Reducing Myoclonus after Etomidate

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Background: The authors hypothesized that myoclonus after etomidate is dose-related, could be suppressed when small doses of etomidate were administered before induction, and is unassociated with seizure-like activity on electroencephalogram (EEG).

Methods: Three studies were performed. In the first study, 36 men were randomly assigned to receive 0.025, 0.050, 0.075, 0.100, 0.200, or 0.300 mg/kg of etomidate. In a second crossover study, eight men were randomly allocated to receive either a pretreatment dose of 0.050 mg/kg etomidate or placebo 50 s before 0.300 mg/kg etomidate was injected. EEG was recorded for subjects in the first two studies. In a third study, 60 patients were randomly allocated to one of three pretreatment doses of etomidate: 0.030, 0.050, or 0.075 mg/kg before 0.300 mg/kg was given.

Results: In Study 1, myoclonus was not observed after 0.025 or 0.050 mg/kg etomidate. One volunteer had myoclonus after 0.075 mg/kg and another after 0.100 mg/kg etomidate; three had myoclonus after 0.200 mg/kg; and five after 0.300 mg/kg. Incidence of myoclonus was dose-related ($P \leq 0.01$). In Study 2, two volunteers (25%) with etomidate pretreatment had mild myoclonus compared to six (75%) with placebo pretreatment ($P \leq 0.05$). EEG changes, other than delta waves, were not seen during myoclonic epochs. In Study 3, myoclonus was less likely after the small pretreatment doses (0.030 or 0.050 mg/kg) than after the large dose (0.075 mg/kg, $P \leq 0.01$).

Conclusions: Incidence and intensity of myoclonus after induction with etomidate are dose-related, suppressed by pretreatment, and unassociated with seizure-like EEG activity. (Key words: Anesthesia; epilepsy; side effects.)

ETOMIDATE is a hypnotic that is thought to act mainly on the telencephalic neocortex.[1] Myoclonus is a bothersome side effect of anesthesia induction with etomidate.[1–3]

Because most of the other bothersome or even serious side effects associated with etomidate induction were related to the vehicle propylene glycol (Amidate®, Abbott, Chicago, IL),[3–6] the vehicle has been changed to a fat emulsion (Etomidate-Lipuro®, B. Braun Melsungen, Melsungen, Germany). With the new solvent, pain on injection, venous irritation, and hemolysis were virtually abolished.[3–6] However, the incidence of myoclonus during induction was not affected by the solvent.[3,5,6] When anesthesia is induced with etomidate, 50–80% of patients who are not premedicated experience myoclonus.[1–3,7]

The neurologic mechanism of myoclonus is unclear.[8,9] One possibility is that it represents some form of seizure activity.[8–12] On the other hand, some argue that it is a disinhibition phenomenon,[1] presumably because large doses of etomidate depress cortical activity before they depress subcortical activity.[1,2,8,9] Our goal was to evaluate these possibilities. We monitored the electroencephalogram (EEG) during induction of general anesthesia with etomidate. We also pretreated volunteers and patients with small doses of etomidate in an effort to suppress subcortical activity and to reduce the incidence of myoclonus.

Methods

With institutional review board approval and volunteer or patient consent, three studies were performed: (1) a dose–response study in volunteers to determine the incidence of myoclonic movements at different doses; (2) a crossover single-dose study with and without pretreatment in volunteers to determine whether pretreatment,

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synonomously called priming affected the incidence of myoclonus; (3) a dose-ranging study in patients to determine what pretreatment dose affected the incidence of myoclonus. All volunteers and patients were free of neuropathologic signs and symptoms or diagnosis of neurologic diseases. They had not participated in any other study and had not used sedative hypnotic medication or alcohol for at least 7 days before the start of the study. Heart rate, pulse oximetry readings, and electrocardiogram (ECG) (Sirecust 300, Siemens, Erlangen, Germany) were recorded continuously. Noninvasive blood pressure measurements were recorded every minute (Dinamap 1846 SX, Critikon, Tampa, Florida, USA). Etomidate Lipuro® (B. Braun Melsungen, Germany) was used in all three studies.

