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CASE REPORT

Seizure after intrathecal baclofen bolus in a multiple sclerosis patient treated with oxcarbazepine

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Abstract Epileptic seizures associated with intrathecal baclofen (ITB) application have been observed in patients with traumatic brain injury. A higher incidence of seizures has also been reported in patients with multiple sclerosis (MS) receiving ITB. To our knowledge, no case of a first epileptic seizure has been reported in the context of ITB bolus testing in MS. We report a 41-year-old female patient with primary progressive MS receiving olanzapine and oxcarbazepine for psychotic disorder. Five years prior she began to develop severe spastic quadriparesis, rendering her a candidate for ITB treatment. After ITB test bolus application, however, she experienced a first epileptic seizure. Our observation indicates that ITB may trigger seizures in patients with MS. The observed seizure occurred during ITB bolus testing despite antiepileptic co-medication, which concurs with previous reports suggesting that rapid changes in the dose of ITB may carry a higher risk of seizure induction.

Keywords Epileptic seizure · Intrathecal baclofen · Multiple sclerosis

Introduction

Status epilepticus complicating intrathecal baclofen (ITB) overdose has been reported in a patient with traumatic brain injury [1]. Epileptic seizures associated with ITB application have also been reported in three patients with traumatic brain injury [2], two of whom experienced their first seizure following an ITB test bolus.

Patients with multiple sclerosis (MS) undergoing treatment with ITB also have a higher incidence of epileptic seizures. These are often associated with additional triggering factors such as fever, accidental baclofen overdose, reduction of serum sodium, or post-operative setting [3]. More than two-thirds of seizures in MS are generalized tonic-clonic seizures [4].

To our knowledge, there are no reports about the first manifestation of epileptic seizures after ITB bolus testing in MS. We report a patient with MS, treated with oxcarbazepine and olanzapine for psychotic disorder, who developed a first epileptic seizure in the course of an ITB screening test.

Case report

A 41-year-old female suffered from primary progressive MS; onset of the disease 13 years prior was characterized by dysphagia, paraparesis, and complex hallucinations. The diagnosis was ascertained by clinical course, visual evoked potentials [P100 with increased latency (130 ms) and normal amplitude following right ocular stimulation], cerebrospinal fluid examination (presence of oligoclonal bands, increased protein (55 mg/dl, normal value 30–50 mg/dl), IgG (7 mg/dl, normal value 1–5 mg/dl), IgG index (0.8, normal value 0.3–0.6), cell count (15 mm^{-3}, normal value 1–5 mm^{-3})], and brain and cervical magnetic resonance imaging (multifocal periventricular, subcortical, and temporal T2-weighted white matter lesions). Initial psychiatric evaluation because of the hallucinations early

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in the course of the disease established a "psychotic disorder with hallucinations due to multiple sclerosis" (ICD 293.82). The patient was initially treated with haloperidol for 9 years, followed by oxcarbazepine (900 mg/day) and olanzapine (5 mg/day), yielding satisfactory control of psychotic symptoms.

Six years after onset the patient presented with spastic paraparesis and inability to walk without help, followed 2 years later by severe spastic tetraparesis which eventually rendered her bed-ridden, able to sit in a wheelchair for only up to 1 h per day. At that time her expanded disability status scale (EDSS) score was 8.0. Personal and family histories were negative for epilepsy, and she had no history of febrile convulsions or brain trauma. No toxic, metabolic or electrolyte abnormalities were identified.

The patient's spasticity was resistant to oral antispastic medication, including diazepam (up to 15 mg/day), dantrolene (up to 75 mg/day), tizanidine (up to 24 mg/day), gabapentin (up to 2400 mg/day), and baclofen (up to 75 mg/day). Higher doses were not tolerated due to drowsiness. She was therefore admitted to our institution for an ITB screening test. At that time, brain and cervical magnetic resonance imaging revealed no increase in subcortical, periventricular and cerebellar T2-weighted white matter lesions. Oral baclofen (75 mg/day) was tapered off within 4 days with no signs or symptoms of withdrawal. Two hours following intrathecal injection of 40 μg baclofen, tendon reflexes were completely suppressed and muscle hypertonus decreased in the lower limbs (Ashworth scale from 4/4 to 3/4). One hour later, the patient experienced a first grand mal seizure, lasting 2 min. A postictal electroencephalogram revealed diffuse theta activity and occasional sharp transients prevalent in frontal regions. On the day following the ITB bolus test, oral baclofen was reintroduced (75 mg/day). An electroencephalogram 2 days later was normal, and no other seizures occurred during the ensuing 3 months. Notably, 4 months prior to ITB bolus testing, the patient's oral baclofen (75 mg/day) was interrupted uneventfully for 4 days because of an error made by a new caregiver. Although the patient had responded well to the ITB test bolus in terms of reduction of spasticity, she decided against pump implantation, despite reassurance from her treating neurologists that the risk of seizures could be well controlled by medication.

