Idiopathic Recurring Stupor: A Case with Possible Involvement of the Gamma-Aminobutyric Acid (GABA)ergic System

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A patient had recurrent spontaneous episodes of stupor or coma in the absence of toxic, metabolic, or structural brain damage. Ictal electroencephalography showed fast 14 Hz background activity; sleep studies excluded narcolepsy. Flumazenil (Anexate), a benzodiazepine antagonist, promptly resolved the episodes and normalized the electroencephalogram. Radioreceptor binding studies showed the presence of a ligand to the central benzodiazepine receptor in plasma and cerebrospinal fluid during the episodes, suggesting a gamma-aminobutyric acid (GABA)ergic system involvement in the origin of the attacks.

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Transient partial or complete loss of consciousness may be due to toxic, metabolic, or vascular encephalopathies or structural, especially III ventricle and midbrain, central nervous system (CNS) damage. Abnormal sleepiness sometimes resembling stupor or coma characterizes narcolepsy, Kleine–Levin syndrome, and idiopathic CNS hypersomnolence. Recurring coma and abnormal behavior in the absence of toxic, metabolic, or vascular factors have recently been reported [1].

We detail here a similar patient, who had recurrent spontaneous episodes of stupor and coma in the absence of known causes and sleep pathologies. During these episodes, blood plasma and cerebrospinal fluid (CSF) were found in radioreceptor binding studies to contain benzodiazepine (BZ)-like activity, that is, a compound or compounds showing affinity for the BZ receptor. The BZ receptor is a site at the gamma-aminobutyric $acid_A$ ($GABA_A$) receptor–chloride channel complex. Thus, actions at the BZ receptor influence central GABAergic inhibition. BZ receptor antagonists block the BZ receptor. In our patient, flumazenil, a BZ receptor antagonist, reversed both stupor and coma, thus suggesting an involvement of the GABAergic system in the pathogenesis of the attacks.

Patient Report

A previously healthy 63-year-old man, without relevant family or personal history, began to present at age 61 years spontaneous comatose episodes at intervals of 3 to 60 days, characterized by increasing drowsiness, confusion, slurring of speech, and staggering. In approximately 30 minutes, drowsiness progressed to pronounced obtundation and, on many occasions, to deep "sleep" lasting 8 to 10 hours. Relatives could awaken the patient with difficulty by vigorous stimuli only; thereafter, he would immediately go back to sleep. At the end of the attacks, the patient remained confused for some hours and did not recall the episode. Attacks could occur anytime during the day; on some occasions, the patient was found unresponsive in bed, early in the morning. No emotional, psychological, nutritional, or other toxic factors triggering the episodes were evident.

Ictal Studies

We monitored six spontaneous episodes on admission of the patient to our clinic. During the episodes, the patient lay hypotonic in bed with eyes closed, looking asleep. Vigorous painful stimuli could awaken the patient who then could perform simple tasks, but after a few seconds he resumed sleep. Eyelids could be raised without resistance, spontaneous blinking was absent, corneal reflexes preserved. Pupils were miotic, reactive to light, eye movements slow but conjugate. No other neurological deficit was present. Breathing was noisy but regular, cyanosis absent. Systemic blood pressure

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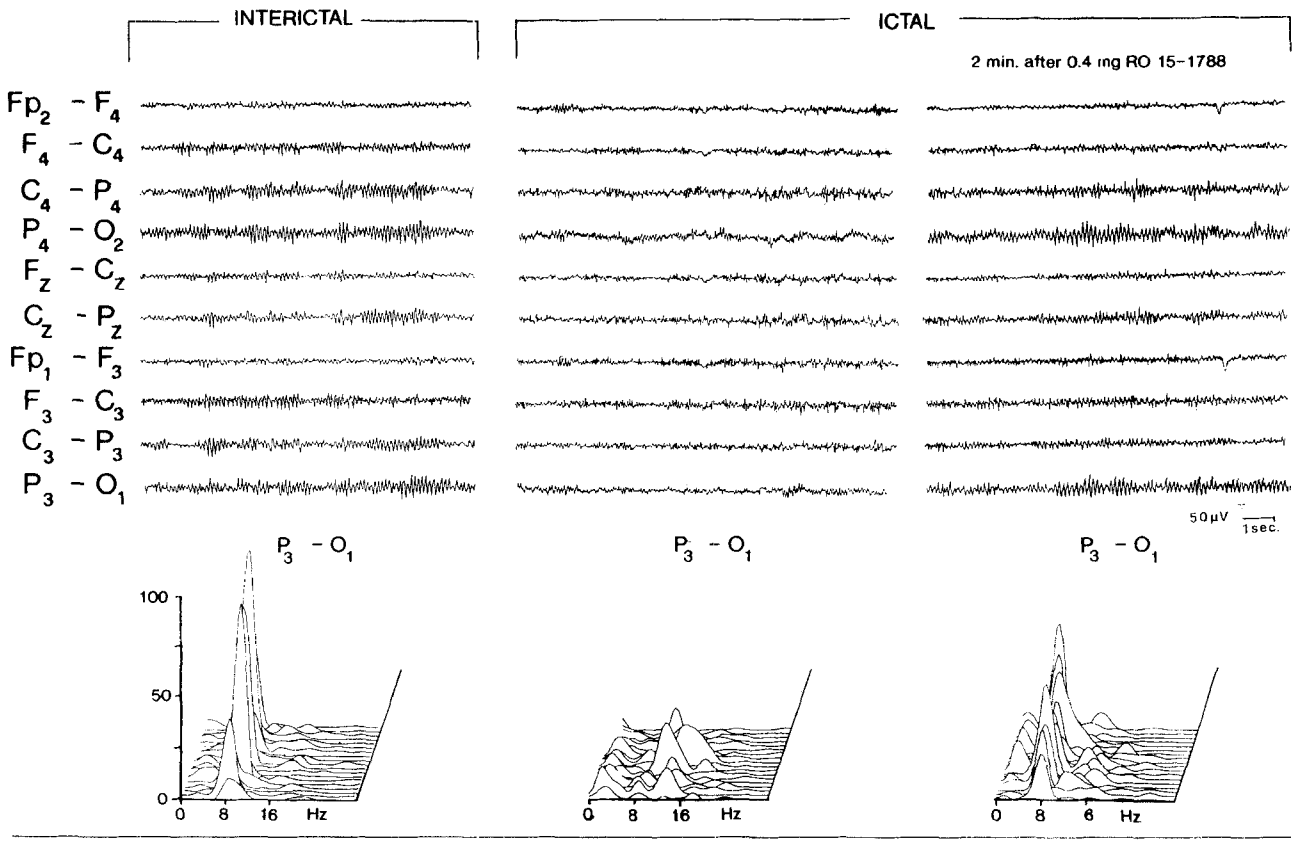