Study 1

In a single-blind, prospective, parallel group design, 36 male unpremedicated volunteers (American Society of Anesthesiologists [ASA] physical status I-II), aged 19–34 yr (mean ± SD, 25 ± 3 yr) were randomly allocated to one of six groups. The men received 0.025, 0.050, 0.075, 0.100, 0.200, or 0.300 mg/kg of etomidate as an intravenous bolus over 10–20 s, depending on group allocation. The lungs of the volunteers were ventilated to maintain an end-tidal carbon dioxide concentration of 32–38 mmHg. Lead II of the ECG was recorded. EEG (Nihon-Kohden, Kyoto, Japan) was recorded with five electrodes over the right hemisphere (frontal, precentral, central, parietal, occipital) corresponding to Fp2, T4, C4, P4, and O2 of international standard positions, with reference on the right mastoid identical to that of previous studies involving anesthetics.[1,2,13] The EEG recordings were later evaluated by a neurologist experienced in EEG in 40-s epochs from each subject. Because myoclonus rarely concerns neck muscles, artifacts in the EEG from muscle movements were rare. Myoclonus was observed visually and assessed by a trained physician who was blinded to treatment group. Myoclonus was defined as an involuntary, short contraction of some muscle fibers, of a whole muscle, or of different muscles of one group, leading to a short observable movement of the corresponding body part, usually not longer than 100 ms. If there was repetition of an isolated myoclonus, the observer was instructed to use the most intense myoclonus in ranking intensity. Duration of a myoclonic epoch was the time between the first and the last myoclonus. Starting points of a single myoclonus were determined by clinical observation and corresponding artifacts in the ECG due to movements of an extremity.

Endpoints of myoclonic epochs were judged visually by a trained observer. Each myoclonus was graded according to intensity. A mild myoclonus was a short movement of a body segment (a finger or a shoulder). A moderate myoclonus was slight movement of two different muscles or muscle groups of the body (face and leg). Severe myoclonus was intense clonic movement in two or more muscle groups (fast abduction of a limb).

Study 2

In a double-blind, crossover design, eight men, aged 19–35 yr (mean ± SD, 28 ± 6 yr) were randomly assigned to receive intravenously either a pretreatment dose of 0.050 mg/kg etomidate or placebo of the same volume. One week later, the volunteers were assigned to the other pretreatment group. Fifty seconds after the end of the pretreatment, 0.300 mg/kg of etomidate was injected into the intravenous line as a bolus over 30 s. Monitoring, anesthetic processes, and rating of myoclonus were as in Study 1.

Study 3

Sixty consecutive consenting patients (34 men, 26 women) of ASA physical status I-II, aged 18–66 yr (mean ± SD, 38 ± 12 yr), and who were scheduled to undergo ear, nose, or throat (ENT) surgery were allocated randomly to one of three groups to receive etomidate as a pretreatment medication. None of the 60 patients had a history of epilepsy. Each patient was premedicated orally with 7.5–11.2 mg of midazolam (La Roche, Basil, Switzerland) 1 h before induction of anesthesia. At induction, a bolus of 0.030, 0.050, or 0.075 mg/kg of etomidate was injected into the intravenous catheter. Fifty seconds later the patient was evaluated for drowsiness, and the dose was repeated if the patient was not drowsy. Fifty seconds after the last evaluation, 0.300 mg/kg of etomidate was administered followed in 90 s by 3.000 µg/kg of fentanyl and 0.500 mg/kg of atracurium (Glaxo-Wellcome, Hamburg, Germany). Anesthesia was subsequently maintained with desflurane (Pharmacia and Upjohn, Erlangen, Germany) 3% and 50–70% nitrous oxide in 30–50% (remainder) oxygen. Monitoring and ventilation was as in Study 1. The occurrence and intensity of myoclonic movements were also noted by a blinded observer as in Study 1. Because the results of Study 1 and 2 showed no evidence for seizures, systematic EEG recording was not used in these patients. Groups were compared with each other using unpaired *t* test and analysis of variance with statistical difference at the $P \leq 0.05$ level considered significant.
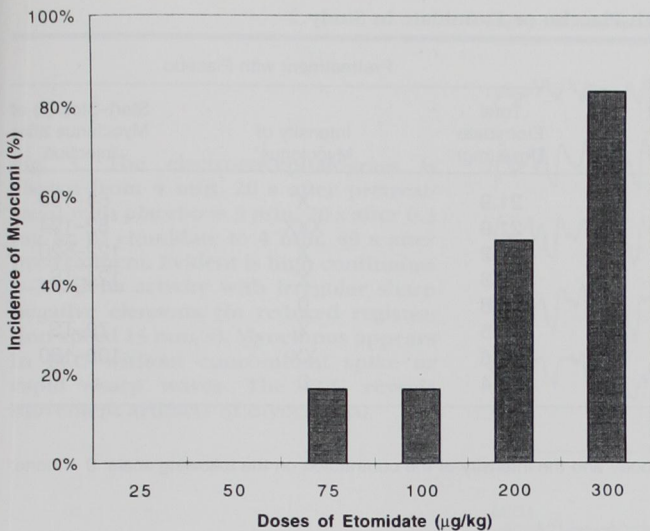
Fig. 1. Incidence of myoclonus after bolus injection of etomidate. The histogram shows the influence of dosage. The results are from a single-blind, randomized study with 36 volunteers, 6 in each group.