Discussion

Seizures observed in the context of ITB treatment have usually been associated with additional triggering factors: brain injury [2], fever, toxic, metabolic or electrolyte abnormalities, accidental baclofen overdose, sudden withdrawal of oral baclofen, reduction of serum sodium, and post-operative setting [3]. None of these causes applied to our patient. Moreover, her history was negative for febrile convulsions, epilepsy, or traumatic brain injury, and she had no active lesions in T2-weighted magnetic resonance imaging scans. Hence, we must consider four possible seizure-triggering factors: ITB, MS, olanzapine, and oxcarbazepine.

Baclofen is a $GABA_B$-agonist with pre- and postsynaptic action, which exerts anticonvulsant [5] as well as proconvulsant effects [1, 6]. A possible explanation for this seemingly contradictory effect may be the delicate balance between presynaptic suppression of recurrent inhibition relative to the activation of receptors mediating postsynaptic inhibition as demonstrated in an in vitro rat model [6]. A proepileptic effect in vivo would result from greater suppression of inhibition than excitation [1]. Kofler et al. [2] confirmed that ITB may trigger seizures in patients with prior traumatic brain injury (10.3%), and an analogous effect may be hypothesized in patients with MS. As previously reported [2], rapid changes in dosage seem to be particularly proconvulsant. Thus, the present case of a seizure following an ITB test bolus confirms previous reports of seizures even with small doses of ITB in the presence of additional risk factors.

Schuele et al. [3] observed a significantly higher incidence of epileptic seizures in patients with MS treated with ITB (7%) as compared to a matched control group of MS patients (1%); three of their ITB patients even experienced epileptic status. Notably, seizures were often associated with additional triggering factors, but none of their patients presented with a seizure during ITB bolus testing. On re-evaluation of concomitant medication, significant drug interaction with other medication precipitating seizures was deemed unlikely [7].

Our patient received olanzapine (5 mg/day) and oxcarbazepine (900 mg/die) for her psychotic disorder. Few seizures associated with olanzapine treatment have been reported to date despite its known proconvulsant potency. Camacho et al. [8] described a myoclonic status induced by olanzapine in a 54-year-old woman with probable Alzheimer's disease, who was also treated with low doses of citalopram and donezepil. Seizures commenced with addition of olanzapine and subsided upon its immediate termination. Spyridi et al. [9] published a case of epileptic status in a 48-year-old psychotic woman treated with olanzapine and mirtazapine. Four days before the event, mirtazapine (30 mg) was initiated, and 2 days later olanzapine was substituted for quetiapine, and mirtazapine increased to 60 mg. After withdrawal of olanzapine, the patient remained seizure-free. Olanzapine was administered for only a few days in both patients, who remained seizure-free upon its discontinuation. Our patient received olanzapine for 4 years, which was continued after the

grand mal episode, yet she remained seizure-free during a 1-year follow-up. We can therefore exclude a direct role of olanzapine in seizure induction, although we cannot exclude an effect of olanzapine on seizure threshold.

The antiepileptic drug oxcarbazepine was insufficient to prevent the seizure in our patient. Kofler et al. [2] reported no additional seizures with concomitant antiepileptic therapy in patients with brain injury, indicating that ITB treatment may be continued if deemed appropriate and necessary.

Our observation indicates that ITB may trigger seizures in patients with multiple sclerosis. The observed seizure occurred during ITB bolus testing, which concurs with previous reports suggesting that rapid ITB dose changes may carry a higher risk of seizure induction [2]. Hence, ITB testing should be considered using continuous infusion via an external pump system in order to reduce the risk of rapid dose changes inherent to bolus application. Nevertheless, epileptic seizures in the context of ITB are usually an isolated phenomenon, can eventually be well controlled with antiepileptic medication, and do usually not preclude ITB-long-term treatment using implanted delivery systems.

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