Interictal electroencephalogram (EEG): Well-organized 10 Hz background activity is reactive to eye opening. Lower histograms: EEG frequency bands. Ictal EEG: Diffuse monomorphic 14 Hz background activity is prevalent on the anterior regions without sleep figures and unreactive to stimuli. After 0.4 mg of intravenous flumazenil, there is a quick reappearance of alpha activity, reactive to eye opening.

(BP) showed average values of 120/80 mm Hg, heart rate (HR) was 60 to 45 beats/min. Arterial Po_2, Pco_2, pH, and HCO_3^+ were normal. Plasma BZ, tricyclic antidepressants, barbiturates, and ethanol as determined by routine assay were absent. Rectal temperature, plasma Na^+, K^+, Cl^-, Mg^{2+}, Ca^{2+}, and osmolarity, serum nitrogen, glucose, protein, and coagulation factors; serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), γ-glutamyl transpeptidase; bilirubin; T_3, T_4, thyroid-stimulating hormone (TSH); electrocardiogram (EKG) were all normal. In particular, venous serum ammonium was normal in the two episodes in which it was monitored. Enhanced computed tomographic (CT) brain scan was normal. A lumbar puncture yielded normal-pressure CSF with 59 mg/100 cm^3 of proteins, 54 mg/100 cm^3 of glucose, 0.9 lymphocytes/mm^3, and no oligoclonal bands. Brainstem and somatosensory evoked potentials were normal.

Scalp EEG, performed under audio–visual monitoring and with polygraphic parameters added (EKG, thoracic respirogram, noninvasive BP), always showed diffuse monomorphic 14 Hz background activity prevalent on the anterior regions, without sleep figures and unreactive to stimuli (Fig). Saline infusion and naloxone (10 mg i.v.) given under video-EEG monitoring did not change clinical status or EEG. In four episodes, flumazenil (Ro 15-1788; Anexate (Hoffmann-La Roche, Basel, Switzerland, 1 mg i.v.) (0.2 mg every 2 minutes) was administered blindly versus saline. At 0.4 mg, the patient opened his eyes and could reply to simple questions. EEG rapidly changed and a 10 Hz alpha activity appeared, reactive to eye opening (see Fig). At the end of the infusion (10 minutes), the patient was alert and orientated, but unable to recall the onset of the episode or being admitted to the hospital. BP and HR did not change during or after flumazenil infusion. This dramatic response to flumazenil was identical in the four episodes monitored, whereas saline infusion remained ineffective.

The patient was neuropsychologically evaluated under EEG monitoring during a milder episode (during which he was simply drowsy) and again soon after flumazenil. Disturbed visual attention, increased reaction times, impaired long-term verbal and immediate spatial memory were found, which normalized after flumazenil (1 mg i.v.).

Flumazenil 10 plus 20 mg given orally (by the patient's wife) was effective in reversing a mild stuporous episode that had occurred at home after discharge.

