

Interictal acute psychoses in temporal lobe epilepsy during withdrawal of anticonvulsant therapy

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SUMMARY Acute interictal psychotic attacks during withdrawal of medication are described in two patients with temporal lobe epilepsy submitted to depth EEG study with a view to surgical treatment. The patients were on chronic treatment with clonazepam associated in one with phenobarbitone and in the other with phenobarbitone plus carbamazepine. Our observations suggest that the acute withdrawal of clonazepam, the plasma levels of which were monitored, may play a part in producing psychotic attacks characterised by dysphoric manifestations, irritability, aggressiveness, anxiety, and hallucinations. These symptoms could be interpreted as a withdrawal syndrome.

A relatively high incidence of psychiatric disorders has been found in patients suffering from temporal lobe epilepsy (Bruens, 1975; Pond, 1975). These psychoses have been classified as psychotic states with and without disturbances of consciousness (Bruens, 1975; Helmchen, 1975).

The first condition is a postparoxysmal state (ictal psychosis) characterised by confusion, disorientation, delusion, and hallucination. EEG recording may show generalised spikes, paroxysmal sharp waves, temporal theta and delta waves.

Psychotic states with a normal level of consciousness (interictal psychoses) are brief episodic attacks (depressive and dysphoric states) sometimes prolonged by chronic manic-depressive syndromes and paranoid or schizophrenia-like patterns. Interictal epileptic EEG activity may disappear during these episodes ("forced normalisation") (Landolt, 1958). In some patients these attacks alternate with epileptic seizures, the so-called "alternative psychoses" of Tellenbach (1965) and Janz (1969).

McDanal and Bolman (1975) and Wolf (1977) have drawn attention to the role of antiepileptic drugs in determining acute epileptic psychoses. They demonstrated that anticonvulsant plasma levels during psychotic attacks may be normal or low and that their aetiology is not necessary toxic,

as previously thought (Gibbs, 1951; Hill *et al.*, 1957).

In this paper we present two patients suffering from temporal lobe epilepsy who had psychotic attacks during withdrawal of anticonvulsant drugs during preoperative depth EEG study. Close correlations between the clinical picture, depth EEG activity, and plasma levels of clonazepam are described.

Method

In patients considered for surgery, preoperative EEG studies with depth electrodes (depth EEG) and withdrawal of therapy are sometimes used for diagnostic purposes. In the two patients reported here, multilead stainless steel electrodes were implanted stereotactically according to Talairach's technique (Talairach *et al.*, 1974; Cabrini *et al.*, 1975; Marossero, 1975).

Four and five days respectively after implantation of the electrodes anticonvulsant medication was withdrawn. Evaluation of plasma levels of anticonvulsants permitted the maintenance of a plasma concentration which allowed the appearance of electrical seizures but not of severe clinical manifestations (Baruzzi *et al.*, 1977; Marossero *et al.*, 1977).

The determinations of anticonvulsant plasma levels were done by gas-liquid chromatography with the analytical procedures described by McGee (1970) for phenobarbitone, by Morselli *et al.*

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(1973) for carbamazepine, and by Gerna and Morselli (1976) for clonazepam. Drug concentrations were considered to be in therapeutic range when they fell within the following limits: phenobarbitone 15–40 µg/ml; carbamazepine 4–10 µg/ml; clonazepam 15–70 ng/ml.

Psychiatric evaluation was performed during a series of interviews. The patients were given a battery of psychological tests including the Thematic Aperception and complete Wechsler-Bellevue Intelligence Scale.

Case reports

CASE 1

This 28 year old man (PN) has been affected since the age of six years by weekly attacks of partial epileptic seizures with complex symptomatology, characterised by bodily sensation, impairment of consciousness, behavioural automatisms, and motor phenomena. From the age of 10 years occasional secondarily generalised seizures occurred. There is no history of birth trauma or other pathological events to which the seizures could be related.

Neurological examination showed no interictal deficits. Psychological and psychiatric studies showed moderate psychic impairment. At Wechsler-Bellevue Intelligence Scale examination he had a verbal IQ of 98 and performance IQ of 101. No previous psychiatric episode had occurred.

The patient was unresponsive to antiepileptic medication. In the year before admission he was treated with phenobarbitone (150 mg/day) and clonazepam (3 mg/day). Anticonvulsant plasma level monitoring showed values of about 21.5–27.8 µg/ml for phenobarbitone and 14–17 ng/ml for clonazepam. Neuroradiological examination was normal.

