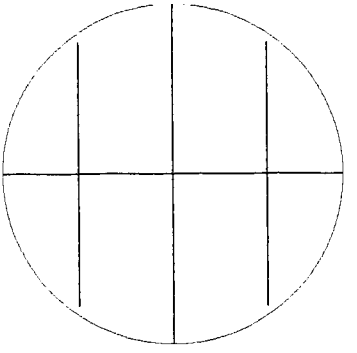
1. overwegend links voor / midden / achter
2. overwegend rechts voor / midden / achter
3. beiderzijds / wisselend voor / midden / achter
4. mediaanlijn voor / midden / achter
5. niet van toepassing (geen afwijkingen)

H. Waar zijn de overige afwijkingen voornamelijk gelocaliseerd?

1. overwegend links voor / midden / achter
2. overwegend rechts voor / midden / achter
3. beiderzijds / wisselen voor / midden / achter
4. mediaanlijn voor / midden / achter
5. niet van toepassing (geen afwijkingen)

I. Lokalisatie epileptische afwijkingen

Geef op de tekening de plaats van de afwijking(en) aan.



CONCLUSIE

A. Eindbeoordeling (meerdere categorieën mogelijk)

1. normaal
   normaal achtergrond-patroon,tijdens slapen of waken zonder focale of gegeneraliseerde al dan niet paroxysmaal optredende afwijkingen
2. afwijkingen specifiek voor epilepsie
   voorkomen van pieken, polypieken, piekgolfcomplexen of polypiek-golfcomplexen
3. anderszins gestoord EEG paroxysmaal
4. anderszins gestoord EEG niet paroxysmaal

B. Kunt U aangeven hoe waarschijnlijk U de volgende uitspraken vindt? (zeker > 80%, waarschijnlijk 51-80%, mogelijk 20-50%, onwaarschijnlijk <20%)

1. Het EEG is normaal
   zeker / waarschijnlijk / mogelijk / onwaarschijnlijk
2. Het EEG vertoont afwijkingen passend bij epilepsie
   zeker / waarschijnlijk / mogelijk / onwaarschijnlijk
3. Het EEG vertoont andere stoornissen paroxysmaal
   zeker / waarschijnlijk / mogelijk / onwaarschijnlijk
4. Het EEG vertoont andere stoornissen niet paroxysmaal
   zeker / waarschijnlijk / mogelijk / onwaarschijnlijk

C. Indien U bij epilepsie: mogelijk, waarschijnlijk of zeker heeft aangekruist; type afwijkingen

1. focaal
2. partieel
3. bilateraal
4. gegeneraliseerd
5. partieel met secundaire generalisatie
6. multifocaal
7. niet van toepassing (geen afwijkingen passend bij epilepsie)

E. Raadt U op grond van dit EEG aan een Ct-scan te laten maken?

1. nee
2. ja

F. Afwijkingen in het ECG?

1. nee
2. ja namelijk : .....
3. niet van toepassing, geen ECG geregistreerd

G. Is het EEG beoordeelbaar

1. ja
2. nee: .....

H. Opmerkingen

.....

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