LETTER TO THE EDITOR

To the Editor

Spontaneous Intracranial Hypotension Induced Headaches and Onabotulinum Toxin A: A Case Report

Keywords: Chronic headaches, Cerebrospinal fluid leak

Onabotulinum toxin A (BTX) is an established prophylactic treatment for chronic migraine.[1] Few studies have demonstrated the efficacy of BTX in other headache disorders, including spontaneous intracranial hypotension (SIH). SIH is associated with a state of low cerebrospinal fluid (CSF) pressure due to a spontaneous leak occurring within the spinal axis. According to the International Classification of Headache Disorders (v. 3 beta), the diagnosis of headache attributed to low CSF pressure can be made with any headache phenotype that has developed in temporal relation to a low CSF pressure (<60 mm CSF) or leakage.

The speculated mechanism of SIH headache is secondary to hyperactivation of sensory afferent inputs from the meninges secondary to increased traction from low CSF volume/pressure.[2,3] Compensatory dilation of pain-sensitive intracranial venous structures may also play a role in the production of pain. We are reporting a case of a man with refractory SIH-induced headaches who has complete symptomatic relief of headaches for nearly the entire duration of time between BTX injections. From our literature search, there has been one case report describing a patient with SIH who has had pain improvement with BTX injections, but they continued to experience daily headache after 7 years of injections.[2]

A 55-year-old right-hand dominant Caucasian male with a history of well-controlled ulcerative colitis (no medication) was referred to our headache clinic for SIH. He was working as an engineer and was physically very active. He began experiencing daily headaches with associated orthostatic features since May of 2009 with no history of head or neck trauma. The severe headaches would originate bifrontally and radiate to the back without migrainous features. There were no other neurological and systemic symptoms. Neurological examination was unremarkable. He was diagnosed with SIH based on computed tomography (CT) radionuclide cisternogram and magnetic resonance imaging (MRI) of the brain and spine. Early bladder activity was detected on CT radionuclide cisternogram. Bilateral subdural fluid collections, dural enhancement, prominent venous sinuses, and sagging of the brainstem were demonstrated on the MRI head with gadolinium (Figure 1). A few small nerve root sleeve diverticula were identified on post-intrathecal gadolinium MR myelogram (Figure 2).

A nondirected lumbar epidural blood patch (EBP) was performed, and the patient had complete resolution initially. His headache symptoms recurred after 3 months, and a cisternogram was performed, which showed prominent nerve root sleeves at T10–11 and T11–12, but no actual leak was found. A directed EBP was performed (26.5 ml of autologous blood injected at the T10–11 interspace under fluoroscopy) with transient resolution of symptoms.

Subsequently, he received five more directed EBPs between 2011 and 2013 with temporary resolution of symptoms, with each EBP lasting a few weeks to a few months (between 5 and 39 ml of autologous blood were injected between the T8 and L1 interspaces under fluoroscopy). A follow-up MR myelogram demonstrated multiple nerve root sleeve diverticula at T11–12, left T9–10, and left T1–2. Again, no evidence of CSF extravasation was seen. A fibrin glue injection procedure was subsequently performed at bilateral the T9–10 and T11–12 levels—with only short-lasting relief. Trials of regular analgesics, caffeine, hydration, and prednisone only provided transient relief.

Treatment with BTX was considered after years of refractory headache. In October of 2014, the patient received his first set of injections with BTX (200 units) administered according to the standard migraine protocol (PREEMPT protocol, 155 units in 31 sites and 45 units injected in a follow-the-pain pattern). The first and second treatments provided minimal relief. However, the