On the basis of the clinical and EEG data, seven indwelling depth electrodes were placed stereotactically in the frontal, temporal, and parietal cortices, in the amygdala, Ammon's horn, and the fusiform gyrus on the right side, and in the mid-temporal cortex and Ammon's horn on the left side.

The clinical picture, depth EEG activity, and pharmacological correlations during the steady state condition, withdrawal and readministration of therapy are shown in Figs. 1 and 2.

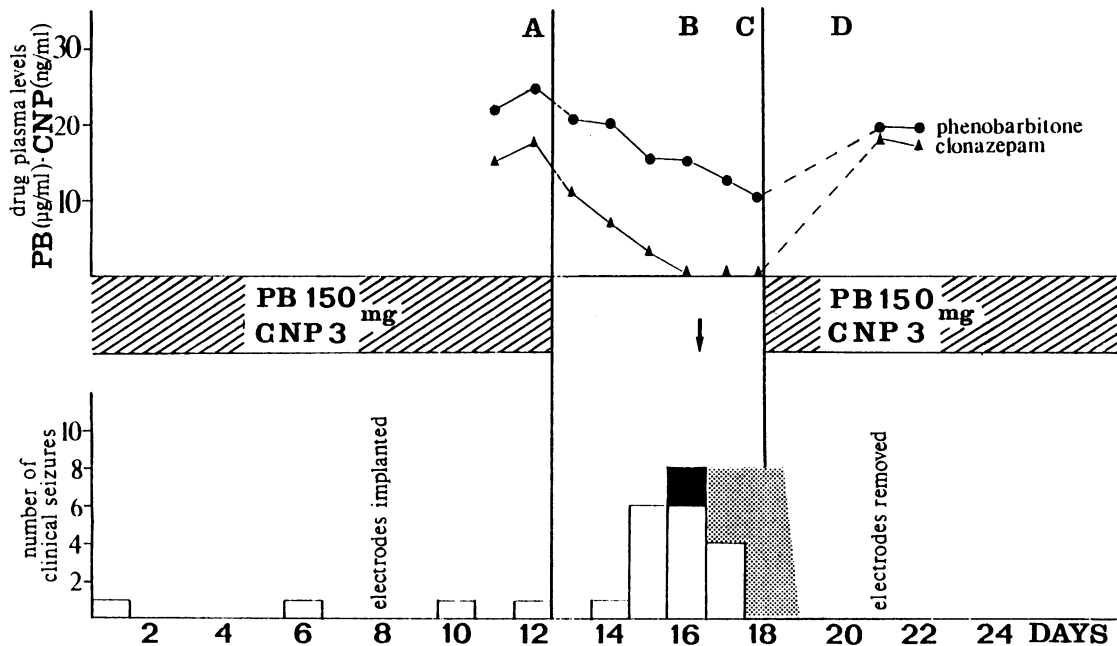


Fig. 1 Case 1. Correlations between clinical picture, daily drug dosage, and anticonvulsant plasma levels during steady state condition, withdrawal, and readministration of therapy. A, B, and C correspond to the days of registration of depth electrical activity reported in Fig. 2. In D the electrical activity is similar to that in A. (↓ diazepam 5 mg/iv). PB=phenobarbitone, CNP=clonazepam, □=psychomotor, ■=secondarily generalised, ▨=acute psychotic attack.