Results

Study 1

The occurrence of myoclonus was dose-related ($P \leq 0.01$) with greater incidence after higher doses. Myoclonus was not observed after administration of etomidate doses of 0.025 and 0.050 mg/kg. Myoclonus was observed in one volunteer who received 0.075 mg/kg, in one who received 0.100 mg/kg, in three who received 0.200 mg/kg, and in five who received 0.300 mg/kg (fig. 1). In the volunteers who received 0.200 mg/kg or 0.300 mg/kg of etomidate, mild myoclonus occurred 27–51 s after the beginning of the hypnotic effect. The duration of myoclonic epochs during induction of anesthesia

never exceeded the stage with slow waves on EEG and unresponsiveness. Of the 36 volunteers, 10 had mild myoclonus, and myoclonic epochs lasted 30–400 s (mean, 143 s; table 1). Myoclonus was accompanied by an increased frequency of delta waves (normal sleep slow waves, not seizure waves) on EEG.

Study 2

After the pretreatment dose of etomidate, only two of eight volunteers exhibited single, mild myoclonus (25%); in the placebo group, six of eight volunteers exhibited mild, moderate, or severe myoclonus (75%, table 2). In the placebo group, one volunteer had severe myoclonus repeatedly, randomly scattered over an epoch of 112 s, with EEG evidence of rapid sharp waves (fig. 2). One volunteer had mild myoclonus after both etomidate and placebo pretreatment, but myoclonic intensity was more severe after placebo (fig. 3). The myoclonus was observed only with synchronous slow and continuous high waves on the EEG, not typical of seizure. There were no EEG changes other than delta waves during myoclonic epochs (fig. 3).

Study 3

The incidence of myoclonus after the three pretreatment doses was not different. Of the 20 patients who received 0.030 mg/kg, four required an additional 1–3 doses of etomidate to ensure that they were drowsy. In this group, four (20%) patients had mild or moderate myoclonus. In the other groups mild or moderate myoclonus was experienced by 5 of 20 patients in the 0.050 mg/kg group and 7 of 20 in the 0.075 mg/kg group (table 3). In the last group, two patients had myoclonus that appeared 60 s after the pretreatment dose (patients 10

Table 1. EEG Activity in Volunteers during Myoclonus in Study 1

Volunteer Number	Dose (mg/kg)	First Myoclonus (s) after Injection	Duration (s) of Myoclonic Epoch	EEG Activity during Myoclonus*
12	0.075	225	TS	δ-waves, κ-complex
27	0.100	240	30	High θ-waves, transition to δ-waves, κ-complexes
19	0.200	120	TS	Continuous δ-waves
24	0.200	200	80	Mainly δ-waves
36	0.200	120	120	Mainly δ-waves
25	0.300	160	80	Mainly δ-waves
26	0.300	360	40	Mainly δ-waves
31	0.300	80	400	Continuous high δ-activity, lack of reaction
33	0.300	80	40	Mainly δ-waves
35	0.300	120	240	Continuous high δ-activity, lack of reaction

TS = duration of the myoclonic epoch too short to be recorded.

* There was no evidence of a seizure complex in any volunteer.