Interictal Studies

Neurological examination showed only questionable facial asymmetry, minimal postural tremor of the upper limbs, and slight prevalence of tendon reflexes on the left side. Pulmonary, liver, kidney, thyroid, and heart function, hepatic

and heart echography, and carotid echo Doppler studies were normal. BP was 120/80 mm Hg. HR was 60 beats/min. Blood and urinary examinations, ammonia, and basal and postexercise lactate were normal. CSF was normal. Brain CT, magnetic resonance imaging and single-photon emission computed tomographic scans, brain ^{31}P-magnetic resonance spectroscopy, and four-vessel cerebral angiography were also normal. EEG showed a well-organized 10 Hz background activity without abnormalities (see Fig). The patient underwent 24-hour polysomnographic recordings and repeated 24-hour ambulatory EEG monitoring. Sleep patterns were characterized by fragmentation and reduced efficiency of sleep; light sleep stages were increased at the expense of deep and REM (rapid eye movement) sleep; REM latency was reduced; alpha-like EEG activity was intermixed with background and delta-activity in light and deep sleep (so-called alpha–delta pattern [2]); physiological EEG sleep figures were normally represented; Sao_2 remained normal. A Multiple Sleep Latency Test (MSLT) failed to reveal daytime drowsiness. Neuropsychological tests [3] showed normal intellectual level (IQ 100, verbal IQ 110, performance IQ 87), normal attentive motor and memory functions, and no mental deterioration. Mood was normal. Human leukocyte antigen (HLA) DR2 was absent. Tests of cardiovascular reflexes were all normal. Diazepam (20 mg i.v.) provoked normal sleep and typical EEG patterns (fast rhythms and stage 2 sleep), different from the ictal EEG. No unusual sensitivity was noted.

Biochemical Studies

Samples of CSF and plasma taken between and during the episodes (on two different occasions) were stored in liquid nitrogen and shipped to two investigators (E.P.B. and P.S.) at F. Hoffmann-La Roche.

Plasma and CSF samples were diluted 1:1 with 0.9% saline followed by precipitation of protein by adding 130 μl of 0.1 M sulfosalicylic acid per sample of 1 ml. After 10 minutes of incubation, the samples were centrifuged, the supernatants removed, and the pH adjusted to 7.4 by adding 1 M Tris.

To determine the content of BZ-like factors, competitive BZ receptor binding studies were done using [^{3}H]-flumazenil as radioligand and rat cerebral cortical membranes as receptor preparation [4]. Nonspecific binding was determined in the presence of 3 μM diazepam and subtracted from each value. The standard curve was obtained with diazepam at concentrations from 0.3 to 1,000 nM in the presence of control plasma. All the results were corrected by the appropriate dilution factors. Ictal plasma (obtained during two separate episodes) and CSF samples showed higher BZ-like activity than interictal samples (Table).

Plasma and CSF Content of Benzodiazepine-like Activity

Samples	Diazepam-equivalent Concentration (nM)
Plasma	
Ictal (May 3, 1988)	165 ± 22
Interictal (July 1, 1988)	7 ± 2
Ictal (September 21, 1988)	56 ± 11
CSF	
Ictal (May 3, 1988)	26 ± 5
Interictal (July 1, 1988)	0

Values are the mean ± SEM. Benzodiazepine-like activity in plasma and cerebrospinal fluid (CSF) samples was determined by a benzodiazepine receptor binding assay after precipitation of protein by sulfosalicylic acid (see text). Similar results were obtained with aliquots that were heat denatured or not precipitated at all.

Discussion

Toxic, metabolic, vascular, and structural brain abnormalities were all excluded in our patient by the normal biochemical and radiological findings. Hepatic encephalopathy (HE) and hyperammonemic coma due to metabolic derangement [5–8] in particular were excluded. Recurring hypersomnia of Kleine–Levin syndrome [9], sleep apnea syndrome, narcolepsy, and idiopathic CNS hypersomnia were excluded [10, 11] by the ictal polygraphic and interictal MSLT. HLA-DR2 antigens, typical of narcolepsy patients [12], were absent.

Ictal and interictal scalp EEG never showed epileptic abnormalities. The peculiar monomorphic EEG 14 Hz background activity during the episodes was never found in interictal awake or sleep recordings. Such an EEG pattern differs from other known EEGs of stupor and comas, and is reminiscent of the fast EEG activities induced by BZ. Diazepam, however, in our patient induced EEG sleep patterns different from those recorded during the episodes.

The stupor and EEG were normalized by infusion of flumazenil (1 mg). Flumazenil, which binds with high affinity to the CNS BZ receptor, is a potent and selective antagonist of central BZ effects both in laboratory animals and in humans [13, 14]. Accordingly, flumazenil reverses the effects of BZ overdose in humans [15]. Flumazenil was also reported to attenuate some ethanol effects in humans [16] and to ameliorate HE [7, 8, 17–21]. An endogenous BZ ligand has been found in CSF of rabbits after induction of experimental HE [22, 23]. Central BZ receptor binding activity has also been found in the CSF of humans with HE [22–24], and HE improvement after flumazenil has been explained by the displacement of an endogenous BZ-like substance from the central BZ receptor [19, 23].

In our patient, plasma and CSF samples taken during ictal episodes were more active than interictal or control samples in displacing [^{3}H]flumazenil from rat cerebral cortex membranes in receptor binding studies. These findings and the clinical effects of flumazenil suggest an involvement of a BZ receptor agonist in the pathogenesis of the attacks.

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