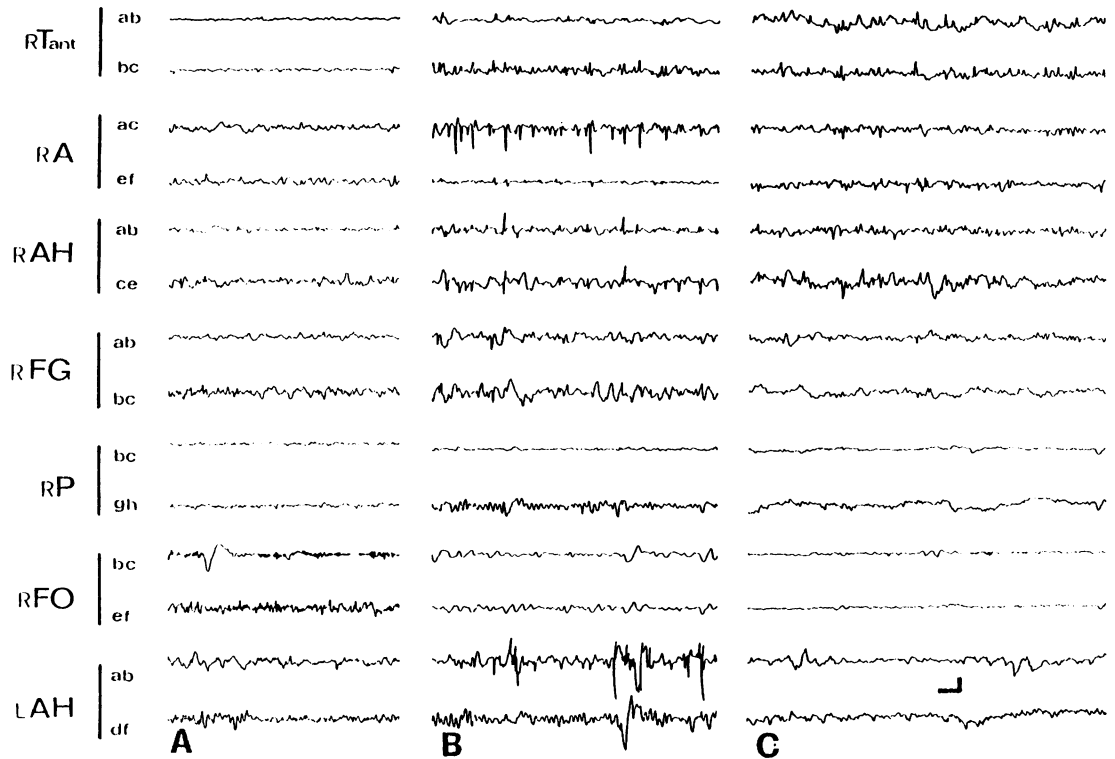


Fig. 2 Case 1. Interictal depth EEG recording. (A) Steady state: rare irritative activity in right rhinencephalic structures. (B) Fourth day after withdrawal of treatment: asynchronous high voltage fast spikes in right amygdala and low voltage spikes in right temporal cortex and Ammon's horn. Independent high voltage spikes in left amygdala. (C) During acute psychotic attack: marked reduction of irritative activity with low voltage abnormalities in the right temporal cortex. Calibrations: \downarrow 50 μ V; — 1 second. Placement of electrodes: right side: amygdala (A), Ammon's horn (AH), fusiform gyrus (FG), parietal cortex (P), anterior temporal cortex (T ant); left side: Ammon's horn (AH), a, b, and c are deep leads, d, e, f, g, and h are superficial leads.

During the steady state condition the patient had few seizures and no mental changes. Anticonvulsant plasma levels were 21.8–23.8 μ g/ml for phenobarbitone and 14–17 ng/ml for clonazepam. Interictal depth recording showed theta activity in the rhinencephalic structures and fast activity in the right fronto-orbital region. There was also occasional irritative activity in the right rhinencephalic structures (Fig. 2A).

During withdrawal of treatment the clinical picture was characterised by a progressive increase of partial seizures and the appearance of secondarily generalised seizure. Interictal depth EEG during the period of the progressive increase of the number of seizures showed asynchronous high voltage fast spikes in the right amygdala and low voltage spikes in the right temporal cortex and Ammon's horn. Independent high voltage spikes were also present in the left amygdala (Fig. 2B).

During the fifth day of therapy withdrawal (when plasma levels were 13.5 μ g/ml for phenobarbitone and clonazepam was not detectable) the patient had an acute dysphoric state characterised by loss of verbal contact with unimpaired consciousness, childish excitement, outbursts of aggressiveness, hallucinations with religious preoccupations, and severe anxiety. Fine tremor of both hands was also present. During this state the psychomotor seizures disappeared, and depth EEG recording showed a marked reduction of irritative abnormalities. Only a rare low voltage irritative activity in the rhinencephalic structures and temporal cortices was present (Fig. 2C).

On the second day after the readministration of antiepileptic therapy, when plasma levels reached the values of about 14 μ g/ml for phenobarbitone and 7 ng/ml for clonazepam, the dysphoric state disappeared. The patient had no seizures in the

next six days, while depth EEG records showed the same electrical patterns as in the steady state recordings.

CASE 2

This 37 year old woman (CA) suffers from daily partial epileptic seizures with complex symptomatology, characterised by impairment of consciousness, autonomic symptoms, and automatisms with occasional secondarily generalised seizures.

Neurological examination was normal. Psychological study showed only moderate mental impairment. Wechsler-Bellevue Intelligence Scale examination showed a verbal IQ of 105 and a performance IQ of 94. No previous psychiatric episode had occurred.

