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External Ophthalmoplegia, Alpha and Spindle Coma in Imipramine Overdose: Case Report and Review of the Literature

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A 13-year-old boy with imipramine overdose developed seizures, respiratory arrest, and coma. Abnormalities of oculovestibular reflexes, electroencephalograms, and brainstem auditory evoked potentials were monitored in relation to measurements of drug levels. An alpha-coma electroencephalographic pattern evolved into one evidencing spindle coma and eventually into a normal pattern. Prolonged brainstem auditory evoked potentials also normalized as coma and oculocephalic reflex abnormalities resolved. In spite of the history that suggested hypoxic damage, the absence of reflex eye movements in a comatose patient and the presence of alpha and spindle-coma electroencephalographic patterns, even with prolonged brainstem auditory evoked potentials, are not reliable prognostic indicators in tricyclic drug overdose.

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Electroencephalographic (EEG) patterns described in alpha coma or in spindle coma have been shown to occur mainly following diffuse hypoxic-ischemic brain damage, brainstem infarctions, or head trauma. Few

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subjects have been reported in whom these EEG changes occurred as a consequence of drug overdose [5, 6, 9]. An absence of oculovestibular reflexes in a comatose patient appearing soon after a hypoxic event usually implies a grave prognosis [15]. Oculovestibular reflexes may be suppressed, however, by anxiolytic, most sedative, and antidepressive drugs [10, 12, 15, 16]. Only five subjects poisoned by tricyclic drugs have been described since the first report [12]. EEGs and brainstem auditory evoked potentials (BAEPs) were not obtained in these six previous patients. We describe an adolescent with imipramine overdose in whom seizures developed, respiratory arrest progressed to coma, and abnormalities of oculovestibular reflexes occurred. Serial EEGs and BAEPs closely related to measurements of drug levels showed the rapid evolution of an alpha-coma pattern into a spindle-coma one, with latency delays in BAEPs and both EEGs and BAEPs returning to normal as the patient recovered.

Case Report

A 13-year-old boy was admitted to the hospital after ingestion of approximately 1,000 mg of imipramine. On the same day the patient had a generalized tonic-clonic seizure. At another hospital he had required intubation after a respiratory arrest. Arterial blood gas measurements showed partial pressures of 52 for oxygen and 39 for carbon dioxide, and a pH of 7.05, a scenario suggestive of an anoxic insult. On admission to the Children's Hospital Medical Center, he had another seizure. A toxic screen revealed a serum imipramine level of 1,021 $\mu\text{g}/\text{cc}$ (therapeutic level, 150 $\mu\text{g}/\text{cc}$) and desipramine level of 420 $\mu\text{g}/\text{cc}$ (therapeutic level, 100 $\mu\text{g}/\text{cc}$). An EEG showed an invariant pattern of 10 to 12 Hz rhythms, with anterior predominance unreactive to stimuli (Fig 1). On the third hospital day the patient was still comatose. Oculocephalic reflexes were absent. Ice-water irrigation produced dysconjugate abduction of the ipsilateral eye only. An EEG taken then showed random or sequential 0.5 to 2 Hz delta waves, on which spindles at 10 to 12 Hz were superimposed, with some reactivity to stimuli (Fig 2). BAEPs to 60 decibel HL click stimulation showed a bilateral delay of conduction time between waves II and V outside of the normal mean plus 3 standard deviations (Fig 3). The imipramine levels were unchanged. On the sixth hospital day the imipramine level had dropped to 40 and the desipramine level to 181 $\mu\text{g}/\text{cc}$. The boy showed fluctuating alertness with periods of lucidity alternating with brief episodes of agitation and mild confusion. There was nystagmus on gaze in all directions, and finger-to-nose testing showed mild dysmetria. An EEG now showed well-developed 9 Hz (30 to 50 μV) alpha rhythms posteriorly that blocked to eye opening. Anteriorly, low-voltage beta activity was mixed with 4 to 5 Hz theta activity. BAEP conduction times were now normal when the left ear was stimulated, whereas a very mild delay persisted between waves II and V when the right ear was stimulated. Two days later the patient was fully recovered and the neurological examination showed no abnormalities. Follow-up EEG and BAEP testing two weeks after discharge also revealed no abnormalities.

