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# Termination of anticonvulsive drug treatment and the electroencephalogram

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The value of the EEG in the decision to terminate antiepileptic treatment has been investigated on the basis of longitudinal EEG studies in 433 children and adolescents with epileptic seizure disorders. The data were subjected to uni- and multivariate statistical analysis. Most valuable information concerning the risk of seizure recurrence was derived from (i) the EEG findings obtained just before tapering of medication; (ii) the course of EEG after termination of treatment; and (iii) the maturation of EEG background activity. Thus, the EEG is a valuable tool in the decision of continuation or termination of antiepileptic treatment.

The value of EEG in the diagnosis of epileptic seizure disorders has been established beyond doubt. There are, however, differences of opinion with regard to the usefulness of EEG concerning the choice and especially the termination of anticonvulsive medication. For this reason, a prospective study of the long-term prognosis of childhood epilepsies after discontinuation of anticonvulsive treatment was carried out. In the study, special attention was paid to the EEG findings which will be discussed in the following.

## Material and Methods

The study was based on 433 children and adolescents (235 males, 198 females) with various types of epileptic seizures. The age (at the time of discontinuation of treatment) ranged from 2 to 20.5 years. The EEG was carried out with an 8-channel apparatus (Messgeräte Zwönitz) with the use of standard parameters (paper speed, amplification, filter). If feasible, the resting EEG was complemented by hyperventilation and intermittent photic stimulation as well as sleep following sleep deprivation. EEG records were carried out as follows: (1) once or several times before onset of treatment; (2) after initiation of treatment; (3) during treatment, depending on the course (usually in 12-month-intervals); (4) before tapering of medication; (5) during tapering of medication; (6) after termination of treatment at intervals of 4 weeks, 3, 6 and 12 months, then at one-year-intervals.

EEG findings were broken down and categorized as follows: (1) normal EEG; (2) EEG with non-paroxysmal activity (continuous or intermittent rhythmical theta or delta activity with or without a tendency to generalization); (3) EEG with paroxysmal or epileptiform activity (spikes, sharp waves, polyspikes, alone or in combination with slow waves, i.e. forming spike-wave complexes). Marginal or borderline EEG tracings (within very broad normal limits of variability for age) were listed as "normal EEG". All of the acceptable and meaningful EEG data were subjected to statistical analysis using the chi square

test as well as multivariate discriminance and variance analysis. Significance was based on a limit of 1% of probability of error ($p < 0.01$).

The prognostic value of the EEG finding was determined on basis of the recurrence or non-recurrence of seizures after termination of the anticonvulsive therapy.

## Results

The EEG findings were assessed with regard to the clinical course.

### *EEG findings before the beginning of treatment*

There was no significant statistical correlation between the EEG before onset of therapy and future tendency to recurrences.

### *EEG findings during treatment*

The difference between these recurrence rates was considered significant but the p value of 0.016 was still within the probability of error.

### *Intermittent occurrence of epileptiform activity*

This implies spontaneous (unprovoked) appearance and disappearance of epileptiform activity in the course of antiepileptic treatment. This criterion appeared to be unrelated to recurrences. The relapse rate was the same (36%) in patients with and without intermittent paroxysmal abnormalities.

### *Bioelectrical maturation*

This term pertains to the normal process of EEG maturation along with advancing age from infancy to adolescence, especially with regard to the frequency spectrum. Presence or absence of normal maturational tendencies during treatment were investigated.

Thus, patients with disturbed maturational development in the EEG proved to have a significantly higher risk for seizure recurrence ($p < 0.001$).

Table V indicates that the presence of epileptiform activity in the EEG prior to discontinuation of anticonvulsants was associated with a significantly increased rate ($p < 0.001$).

The tendency to relapse was similar in all groups and there was no significant difference in the percentage of relapses within the different groups of seizures. The statistical relations between the frequency of recurrence and the presence of epileptiform activity in the EEG prior to discontinuation of therapy in each group of seizures were as follows: absences ($p < 0.01$), tonic-clonic siezures ($p < 0.05$), benign centro-temporal epilepsy ($0 < 0.05$), West and Lennox-Gastaut syndrome ($p < 0.01$), combined seizures ($p > 0.05$). In the other groups a statistical analysis could not be made because the number of the patients was too small and not all variables were available.