The patient was unresponsive to antiepileptic medication. In the 12 months before admission for surgery she was treated with phenobarbitone (200 mg/day), carbamazepine (800 mg/day), and clonazepam (6 mg/day). Anticonvulsant plasma levels showed values of about 27–30 $\mu\text{g/ml}$ for phenobarbitone, 4–6 $\mu\text{g/ml}$ for carbamazepine and 18–24 ng/ml for clonazepam.

The EEG study showed rhythmic low voltage spikes in the left temporal region and asynchronous irritative activity in the anteromedial right temporal region. Neuroradiological examination (including CAT scan) was normal.

On the basis of the clinical and EEG data, eight indwelling depth electrodes were placed stereotactically in the left parietal and temporal cortices, amygdala, and Ammon's horn, and in the right mid-temporal cortex and Ammon's horn.

The clinical picture, depth EEG recordings, and plasma level correlations are charted in Figs. 3 and 4.

During the steady state, the patient had few psychomotor seizures and no mental change. The values of anticonvulsant plasma levels were 25–30 $\mu\text{g/ml}$ for phenobarbitone, 4–6 $\mu\text{g/ml}$ for carbamazepine, and 17–20 ng/ml for clonazepam. Depth recordings showed low voltage fast activity in the left frontal region, high voltage slow waves in the left temporal cortices, and high voltage spikes in the left amygdala and Ammon's horn. There were no irritative abnormalities recorded from the right rhinencephalic structures (Fig. 4A).

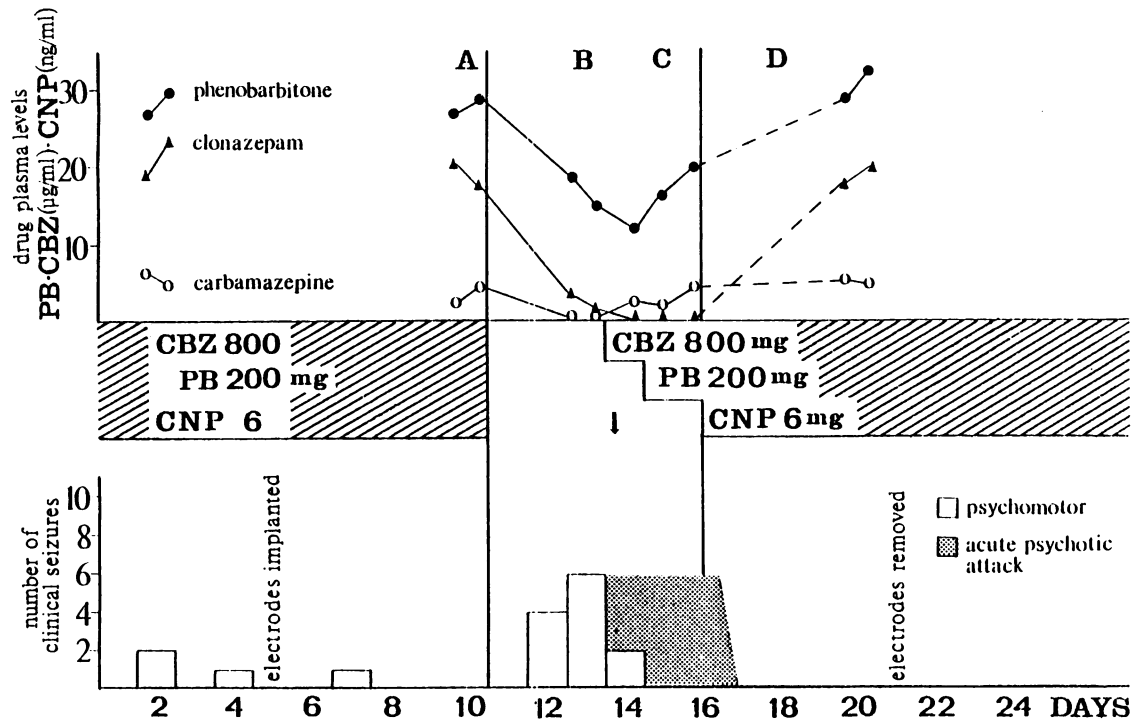


Fig. 3 Case 2. Correlations between clinical picture, daily drug dosage, and anticonvulsant plasma levels during steady state condition, withdrawal, and readministration of therapy. A, B, and C correspond to the days of registration of depth electrical activity reported in Fig. 4. In D the electrical activity is similar to that in A. (\downarrow diazepam 5 mg iv). CBZ=carbamazepine, CNP=clonazepam, PB=phenobarbitone.