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Table 2. Incidence of Myoclonus in Volunteers after Pretreatment with Placebo or Etomidate in Study 2

Volunteer Number	Pretreatment with Etomidate			Pretreatment with Placebo		
	Total Etomidate Dose (mg)	Intensity of Myoclonus*	Start–Stop (s) of Myoclonus after Injection	Total Etomidate Dose (mg)	Intensity of Myoclonus*	Start–Stop (s) of Myoclonus after Injection
1	25.5	0		21.9	X	64–130
2	25.5	X	70–179	21.9	XXX	82–194
3	25.9	X	30–TS	22.2	X	122–520
4	24.2	0		20.8	X	124–TS
5	19.6	0		16.8	0	
6	29.6	0		25.5	X	79–TS
7	33.4	0		28.6	XX	100–180
8	28.4	0		24.4	0	

TS = duration of the myoclonic epoch too short to be recorded.

* Grading of myoclonus included its extension over small or large segments of the body and the intensity of the contraction on the following scale: 0 = none; X = mild; XX = moderate; XXX = severe.

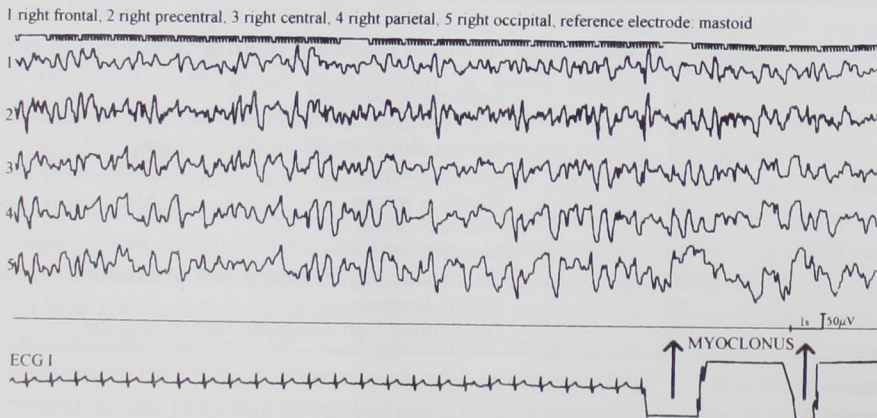and 18, table 3). Of the 60 patients in Study 3, 27% had myoclonus.

Discussion

These data and observations do not support the belief that seizures are an etiology for the myoclonic movements associated with etomidate for induction of anesthesia in normal people. We have documented 154 etomidate inductions of anesthesia with EEG monitoring without clinical seizures or patterns of spikes characteristic of seizures.[1-3,6] Our observation that low doses of etomidate reduce the incidence of myoclonus and the EEG data we present are consistent with the assumption that subcortical disinhibition is a possible origin of myoclonus during anesthesia with etomidate.

Abolition of myoclonus occurs when premedication is given with benzodiazepines or fentanyl, drugs known to inhibit subcortical neuronal activity.[1,2,7,14-18] In study 3

we used midazolam as a premedication 1 h before induction of anesthesia for ethical reasons. We chose midazolam because of its short effect. We knew from previous studies that this regimen has no effect on the incidence of myoclonus.

Physiologic or nocturnal myoclonus has been reported with the first stages of light sleep and is associated with EEG activity of low mixed alpha and theta waves, with arousal (awakening) reactions, and with dreams.[19-21] Non-epileptic myoclonus is differentiated from epileptic myoclonus by the absence of generalized or diffuse paroxysmal EEG activity characteristic of epileptic discharges.[19,22,23] Non-epileptic myoclonus may not show changes on EEG or may be reflected by isolated, rapid, sharp transients or spikes in EEG, which can appear 10–20 ms before or after the myoclonus. In our Studies 1 and 2, myoclonus after etomidate was preceded or followed in two individuals by sharp transients or small, rapid triphasic waves on EEG. In 16 individuals there

1 right frontal, 2 right precentral, 3 right central, 4 right parietal, 5 right occipital, reference electrode: mastoid

Fig. 2. The electroencephalogram is shown from 2 min after pretreatment with placebo = 70 s after 0.3 mg/kg of etomidate to 2 min, 27 s. Slow activity is mixed with irregular 1–3/s delta waves and superimposed 4–5/s theta waves. Myoclonus was first observed with a concomitant rapid sharp wave complex (triphasic) right precentral (and artifact in ECG); the second myoclonus was without similar EEG changes. ECG artifacts of limb movements are shown with first and second myoclonus.