There was no significant relation between patients with epileptiform activity in the resting EEG and those with epileptiform activity during activation procedures. The morphology of the paroxysmal discharges (spike-wave-complexes, spikes, sharp waves) and their spatial distribution (gener-

TABLE I

Frequency of relapses in relation to the disappearance of epileptiform activity in the cour seof long term treatment

| EEG findings | Number of patients | Patients without relapse | Patients with relapse |
|---|---|---|---|
| Epileptiform activity | 60 | 30 | 30 |
| No epileptiform activity | 257 | 187 | 70 |

The difference between the recurrence rates was highly significant ($p < 0.001$).

TABLE II

Rate of relapses in relation to the disappearance of epileptiform activity along with stabilized seizure freedom

| EEG findings | Number of patients | Patients without relapse | Patients with relapse |
|---|---|---|---|
| Epileptiform activity | 79 | 45 | 34 |
| No epileptiform activity | 238 | 172 | 66 |

TABLE III

Rate of relapses in relation to the reappearance of epileptiform activity and their persistence in the course of treatment

| EEG findings | Number of patients | Patients without relapse | Patients with relapse |
|---|---|---|---|
| Epileptiform activity | 19 | 4 | 15 |
| No epileptiform activity | 414 | 272 | 142 |

The difference between these recurrence frequencies was highly significant ($p < 0.001$).

TABLE IV

Rate of relapses in relation to bioelectrical maturation

| EEG findings | Number of patients | Patients without relapse | Patients with relapse |
|---|---|---|---|
| Normal EEG maturation | 289 | 204 | 85 |
| No normal EEG maturation | 144 | 72 | 72 |

TABLE V

Frequency of relapses in relation to the EEG findings prior to discontinuation of antiepileptic treatment

| EEG findings | Number of patients | Patients without relapse | Patients with relapse |
|---|---|---|---|
| Epileptiform activity | 83 | 36 | 47 |
| No epileptiform activity | 350 | 240 | 110 |

alized, focal, diffusely scattered) proved to be an insignificant criterion.

*EEG findings after termination of treatment*

In 130 patients, the EEG showed persistence, reappearance or first appearance of epileptiform activity after termination of treatment and/or in the ensuing follow-up period. Of the patients, 74 (56.9%) had a relapse. On the other hand, only 83 out of 303 patients (27%) without epileptiform activity in the EEG had a recurrence of seizures. The difference between these groups was significant statistically ($p < 0.001$).

Statistical evaluation of all available EEG data by means of multivariate analysis showed that two prognostic factors were most valuable, a) the EEG findings prior to discontinuation of antiepileptic therapy, and b) the maturational development of EEG background activity in the course of treatment.

TABLE VI

Frequency of relapses with different types of seizure in relation to the EEG findings before discontinuation of antiepileptic therapy (EEG ∅ = EEG without epileptiform activity, EEG + = EEG with epileptiform activity)

| Types of seizures | Number of patients | Patients without relapse | | Patients with relapse | |
|---|---|---|---|---|---|
| | | EEG ∅ | EEG + | EEG ∅ | EEG + |
| Absences | 127 | 72 | 7 | 35 | 13 |
| Tonic-clonic seizures | 124 | 61 | 16 | 29 | 18 |
| Benign centrotemporal epilepsy | 62 | 34 | 4 | 16 | 8 |
| Combined seizures | 40 | 21 | 2 | 13 | 4 |
| West syndrome | 17 | 15 | 1 | 1 | — |
| Lennox-Gastaut syndrome | 14 | 9 | 1 | 1 | 3 |
| Unilateral seizures | 12 | 5 | 1 | 6 | — |
| Simple partial seizures | 6 | 4 | 1 | 1 | — |
| Complex partial seizures | 9 | 3 | 2 | 3 | 1 |
| Bilateral massive myoclonus | 2 | — | — | 2 | — |
| Unclassified seizures | 20 | 16 | 1 | 3 | — |
| Summary | 433 | 240 | 36 | 110 | 47 |

## Discussion

There has been an increasing number of follow-up studies of epileptic patients after termination of anticonvulsive therapy. Thus far, however, only a small number of authors have dealt with the role of the EEG in the decision to terminate drug therapy [1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 14, 15]. The results of these investigators differed considerably. According to some [6, 8, 9, 12], the EEG recorded prior to decreasing the doses is of little or no value with regard to the risk of seizure recurrence. Other investigators [2, 5, 11, 15], however, emphasized the prognostically favourable significance of reduced epileptiform activity during anticonvulsive therapy.