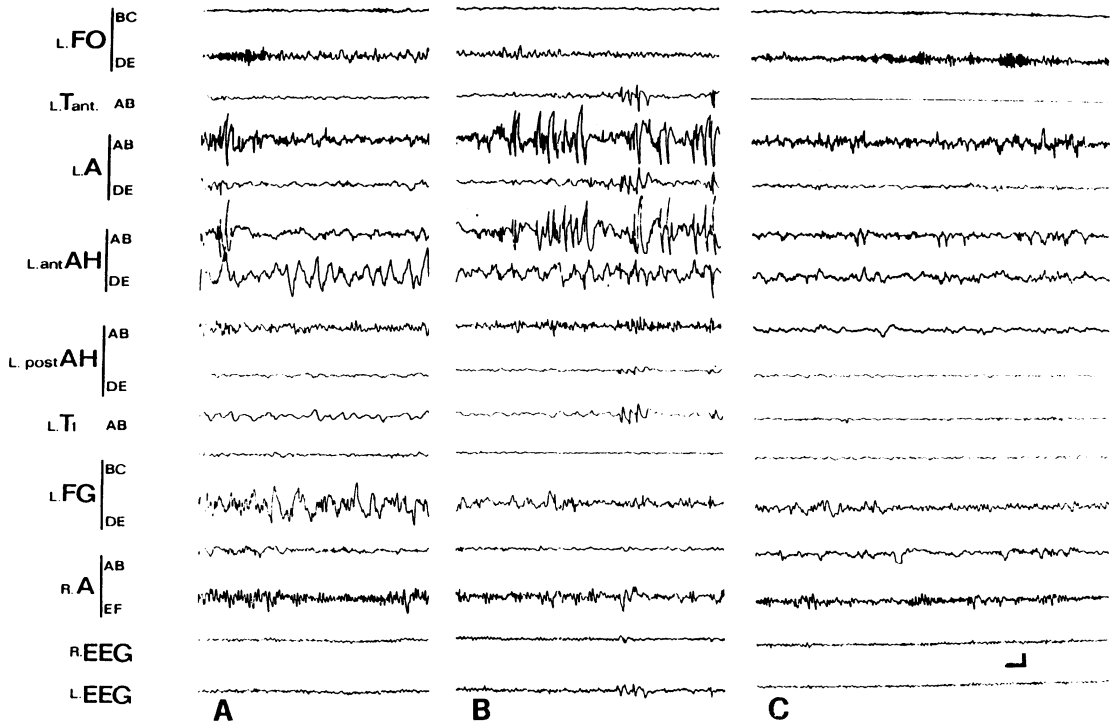


Fig. 4 Case 2. Intercictal depth EEG recording. (A) Steady state: high voltage spikes in left amygdala and Ammon's horn. High voltage slow waves in left temporal cortex and low voltage fast activity in frontal region. (B) Third day after withdrawal of treatment: high voltage rhythmic spikes and polyspikes in left amygdala and Ammon's horn and in mid-temporal cortex. (C) During acute psychotic attack: disappearance of irritative activity in temporal cortex and rhinencephalic structures. Fast activity in right frontal region. Calibrations as in Fig. 2. Placement of electrodes: left side: amygdala (A), anterior and posterior Ammon's horn (ant/post AH), fusiform gyrus (FG), fronto-orbital cortex (FO), temporal cortex (Tant/Ti); right side: amygdala (A); a, b, and c are deep leads, d, e, and f are superficial leads.

Withdrawal of drugs provoked a progressive increase in the number of seizures starting from the second day, when the plasma levels were about 22 $\mu\text{g/ml}$ for phenobarbitone, 1.5 $\mu\text{g/ml}$ for carbamazepine, and 8 ng/ml for clonazepam. On the fourth day (plasma levels: phenobarbitone 12.5 $\mu\text{g/ml}$, carbamazepine 2 $\mu\text{g/ml}$, clonazepam not detectable) the seizures disappeared and the patient had an acute dysphoric attack characterised by childish excitement with unimpaired consciousness, irritability, outbursts of aggressiveness, and hallucinations with religious preoccupations and sexual fantasies.

