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Neurological evolution of severe baclofen intoxication: from brain death mimic to recovered brain function

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SUMMARY

Patients with brain death have by definition irreversible and complete loss of brainstem reflexes. Before a definite diagnosis of brain death can be confirmed, all potential confounders must be thoroughly excluded. Baclofen intoxication is a rare cause of brain death mimic characterised by transient deep coma and absence of brainstem reflexes and might be mistaken with brain death. We report the case of a female patient in her 70s who ingested baclofen with suicidal intent and was admitted with a deep coma and loss of all brainstem reflexes and a spontaneous burst-suppression pattern in the electroencephalography which resolved over 10 hours. After a state mimicking brain death for 6 hours, the patient experienced complete recovery. Severe baclofen intoxication can mimic brain death clinically and is associated with temporary pathological electroencephalographic findings. Awareness of this toxidrome is crucial, as appropriate management can lead to full recovery.

BACKGROUND

Intensive care physicians are routinely confronted with patients with absent brainstem reflexes due to profound cerebral injury. In such cases, standardised examination regarding potential brain death is initiated. In this context, it is of utmost importance to address all possible confounders before the diagnosis of brain death can be safely established.[1]

There is a limited body of scientific literature on severe baclofen intoxication, resulting in a burst-suppression pattern in the EEG and a clinical manifestation with profound coma and the absence of all brainstem reflexes resembling brain death[2–4] and few cases of intrathecal overdosing.[5 6] However, most of these studies were lacking a comprehensive time course of the clinical manifestation and their resolution, respectively.

We present a female patient with severe baclofen intoxication mimicking brain death clinically for the first 6 hours after admission with an initial burst-suppression pattern which resolved within 10 hours under continuous EEG (cEEG) monitoring. The patient ultimately made a full recovery.

CASE PRESENTATION

A female patient in her 70s was admitted to the emergency department (ED) after losing consciousness at home. Her husband reported that the patient complained of feeling unwell before collapsing and experiencing generalised tonic-clonic convulsions. On the arrival of the paramedics, the patient had a Glasgow Coma Score (GCS) of 4 (eyes closed, extension of all extremities on painful stimuli, no verbal response) without any further motor signs. She had a rhythmic bradycardic pulse (52 beats per minute) and hypertensive blood pressure value of 184/118 mm Hg and was bradypnoeic (respiratory rate 11 breaths per minute) with normal pulse oximetry (peripheral oxygen saturation 95%). The airways were secured with a nasopharyngeal tube, and the patient was brought to the emergency department.

The patient had a history of advanced idiopathic Parkinson's disease (Hoehn and Yahr Scale 4). Her medication included levodopa/benserazide, extended release pramipexole and amantadine. She was prescribed baclofen per os as needed. According to her husband, she suffered from progressive dyskinesia, dysarthria and gait instability with frequent falls despite several adjustments to her medication.

INVESTIGATIONS

Given the limited information on arrival to the emergency department, an initial diagnosis of a postictal comatose state after a suspected tonic-clonic seizure was made, and 2 g levetiracetam was administered intravenously. Due to sustained deep coma and bradypnoea, the patient was intubated and put on mechanical ventilation while being sedated with propofol before obtaining a multimodal contrast-enhanced head CT scan, which revealed no signs of cerebral ischaemia, haemorrhage, arterial occlusion or brain perfusion alterations. The patient was then transferred to our intensive care unit for further treatment.

Initial routine laboratory values, including complete blood cell count, electrolytes, serum pH, troponin, C reactive protein, hepatic, thyroid and renal functional tests, were within normal limits. Urine toxicological screening was negative for the tested agents. Sedation with propofol was stopped after the effect of muscle relaxant given for intubation wore off (as monitored by the repetitive 'train of four' stimulation). The clinical examination now revealed a GCS of 3 and absent brainstem reflexes with loss of gag and cough reflex, loss of pupillary reflex and apnoea without any rigour, neck stiffness or motor symptoms. Figure 1 outlines the evolution of neurological symptoms within the first 96 hours after admission. A cEEG was started 3 hours after admission and initially showed a spontaneous burst-suppression pattern, which was unaltered

