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γ-Hydroxybutyric Acid-Induced Electrographic Seizures

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CASE REPORTS

We describe a case of absence-like electrographic seizures during NREM sleep in a patient who was taking sodium oxybate, a sodium salt of γ-hydroxybutyric acid (GHB). An overnight full montage electroencephalography (EEG) study revealed numerous frontally predominant rhythmic 1.5-2 Hz sharp waves and spike-wave activity during stage N2 and N3 sleep at the peak dose time for sodium oxybate, resembling atypical absence-like electrographic seizures. The patient was later weaned off sodium oxybate, and a repeat study did not show any such electrographic seizures. Absence-like seizures induced by GHB had previously been described in experimental animal models. We present the first reported human case of absence-like electrographic seizure associated with sodium oxybate.

Keywords: seizure, narcolepsy, pharmacology

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γ-hydroxybutyric acid (GHB) is the active ingredient of sodium oxybate and is approved by the Food and Drug Administration for the treatment of cataplexy associated with narcolepsy. GHB and γ-butyrolactone, a prodrug of GHB, have been shown to reliably increase slow wave sleep as well as induce absence-like seizures accompanied by 3-6 Hz spike-wave discharges (SWD) in monkeys and rats. GHB is regarded as the best pharmacological model of typical absence seizures in animal models.[1-4] To our knowledge, there has not been a reported case of GHB-induced absence-like seizure in a human.

REPORT OF CASE

The patient was a 35-year-old man who had narcolepsy with cataplexy as well as obstructive sleep apnea (OSA). He had been taking sodium oxybate for 2 years. The patient had no history of seizures, and his neurological examination was normal.

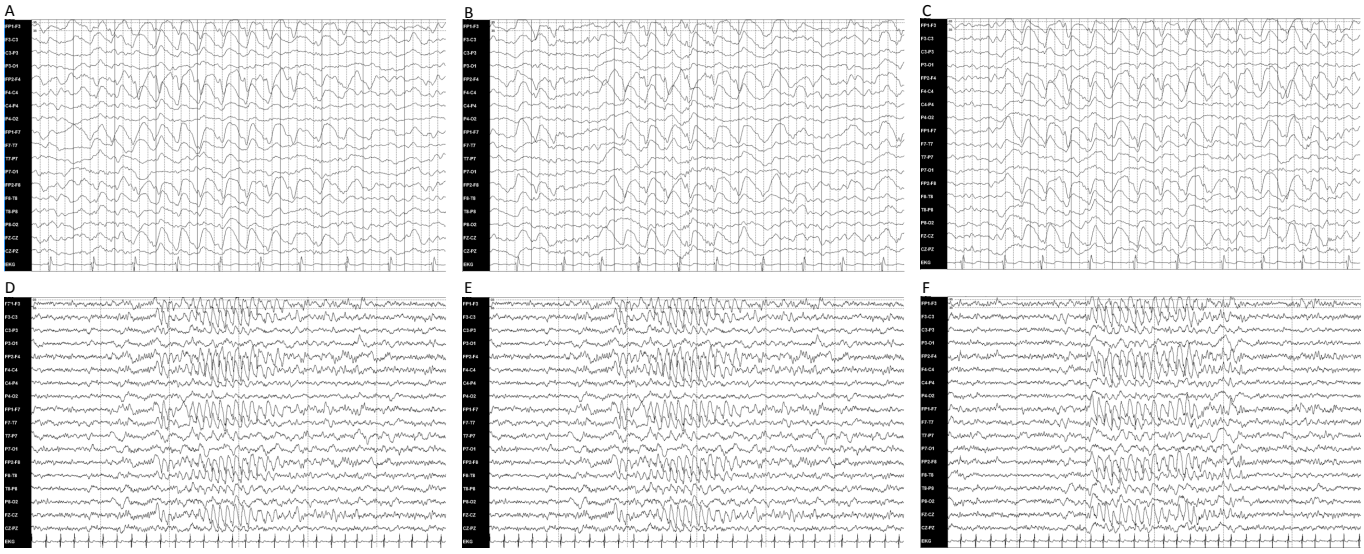
A full-montage electroencephalography (EEG) polysomnography (PSG) was obtained, as the patient's wife reported abnormal sleep behaviors including somnambulism, sleep eating, somniloquy, and possible dream enactment. The patient took sodium oxybate 4.5 g with two separate doses for a total of 9 g on the night of the study as he would regularly at night. His PSG showed moderate-severe OSA with an apnea hypopnea index (AHI) of 29.4 respiratory events per hour of sleep. Additionally, the full-montage EEG revealed > 10 4-10 second runs of rhythmic frontally predominant 100-150 μV, 1.5-2 Hz sharp waves and spike-wave complexes during stage N2 and N3 sleep over a period of ~30 minutes (**Figure 1**). The EEG was otherwise unremarkable. On video review, no abnormal behavior was associated with the epileptiform activity. He was noted to have frequent somniloquy during REM and NREM, with large movements during REM, as well as REM without atonia meeting criteria for REM sleep behavior disorder. However, these episodes were not associated with the runs of spike-wave complexes. Titration of positive airway pressure indicated 8 cm H_2O optimally treated the patient's OSA.