Depth EEG recording during the progressive increase of seizures after withdrawal of therapy showed low voltage spikes in the left anterior temporal cortex and high voltage fast spikes and polyspikes in the left amygdala and Ammon's horn (Fig. 4B). On the other hand, during the dysphoric state the recording showed an almost

complete disappearance of the irritative abnormalities and the appearance of fast activity on the left fronto-orbital and right temporal cortices (Fig. 4C).

Symptomatic treatment with diazepam (5 mg intravenously) was started followed by readministration of carbamazepine (600 mg/day) and phenobarbitone (200 mg/day), without success in controlling the psychotic state. The psychotic symptomatology disappeared only after clonazepam was given (6 mg/day) and when plasma levels were about 22 $\mu\text{g/ml}$ for phenobarbitone, 5 $\mu\text{g/ml}$ for carbamazepine, and 6 ng/ml for clonazepam. At that time depth EEG records showed a picture similar to the steady state recording.

Discussion

After the acute withdrawal of chronic anticonvulsant therapy our two patients presented daily

partial seizures during the first three days without mental changes, when anticonvulsant plasma levels ranged between 30 and 15 $\mu\text{g/ml}$ for phenobarbitone, between 5 $\mu\text{g/ml}$ and "nondetectable" levels for carbamazepine, and between 17 and 4 ng/ml for clonazepam.

Depth EEG showed focal interictal and ictal irritative activity in the temporal cortices and rhinencephalic structures.

On the fourth and fifth day respectively the two patients became seizure-free and presented an acute dysphoric state characterised by childish excitement, severe anxiety, outbursts of aggressiveness, and hallucinations with religious preoccupations and sexual fantasies. Fine tremor of both hands was present in one of the two patients. Plasma levels of phenobarbitone were between 15 and 12 $\mu\text{g/ml}$, carbamazepine levels were between 5 and 4 $\mu\text{g/ml}$, while clonazepam was "not detectable."

Depth EEG recordings during these psychotic states were characterised by the almost complete disappearance of focal irritative activity and the appearance of fast activity in the frontal region with diffuse slow waves. These clinical and EEG pictures are different from those described as dreamy states (Lugaresi *et al.*, 1971). On the other hand, the EEG pattern is very similar to the so-called "forced normalisation" described by Landolt (1958) during acute epileptic psychoses. The electrical abnormalities reported by Heath (1963), Glaser *et al.* (1963) and Bancaud *et al.* (1975) during psychotic attacks in epilepsy were not observed in our cases.

The psychiatric changes disappeared when therapy was readministered and plasma levels raised to the therapeutic range (phenobarbitone between 13–23 $\mu\text{g/ml}$, carbamazepine about 5 $\mu\text{g/ml}$, clonazepam about 5–7 ng/ml). Depth EEG findings became similar to the steady state recording characterised by focal irritative abnormalities.

There is some evidence of a possible pathogenetic role of acute withdrawal of clonazepam in the psychiatric and depth EEG changes reported:

1. The acute psychosis appeared only when the plasma level of clonazepam was not detectable, while levels of phenobarbitone and carbamazepine were near to the lower limit of the therapeutic range (phenobarbitone always over 12 $\mu\text{g/ml}$, carbamazepine about 4–5 $\mu\text{g/ml}$) during the psychotic attacks.
2. The psychiatric changes disappeared only when clonazepam was readministered and reached a plasma level of about 5–7 ng/ml; this correlation was more evident in case 2 (Fig. 3).

3. These observations are similar to those reported by Sjo *et al.* (1975) in patients in whom the abrupt withdrawal of clonazepam produced pronounced dysphoria, irritability, restlessness, sleeplessness, and tremor of the hands. In those patients the clinical signs were also interpreted as withdrawal symptoms, and they disappeared almost immediately when small doses of clonazepam were readministered.

4. Low plasma levels of phenobarbitone, diphenylhydantoin, and carbamazepine after acute withdrawal during depth EEG recording have never been correlated with mental and psychotic abnormalities in our previous studies in patients suffering from partial complex epilepsy with rhinencephalic foci (Baruzzi *et al.*, 1977; Marossero *et al.*, 1977).

In conclusion, our observations suggest the possible role of acute withdrawal of clonazepam in determining acute psychotic attacks characterised by dysphoric manifestations, irritability, aggressiveness, anxiety, and hallucinations. These symptoms can be interpreted as a withdrawal syndrome. Depth EEG recordings confirmed the previous observations of "forced normalisation" during a psychotic attack in epileptic patients. These cases could be considered also as examples of the so-called "alternative psychoses" (Tellenbach, 1965; Janz, 1969).

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