Our data showed that the persistence of epileptiform activity in the EEG prior to the intended discontinuation of treatmentd enotes a higher risk of relapses. On the other hand, it should be remembered that a normal EEG does not rule out the recurrence of seizures. This was shown by a relapse rate of 27% of patients with a normal EEG in our material. Similar relapse rates have been reported by other authors [3, 6, 9].

Our data suggested that not only the EEG findings prior to termination of anticonvulsive therapy had an importance but also the course of the EEG findings after termination of treatment. Patients with persistence, re-appearance or first appearance of epileptiform activity in the EEG after anticonvulsive treatment (i.e. in the follow-up period) had significantly more recurrences. This is in accordance with the observations of Förster and Schmidberger [3].

Thus far, there have been no reports concerning wave morphology and spatial distribution of paroxysmal discharges with regard to treatment and relapses. We were unable to demonstrate such correlations. It must be said, however, that statistical analysis was marred by the small number of patients in each group.

In this context, it might be worthwhile to discuss the problems of "EEG-oriented therapy". It must be emphasized that the clinical course is the most important criterion as far as the optimum therapeutic approach is concerned. On the basis of our data, however, it is advisable to aim at both seizure-freedom and EEG without epileptiform activity in the course of longterm treatment. It should be taken into account whether the abnormal paroxysmal EEG was the expression of a per se recalcitrant form of epileptic seizure disorder, or was due to inadequate antiepileptic treatment, or to poor patient compliance. These possibilities should not interfere with analysis of the patient material. It is also well-known that children with absences may show aborted spike-wave bursts in the EEG in spite of seizure freedom; these abnormalities can be eliminated by further increase of the dosage. The intended normalization of the EEG, however, should not be achieved at the expense of undesirable side effects. Optimum treatment

requires much experience and a special "touch", and the intended seizure freedom and side effects must carefully be weighed against each other.

These considerations have led to another important question, i.e. the termination of therapy in patients who have been seizure-free for several years while the EEG has been persistently showing epileptiform activity. According to Doose [1], the presence of "massive EEG abnormalities" does not rule out termination of treatment. This author recommends in such cases an at least five-year-period of seizure freedom and very cautious reduction of drugs. Groh [5] followed such patients in comparison with patients with improved or normalized EEG.

Our study also showed that, in patients with epileptiform activity in the EEG prior to termination of treatment, a seizure freedom of 3 years or longer was associated with a lower relapse rate. Prolongation of the seizure-free period before discontinuation of therapy evidently diminished the risk of recurrences. One is hence tempted to conclude that, even in such problematic cases, termination of therapy is not necessarily contraindicated provided that the duration of seizure-freedom reaches or exceeds a five-year-period. Still, this rule should not be generalized. A responsible and individual approach is needed even though the patient's (or the parent's) request for termination of treatment is taken into consideration.

Further studies will be needed in order fully to assess the risk of relapses. Presumably, there will always be epileptic patients who require much longer treatment periods than the remaining patient population. As it has been pointed out by other authors [5, 13, 15] the prognosis is reflected not merely by the resolution of epileptiform activity but also by the maturational process affecting the background activity. Our longitudinal EEG studies clearly showed that a lack of bioelectrical maturation is associated with a significantly higher relapse rate. This process of EEG maturation, however, may be obscured by the drug-induced slowing of the background EEG activity. In these patients, termination of anticonvulsive therapy resulted in a "de-camouflage" of the EEG and re-appearance of the true background of activity.

Notwithstanding our reservations against strictly statistical analysis of data, our findings and those of the literature suggest that the EEG at the time of termination of treatment represents a useful criterion. If reasonably used and interpreted, the EEG is of great value in the important decision of continuation or termination of antiepileptic therapy.

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