I right frontal, 2 right precentral, 3 right central, 4 right parietal, 5 right occipital, reference electrode: mastoid

Fig. 3. The electroencephalogram is shown from 4 min, 20 s after pretreatment with placebo = 3 min, 20 s after 0.3 mg/kg of etomidate to 4 min, 40 s after pretreatment. Evident is high continuous 1–3/s delta activity with irregular sharp negative elements (in reduced registration speed 15 mm/s). Myoclonus appears in ECG without concomitant spike or rapid sharp waves. The ECG reveals movement artifacts of myoclonus.
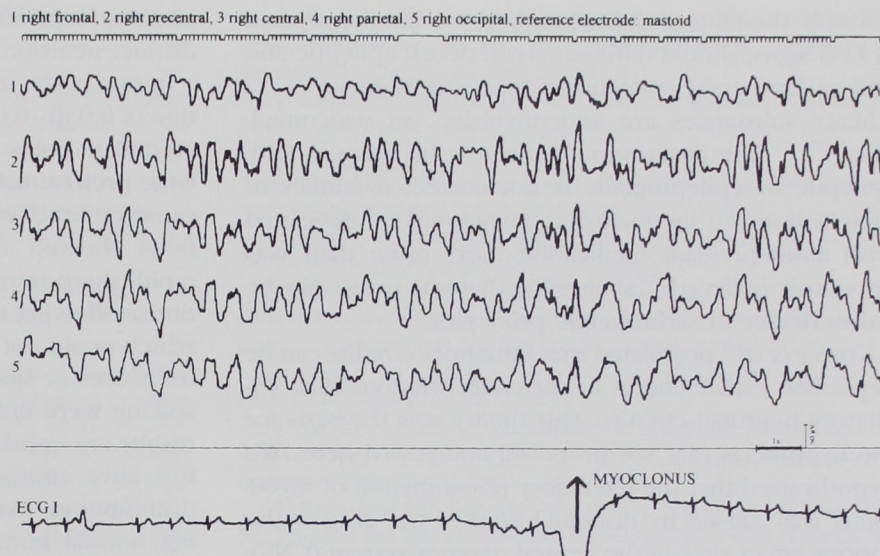
were no EEG changes. Gancher *et al.*[10] described etomidate as an activator of epileptiform activity in patients with medically refractory epilepsy whenever a seizure pattern was observed on EEG. In contrast, we used etomidate in healthy volunteers or in patients without a history of seizures. In the past, we have studied patients with a history of epilepsy who had anesthesia for non-neurologic operations.[2] We did not see an activation of epileptic seizures or the appearance of epileptiform paroxysms on EEG.[1-3,6,13] Other investigators have used large doses of etomidate to terminate episodes of status epilepticus.[24-26] The myoclonus that we observed during our studies was either without corresponding changes in the EEG (fig. 3) or with isolated, short spikes (fig. 2) in the precentral area or vertex sharp waves.

The locus of nonepileptic myoclonus generation may be situated subcortically and is postulated to involve several sites.[20-23] We hypothesized that during anesthesia, myoclonus may have a similar generation. The only difference between myoclonus with etomidate for induction of anesthesia and during normal sleep is that in the former, it appears with high, slow waves in the EEG, and in the latter, it appears with mixed low, slow waves, and alpha waves on EEG. Nocturnal periodic limb movements (also described as sleep starts) are a form of myoclonus in healthy individuals.[20] Hypnagogic or nocturnal myocloni are a physiologic phenomenon in nearly all healthy humans and also in dogs, cats, and other mammals.[21] Humans often report myocloni as startle reactions or during dreams of falling or nightmares. Because the sharp waves or spikes on EEG cannot be distinguished from isolated epileptiform potentials, the

committee for terminology of the International Federation of Societies for Electroencephalography and Clinical Neurophysiology (IFSCN) proposed to call them "transients."[13,23,27] To call such events seizure patterns is misleading. Modern video documentations of night sleep in sleep laboratories show a variety of seizure-like paroxysmal or epileptiform limb or body movements in subjects without epilepsy. To avoid misunderstandings