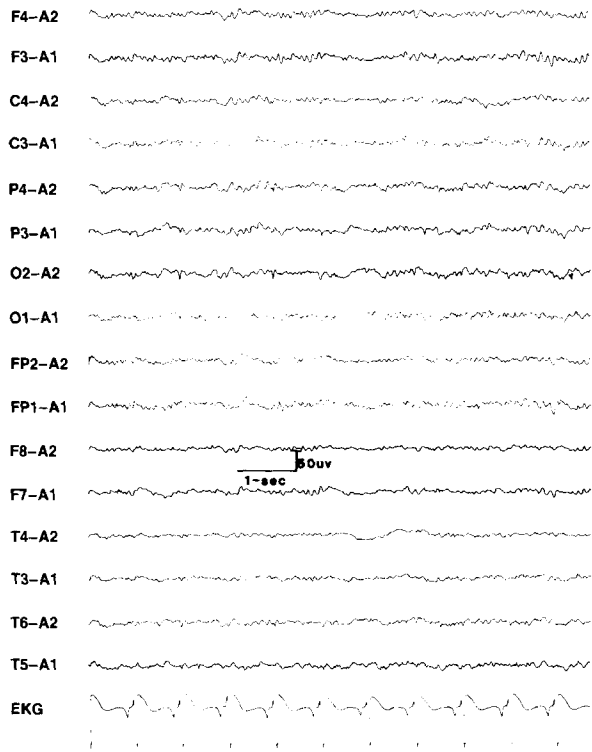


Fig 1. Sample of electroencephalogram on admission, exhibiting an invariant pattern of diffuse 10 to 12 Hz waves, with some anterior predominance, unreactive to all stimuli. All tests, electroencephalograms, and brainstem auditory evoked potentials were obtained in a normothermic state.

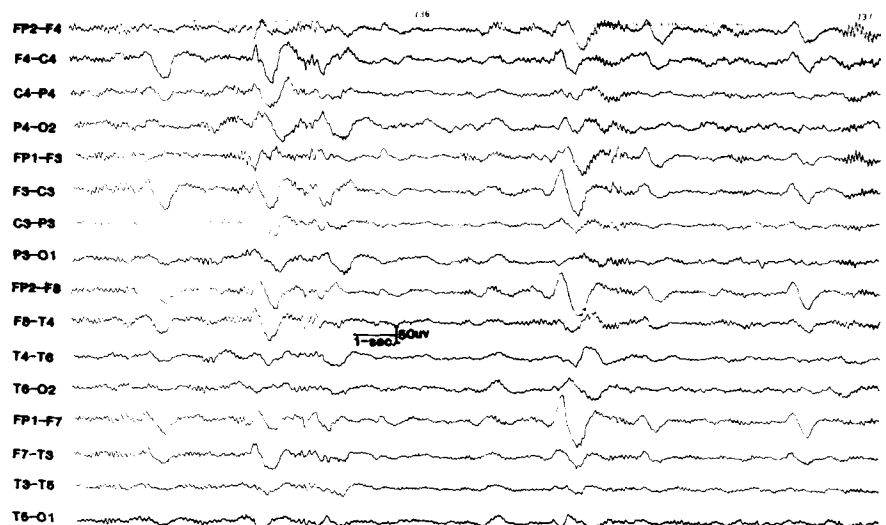
Discussion

The distinction between the EEG patterns of alpha coma and spindle coma is not always clear from perusal of the literature. Often subjects with spindle coma are subsumed under the rubric of alpha coma.

Following the description of alpha-coma EEG patterns in a patient with pontomesencephalic hemorrhage [11], several studies showed its occurrence following acute anoxic brain insults [4, 5, 7, 17, 18]. The alpha-coma pattern is characterized by its anterior predominance and unreactivity. It has generally been considered indicative of irreversible brain damage, with evolution into "suppression-burst" or "isoelectric" EEG patterns. Some papers discussing this EEG pattern after hypoxic encephalopathies cite eventual recovery in a few patients [4, 5].

The spindle-coma EEG pattern was first reported in subjects with hypothalamic or midbrain tumors sparing the thalamus [8]. Similar EEGs were described in patients with traumatic head injuries [1, 3, 13]. These posttraumatic comatose patients show EEG features resembling stages of normal slow-wave sleep, often with some reactivity. Subsequently, spindle coma was demonstrated in populations with a variety of causes [2, 6]. This EEG pattern alone is stated to carry no specific prognostic implication [1, 2, 3, 6, 13]. If there is also evidence of brainstem impairment, however, the outcome has been almost invariably bad, especially if the EEG pattern persists for a few days [2].