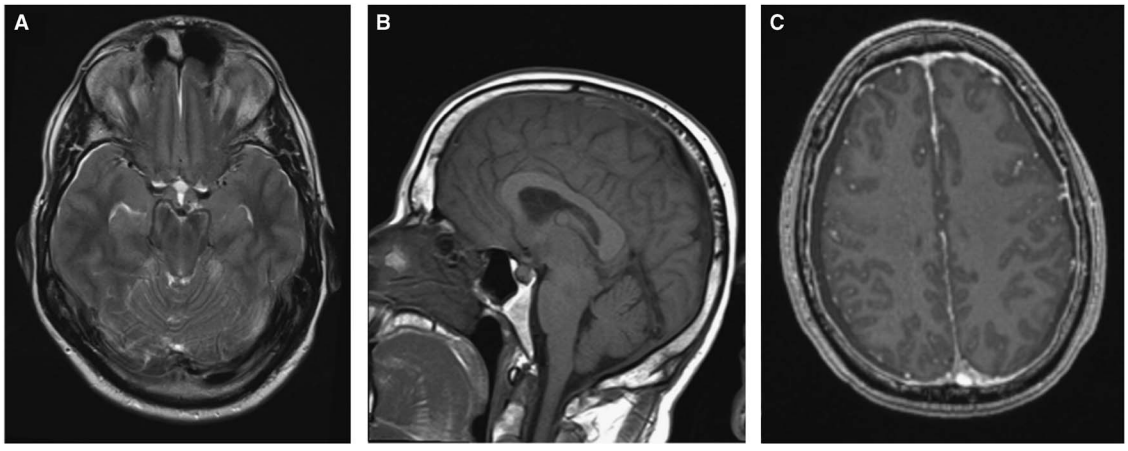

Figure 1: *(A) MRI head (axial T2 sequence) shows effacement of perimesencephalic cisterns and suprasellar cistern from sagging brain. (B) MRI head (sagittal T1 sequence) shows mild sagging of the brain with effacement of the suprasellar and prepontine cisterns. (C) MRI head (post-gadolinium axial T1 sequence) shows diffuse dural enhancement, engorged cortical veins, and symmetric bilateral subdural hygromas.*

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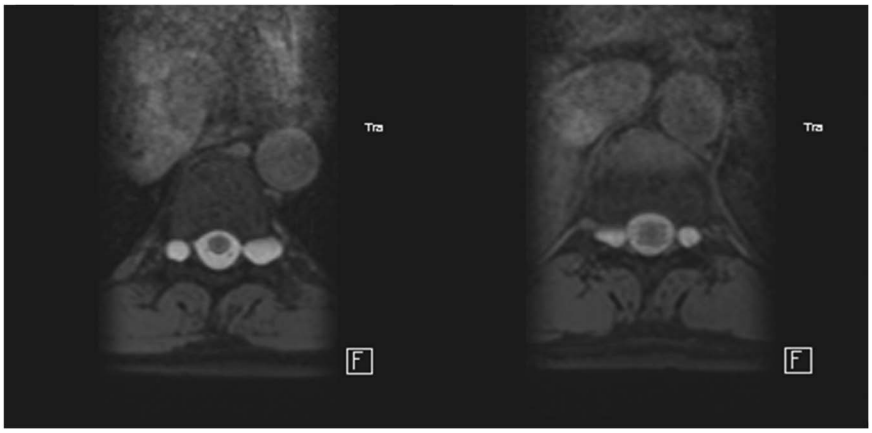

Figure 2: *MRI spine myelogram (axial multiplanar reconstructed [MPR]) shows presence of prominent bilateral multilevel root sleeve diverticula at the T9/10 and T11/12 levels.*

third treatment cycle, provided to him in April of 2015, took 2 weeks to take effect and completely eliminated his daily orthostatic headaches for 9 weeks. This pattern of benefit continued for subsequent injection cycles, and his headache would slowly return with orthostatic features approximately a week before his next due date for BTX (every 12 weeks). The patient has continued to do very well and was last assessed in May of 2017. He has returned to his baseline level of functioning and activity with significant improvement of his quality of life. He denies experiencing any side effects from the treatment.

The mechanism of action of BTX in headache disorders is poorly understood: BTX blocks the release of neuroinflammatory molecules from trigeminal sensory neurons, including substance P, glutamate, and calcitonin gene-related peptide (CGRP) in vitro and in animal studies.[4] Receptors like TRPV1 have been shown to mediate CGRP release, and BTX reduces cell surface expression of these channels.[5] When BTX is administered extracranially, it inhibits the mechanical sensitivity of the suture branches of intracranial meningeal nociceptors.[6] Ultimately, these effects reduce the activity of peripheral and central nociceptive neurons.[5,6]

Furthermore, BTX directly interferes with neuromuscular signaling by cleavage of the SNAP-25 protein. It inhibits vesicular release of the acetylcholine neurotransmitter at the neuromuscular junction and subsequently leads to paralysis of muscles and chemical denervation. As a result, it may reduce afferent input by inducing muscle relaxation.[7]

Increased sensory afferent input from the meninges is the most accepted theory to explain headaches induced by SIH.[2,3] In addition to the above mechanisms, the plausible theory of how BTX works in SIH is the ability of BTX to cross the trigeminal extracranial nerves (injection sites) to the trigeminal nerve endings in the dura. Following injection in the peripheral trigeminal region, BTX is taken up by the extracranial trigeminal afferents and then transported (retrograde) to the trigeminal ganglion. It is then transcytosed to meningeal afferents at the trigeminal ganglion and transported (anterograde) to the dura. Ultimately, it may inhibit neuropeptide (CGRP and substance P) release in the dura.[3] These neuropeptides cause inflammation, including vasodilation, sensory transmission, and mast cell degranulation.[7]

If the site of dural leakage can be identified, CT myelography-assisted targeted EBP is a safe and effective treatment for persistent spinal CSK leaks.[8] However, if a source cannot be identified, this case demonstrates that BTX injections might be an option. Also, SIH-induced headaches may transform into a migraine phenotype, which makes BTX injections an even stronger consideration for treatment. Further research is required to elucidate which patients would respond to the treatment.

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