Table 3. Incidence of Myoclonus in Patients after Different Pretreatment Doses of Etomidate in Study 3: 20 Patients in Each of the Three Pretreatment Groups

Patient Identification Number	Pretreatment Dose (mg/kg)	Total Dose (mg/kg)	Intensity of Myoclonus*	Start (s) of Myoclonus Postinjection
7	0.030	0.48	XX	120
20	0.090	0.60	XX	160
26	0.060	0.70	X	120
34	0.030	0.53	XX	160
2	0.050	0.75	XX	90
6	0.050	0.83	X	60
13	0.050	0.45	X	90
14	0.050	0.67	X	60
20	0.050	0.40	X	60
8	0.075	0.58	X	120
10	0.075	0.73	XX†	60
11	0.075	0.54	X	100
16	0.075	0.60	X	90
17	0.075	0.40	X	90
18	0.075	0.79	XX†	60
19	0.075	0.57	X	90

* Grading of myoclonus included its extension over small or large segments of the body and the intensity of the contraction on the following scale: 0 = none; X = mild; XX = moderate; XXX = severe.

† Myoclonus began after pretreatment dose alone.

not only the clinical definition, but also the description of EEG signs, should differentiate between epileptic and epileptiform and between waves and transients.

Many substances are anticonvulsive yet proconvulsive.[9,28-31] The description of these substances as antiepileptic or epileptogenic is not correct if studies of their action are inconclusive. Myoclonus is associated with antidepressant medication more often than was previously believed,[29] suggesting that one cause may be a disturbance in serotonergic processes.[32]

Kugler *et al.*[2] postulated that inhibitory circuits can be depressed earlier and at lower concentrations than excitatory neuronal circuits. This theory was the basis for the hypothesis that we proposed and tested here. We hypothesized that the excitatory phenomenon of myoclonus was caused by disequilibrium of the drug at the various effect sites in the central nervous system (CNS). Differences in local cerebral blood flow or affinity might produce a temporary disequilibrium of effect, resulting in more rapid depression of cortical inhibition. If over time, inhibitory and excitatory neural circuits are both depressed by etomidate, but the inhibitory are depressed sooner, then pretreatment could reduce the incidence of myoclonus. Conversely, larger initial bolus doses (up to a point) increase the incidence of myoclonus. Our findings support this hypothesis.

Thus, transient disinhibition of subcortical structures after the transition from consciousness to unconsciousness with etomidate may be explained by an unsynchronized onset of the drug action at different sites of action within the CNS. This effect could be the result of local blood flow differences with inhomogenous drug distribution in the CNS. This theory is speculative, and to our knowledge, there are no data in the literature supporting it. Inhomogenous drug action at different sites of the CNS may also be caused by differences in receptor affinity or regional receptor distribution within the CNS. Etomidate and other hypnotics act at the GABA$_A$ receptor,[33-35] which is a pentameric assembly of different glycoprotein subunits (α_{1-6}, β_{1-3}, γ_{1-3}, δ, ϵ).[36] Low concentrations of etomidate potentiate the effect of GABA at its receptor (modulating effect); higher concentrations directly activate the receptor (activating effect).

The ability of etomidate to modulate and activate GABA$_A$ receptors is uniquely dependent on the β-subunit subtype within the receptor.[37-40] The distinct distribution of the GABA$_A$ receptor subunits within the CNS[41] may explain the specific regionally distinct effects of etomidate. The distinct effects of etomidate have been

observed in a different context: etomidate has regionally distinct neuroprotective effects.[42]

In our study, in volunteers and in patients administration of 0.030-0.050 mg/kg etomidate 50-60 s before an etomidate bolus markedly reduced excitatory effects. A large pretreatment dose of 0.075 mg/kg, however, may cause rather than prevent myoclonus. Our EEG observations showed non-seizure phenomena like isolated, rapid, sharp transients, sometimes preceding and sometimes following the myocloni with a delay of 10-20 ms, which could not be distinguished from physiologic vertex waves or sharp waves. Epileptic paroxysms or ictal spiking were not found at the time of myoclonus. Our results are consistent with the hypothesis that myoclonus after etomidate is a phenomenon of subcortical disinhibition, like the phenomenon of restless legs during normal human sleep and is not generated by an epileptic focus.

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