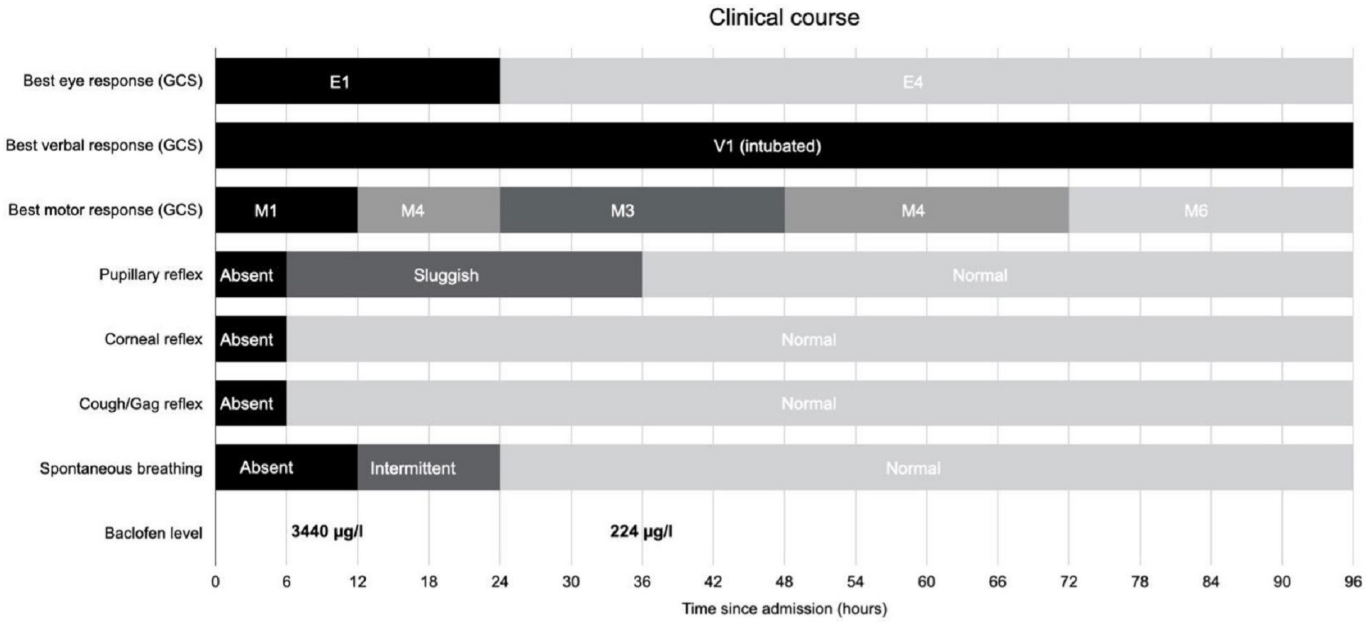

Figure 1 Timeline of clinical signs within the first 4 days since admission. The patient lost consciousness 4 hours before admission. The patient was extubated on day 11 and was discharged from the intensive care unit (ICU) on day 12. (Fig created by Sebastian Berger.)

after rapid administration of 0.5 mg flumazenil (figure 2A). Cerebrospinal fluid analysis demonstrated normal cell counts and protein levels with negative results for common neurotropic pathogens according to multiplex polymerase chain reaction tests.

DIFFERENTIAL DIAGNOSIS

Based on the first-responder information, which could not rule out an unwitnessed cardiopulmonary arrest with spontaneous return of circulation before paramedics' arrival, the suspicion of a severe hypoxic-ischaemic encephalopathy was raised. However, an intoxication was considered a possible differential diagnosis. Hence, a blood sample was sent to an external reference laboratory for rapid baclofen measurement, and all non-dopaminergic medication was paused. Over the next 10 hours (14 hours since loss of consciousness, respectively), cEEG showed a progressive change from a spontaneous burst-suppression pattern to generalised periodic discharges with triphasic morphology (figure 2B) and eventually a continuous theta background activity. Concurrently, brainstem reflexes gradually began to reappear after being absent for 6 hours (figure 1). Eventually, the patient's husband found several empty baclofen blisters, indicating an intoxication with 280 mg baclofen. The diagnosis of a severe baclofen intoxication was soon thereafter confirmed by the baclofen serum measurements of 3440 µg/L (therapeutic range 80–400 µg/L, toxic range above 1000 µg/L).

TREATMENT

The patient slowly recovered with supportive therapy over the next days (figure 1). A second measurement of serum baclofen on day 2 showed a baclofen level in the therapeutic range of 224 µg/mL. Levetiracetam was initially continued because of the risk of seizures associated with baclofen intoxication. On day 4, the patient developed a ventilator-associated pneumonia with *Staphylococcus aureus* which was treated with co-amoxiclav.

OUTCOME AND FOLLOW-UP

Clinical signs resembling brain death lasted for the first 6 hours after admission with gradual return. After 12 hours, spontaneous movement was observed. After 72 hours, the patient was able to follow commands while still being intubated due to lack of sufficient swallow and cough reflex and pronounced weakness, which led to prolonged weaning from the ventilator. Repeated EEG on day 5 revealed a pattern of normal cortical brain activity with a posterior dominant sinusoidal alpha-rhythm (figure 2C).