A brain magnetic resonance imaging (MRI) was later obtained and was normal. A routine daytime EEG including hyperventilation and photic stimulation showed no epileptiform changes. The patient was weaned off sodium oxybate because of his worsening parasomnias, which continued even on lower doses of sodium oxybate but improved significantly when it was completely stopped. This was followed by a repeat baseline PSG with full montage EEG. No rhythmic epileptiform activity was seen, although moderate-severe OSA with a small component of central apnea was noted. CPAP/bilevel titration that night found no optimal pressure due to the increased frequency of central apneas. The patient had one additional standard montage PSG with successful titration of auto servoventilation and no electrographic abnormalities.

DISCUSSION

We report a case of a young man with narcolepsy and OSA who had frontally predominant rhythmic 1.5-2 Hz sharp waves and spike-wave activity resembling absence-like electrographic seizures during sleep associated with the timing of sodium oxybate administration. This patient's EEG abnormalities differ from the semi-rhythmic polymorphic delta activity with sharp components reported in patients taking sodium oxybate. The epileptiform activity resolved after the patient discontinued sodium oxybate. We postulate that these electrographic abnormalities were related to a peak dose effect of GHB. The plasma concentration of GHB has been reported to peak at about 40 minutes after oral ingestion, and it has a half-life between 20 and 30 minutes.[1] The patient took two doses of 4.5 g of sodium oxybate the night of the study, the first dose at 22:16 and a second dose at 02:29. The first electrographic seizure was detected 43 minutes after he took the second dose, which correlates well with a peak dose effect.

Figure 1—EEG records when patient took sodium oxybate.



(**A-C)** 10-sec epochs of the patient's EEG recorded at 43, 45, and 49 minutes after the patient was administered the second dose of sodium oxybate. Frontally predominant rhythmic 100-150 μV, 1.5-2 Hz sharp waves, and rare spike-wave complexes can be seen. The two dotted lines in Fp1-F3 channel represent a scale of negative 35 μV to positive 35 μV. The vertical dark black lines are 1 sec apart and the lighter lines are 0.2 sec apart. **(D-F)** EEG record shown in 30-sec epochs corresponding to **A-C**, respectively. The vertical black lines indicate 5 sec apart.

Exogenous administration of GHB in humans can induce a wide range of neurophysiological states, including seizures, addiction, sedation, memory impairment, and increased slow wave sleep.[5] Such pharmacologic actions of GHB are thought to be mediated through the GABA-B receptor, where GHB may act directly or as a partial GABA-B receptor agonist.[2] In experimental animal models, GHB is well-known to induce absence seizures and SWD. Recent work in rats with GHB-induced absence seizures suggests GHB acts on presynaptic GABA-B receptors resulting in an excessive inhibitory input and an imbalance of excitatory and inhibitory drive in the thalamocortical neurons. This action of GHB results in increased neuronal bursting and synchronization in the thalamocortical loop and is hypothesized to underlie the development of absence seizures.[6] It is unclear at this point whether our case was an anomaly or would have a wider implication in patients who take sodium oxybate, given that he had no clinical seizures.

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