Fig 2. Electroencephalogram obtained on the third hospital day, illustrating the rapid evolution from the previous alpha-coma pattern into a spindle-coma one. Note the delta waves varying in voltage from 20 to 200 μ V, with intermittent spindles at 10 to 12 Hz. Aside from its poor reactivity, this electroencephalogram could be interpreted as exhibiting stage 3 sleep. Occasionally auditory stimuli elicited an abortive K-complex. The patient was still comatose, responding in an unpurposeful manner only to painful stimulation.



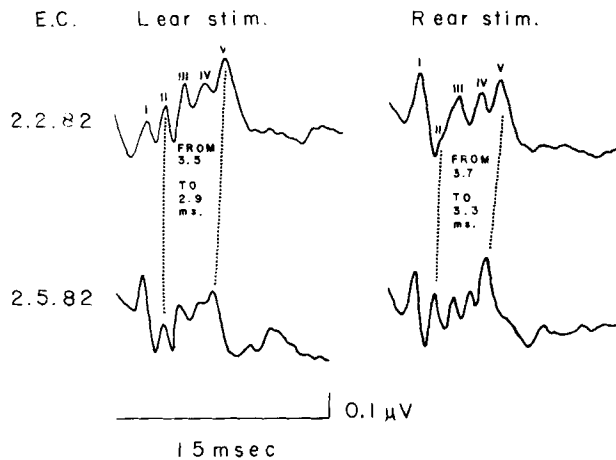


Fig 3. Brainstem auditory evoked potentials obtained on admission and on follow-up, when the patient had almost fully recovered. Top tracings show the latency prolongation present bilaterally between waves II and V. On the bottom, all latencies have returned to within our normal standards with left ear stimulation (less than 1 standard deviation above the mean). With right ear stimulation, there is still mild delay (more than 1.5 standard deviations above the mean). Two weeks later the potentials were normal on stimulation of either ear.

Six cases of alpha coma after sedative, anxiolytic, or antidepressive agent intoxication have been reported [5, 9, 17]. Only one case of spindle coma following drug intoxication (ethanol) has been described [6]. In none of these reports were brainstem evoked potentials recorded or mention made of oculovestibular function. There has been some debate about whether the suppression of oculovestibular function in tricyclic overdose is caused by a peripheral action of tricyclics on the eighth nerve or to a central action on brainstem neurons [10, 12, 16]. In our subject the BAEPs showed normal latencies for waves I and II, whereas wave II, IV, and V were delayed, indicating dysfunction at the pontine and mesencephalic levels. Although BAEPs test only the cochlear portion of the eighth nerve, strong clinical evidence suggests that lesions at these levels alter vestibular function.

Lesions producing alpha-coma or spindle-coma patterns are thought to involve structures at the same general level of the neuraxis, usually destroying or otherwise affecting ascending reticular pathways but leaving thalamocortical connections intact [8, 14, 18]. It is possible, however, that specificity in interference with different portions of the reticular complex takes place in different clinical conditions and possibly in the same clinical setting during evolving influences on distinct neuronal systems.

With studies of our patient's serial EEGs in close relationship to his clinical status and drug levels, we formulate the following conclusions. The early features of alpha coma later developed into spindle-coma pat-

terns. At one point both patterns were present in the same recording. Similar evolutions that might cause erroneous or ambiguous classification with one or the other of these EEG patterns are detected in the literature. The taxonomic features of alpha coma and of spindle coma are not as yet sufficiently clear. We think these patterns should be distinguishable from each other in spite of their similar features because they are likely to represent different clinical states and probably involve different pathophysiological mechanisms. It is possible that when one occurs in the context of a definite structural lesion, it may not cause ambiguities in subsequent recordings. If, on the other hand, the causes of these clinical and EEG patterns are essentially reversible and evolve in their effect on different neuronal systems, there likewise may be rapid evolution in the EEG. For example, an alpha-coma pattern may change into a spindle-coma one and into a full normalization. Thus, the correlations observed in this subject allow the hypothesis that the absence of oculovestibular reflexes, as well as the prolongation of late BAEP waves in a comatose patient with alpha and, later, spindle EEG patterns, might all be caused by evolving degrees of selective suppression on brainstem systems by varying levels of the drug.

As a practical message, this case report illustrates that absence of reflex eye movements in coma and with prolonged BAEPs and EEGs with alpha- or spindle-coma patterns are not always reliable prognostic clues. In contrast with some previous literature, clinical and electrophysiological evidences of brainstem dysfunction do not necessarily indicate irreversible hypoxic damage, even in a patient in whom a respiratory arrest might have raised serious doubts.

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