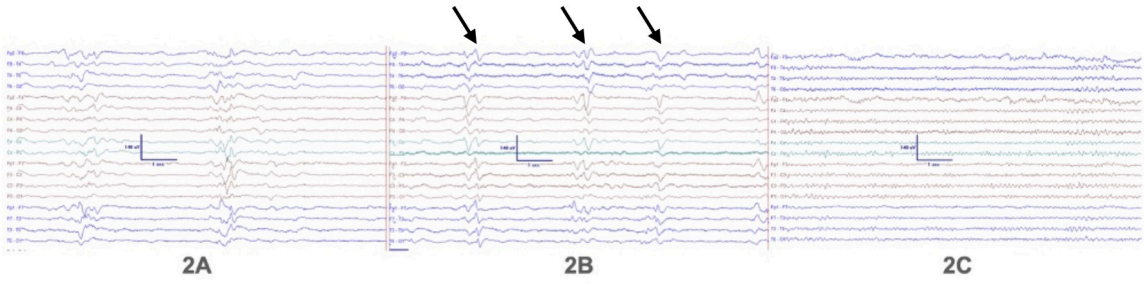

Figure 2 (A) Initial EEG at 3 hours after admission showing a burst-suppression pattern; (B) EEG at 8 hours after admission showing the burst-suppression pattern with generalised periodic discharges with triphasic morphology within the bursts (arrows); (C) Normalisation of the EEG with a posterior dominant alpha-rhythm at 5 days after admission. All EEGs are shown in a longitudinal bipolar right-over-left montage with 0.5 Hz low-pass filter and 70 Hz high-pass filter with a sensitivity of 7 mcV/mm. (Fig created by Urs Fisch.)

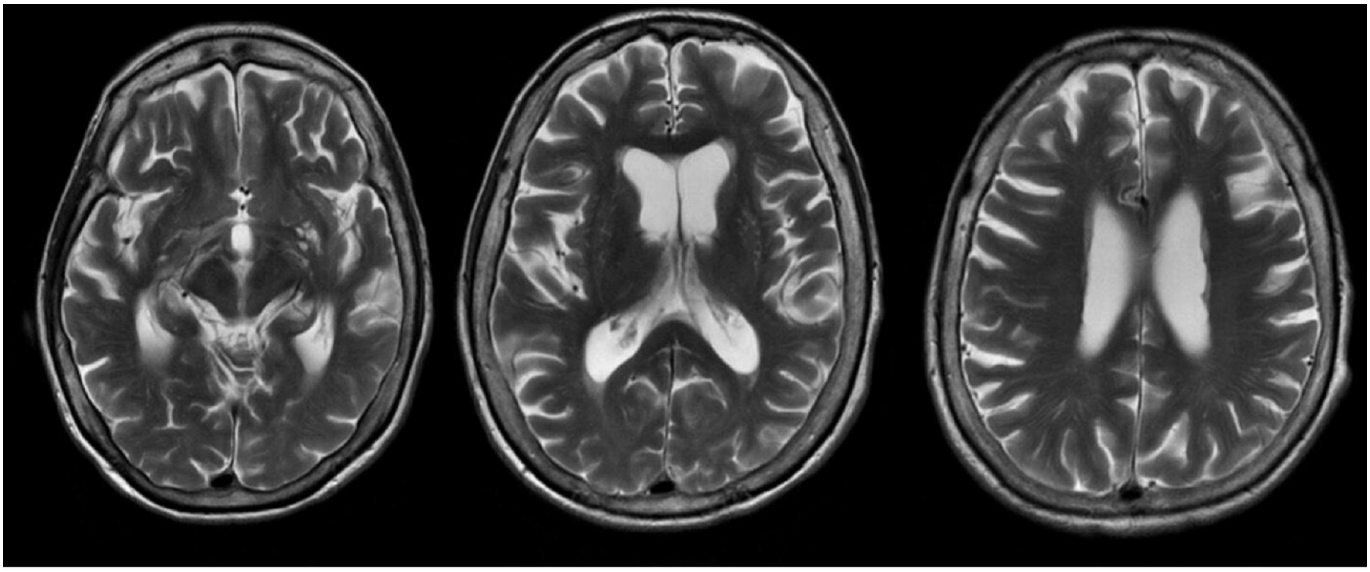

Figure 3 Three-Tesla cranial MRI at day 18 did not reveal evidence for structural brain damage. Exemplary axial slices of T2-weighted sequences are shown. Additional diffusion-weighted and contrast-enhanced sequences were also unremarkable. (Fig created by Sebastian Berger.)

The patient could be extubated on day 11. After extubation, the patient was awake and oriented but showed pronounced generalised muscle weakness without lateralising focal neurological deficits. The generalised weakness was interpreted as a result of the critical illness and her pre-existing condition. She was then transferred to the normal ward on day 12 and subsequently to a regional hospital on day 15. At discharge, the patient still had pronounced dysphagia. A brain MRI with diffusion-weighted and contrast-enhanced sequences on day 18 did not reveal any sign of brain damage, such as hypoxic-ischaemic injury, or other structural alterations (figure 3). Due to the dysphagia, a percutaneous gastrostomy on day 20 was performed but could be removed on day 36 after significant improvement. Next, the patient was transferred to a specialised neurological rehabilitation clinic where she further improved under adjusted medical therapy with amantadine and levodopa/benserazide to again attain ambulation. The patient was then transferred to a psychiatric hospital to treat a major depressive episode with the expectation to return home afterwards.

DISCUSSION

This case study highlights the detailed clinical course and detailed continuous EEG monitoring of a severe baclofen intoxication over time which initially mimicked brain death clinically for 6 hours and presented with an initial burst-suppression EEG pattern which resolved within 10 hours during continuous monitoring. Our case report describes the first hours of the clinical evolution of neurological symptoms including the initial clinical picture of brain death and the continuous improvement of consciousness and brain stem reflexes.

Baclofen is a centrally acting muscle relaxant to primarily treat spasticity. It acts as an agonist for gamma-aminobutyric acid (GABA) B receptors expressed in the central and peripheral nervous system.[7] Common side effects of baclofen include dizziness, sleepiness and autonomous dysfunction, including accommodative dysfunction, hypotonia, nausea, frequent urination and hyperhydrosis. In mild cases of baclofen intoxication, patients may be lethargic, confused or somnolent.[8] A daily dose of more than 200 mg may lead to more severe symptoms, such as hypotension or severe hypertension, bradycardia and bradypnoea.[9] Baclofen intoxication may also provoke epileptic seizures. Potential pathophysiological mechanisms may involve hyperpolarisation of inhibitory neurons through excess GABAB receptor activity resulting in a reduced seizure threshold.[10 11] The treatment of baclofen toxicity is supportive and mainly involves respiratory and circulatory support and treatment of seizures until resolution of symptoms.[8] Previously, case reports of baclofen intoxication with loss of brainstem reflexes and an EEG burst-suppression pattern have been reported.[4 10 12] Similar to our case, other reports also demonstrated normalisation of EEG findings by repeated EEG exams, however, without cEEG.[4 10] This case report adds to the existing literature a detailed description of the clinical course and cEEG over the first hours after hospitalisation.

The patient in our case report had a favourable outcome with a prolonged phase of recovery. An MRI did not find evidence for other causes, such as hypoxic-ischaemic encephalopathy, or structural alterations directly caused by baclofen. We performed a review of the available literature and could not find any previous reports about specific MRI changes associated with baclofen intoxication.

Previously, one case report showed rapid neurological recovery after 48 hours despite a possible ingestion of 1870 mg baclofen, but baclofen serum levels or cEEG documentation were missing.[12] Another case report described a much longer coma of 7 days despite lower initial baclofen levels.[4] A review of similar cases noted a marked variance of measured baclofen serum levels from 600 mcg/mL to 4300 mcg/mL independent of clinical severity of symptoms.[10] The start of recovery did not seem to be dependent on these toxic levels although it is important to note that they were measured at different times after ingestion and there usually was no follow-up measurement.[10] Toxicological screening will usually not routinely detect baclofen, and the measurement of specific baclofen levels is not readily available, which makes it more important to recognise the clinical presentation as a potential toxidrome. Our case report adds to the limited body of evidence that even after a relatively rapid decline in blood levels, clinical symptoms may persist for an extended period and may mimic brain death

for several hours. While specific MRI changes are lacking, cEEG might be a useful monitoring aid for the exclusion of brain death in this context and to monitor the severity of baclofen toxicity and recovery.

Learning points

- Severe baclofen intoxication can clinically mimic brain death for several hours, presenting with deep coma and absent brainstem reflexes with an initial concurrent spontaneous EEG burst-suppression pattern.
- Gradual normalisation of EEG and reappearance of brainstem reflexes within the first 24 hours are noted in severe cases of baclofen intoxication.
- Intensive medical support can lead to full recovery, highlighting the importance of heightened awareness of this toxidrome and accurate diagnosis.
- Baclofen levels are not readily available which makes it important to maintain a high clinical suspicion in similar cases. Additionally, a decrease of toxic baclofen levels to therapeutic levels may be rapid and precede full resolution of symptoms.

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