Treatment with Botulinum Toxin for Refractory Fever Caused by Severe Spasticity: A Case Series

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ABSTRACT

Introduction: Brain and spinal cord injuries may cause very severe spasticity that occasionally may be associated with persistent fever. Case Series: We present 14 patients with spasticity and persistent fever, treated with botulinum toxin type A. Their spasticity improved and the fever resolved within a period no greater than 48 h. In all cases, infectious and other non-infectious causes were ruled out. Conclusions: When sustained tonic muscular activity is associated with a significant increase in body temperature and is refractory to the usual drugs used for hyperpyrexia, type A botulinum toxin may be an effective treatment option to control both spasticity and fever.

Keywords: Botulinum toxin; Fever; Spasticity

INTRODUCTION

The hypothalamus is the regulatory center for body temperature in humans [1], although the diencephalon and spinal cord also contribute [2]. If one of these structures is damaged, temperature elevations above 38.3 °C can occur [3]. Temperature elevations of brain origin are associated with increased plasmatic levels of norepinephrine and dopamine-B-hydroxylase [4]. In fever of spinal cord origin, the amplification of its positive feedback mechanism can induce and increase sympathetic responses [5]. Fever in patients with brain damage is associated with increased mortality [6, 7]; in cases with spasticity, this is a diagnosis of exclusion, and other causes of fever, such as infectious or non-infectious, must be ruled out [8]. Thus, prompt diagnosis of the cause and appropriate treatment are needed.

The production of body heat and fever results from the interaction of various factors, such as cellular metabolism, hormonal regulation, increased metabolism due to catecholamines such as epinephrine and norepinephrine [1], and muscular activity [2].
Muscular activity is a major factor in the production of heat under physiological conditions [1, 2].

On the other hand, spasticity is commonly described as a motor dysfunction in which there is increased muscular tone with an augmented stretch reflex [9]. Spasticity can be severe in patients with brain injury (BI) or spinal cord injury (SCI) [10]. There are various pharmacological treatments for spasticity [2], but botulinum neurotoxin type A (BoNTA) is among the most efficient and safe treatments for this condition [11].

Sustained states of muscle contraction have been reported to cause fever [2, 12–14]. To our knowledge, fever has not been described as a symptom associated with spasticity. Here, we present 14 patients with BI or SCI with severe spasticity who also had refractory fever without an infectious etiology.

METHODS

We report 14 cases treated between July 10, 2010, and December 16, 2016, who had BI or SCI with severe spasticity and refractory fever. Infectious and non-infectious causes of fever were ruled out with cultures and with laboratory and imaging studies.

This project was presented to the ethics and research committee of our hospital and was approved.

RESULTS

The patients included six women (42.86%) and eight men (57.14%) aged 21 to 81 years (mean 45.71 years). The cause of the persistent and refractory muscular contraction was closed head injury in four patients (28.58%), hypoxic ischemic encephalopathy in three (21.43%), cervical SCI in three (21.43%), hypertensive intracerebral hemorrhage in one (7.14%), subarachnoid hemorrhage in one (7.14%), intracerebral hemorrhage secondary to complications of carotid artery stent placement in one (7.14%), and stroke due to thrombotic thrombocytopenic purpura in one (7.14%).

Spasticity was measured using the modified Ashworth spasticity scale [15], and we found severe spasticity in four limbs of eight patients (57.14%) and hemibody spasticity in three patients (21.43%) and in the upper limbs of two subjects (21.43%). All patients were treated for their spasticity with BoNTA; 11 patients (78.57%) received onabotulinumtoxinA, and three (21.43%) received abobotulinumtoxinA.

All patients exhibited improvement of their spasticity. Before treatment with BoNTA, 11 patients (78.57%) had a score of 5, and three (21.43%) patients had a score of 4. At a 2-month follow-up examination, four patients (28.58%) improved to a score of 4, six patients (42.86%) to a score of 3, and four patients (28.58%) to a score of 2 (Table 1).

To our surprise, fever resolved in all patients (100%) in a period no greater than 48 h; at the 2-month follow-up, no recurrence was observed.

DISCUSSION

The patients described in this report had some form of BI or SCI, and as a consequence of this damage, they developed spasticity with concurrent temperature elevation. In all cases, infectious, inflammatory etiology was ruled out.

The treatment of fever in general should be specific for the etiology whenever possible and not just targeted toward the symptom [1]. Similar to reports by other authors, all patients received treatment with antipyretics, muscle relaxants and physical methods without an adequate control [16].

In all cases, there was improvement of spasticity after application of BoNTA, which facilitated neurorehabilitation. Fever resolved in no more than 48 h without any recurrence. Application of BoNTA is an accepted treatment for spasticity [2, 15, 16], and to our knowledge, BoNTA has not been reported for the treatment of fever in patients with spasticity.

There are other pathological entities, such as exertional heat stroke (EHS) [13] and malignant hyperthermia (MH), in which a disorder of calcium homeostasis within muscle cells causes muscle contraction [12]. MH was first described
as a rare complication of general anesthesia [17] but has also been reported in a head injury patient as well as in one with SCI [18, 19]. Even though in most cases with spasticity there is no fever associated with sustained muscle contraction, there is a persistent increase in the free myoplasmic calcium concentration, producing a biochemical reaction that accelerates mitochondrial activity with an increase in oxygen consumption. MH is

| No. | Gender | Age (years) | Diagnosis                                                      | Spasticity anatomical and application area | Spasticity initial score | Spasticity score 2-month follow-up | Botulinum toxin type and units |
|-----|--------|-------------|----------------------------------------------------------------|-------------------------------------------|--------------------------|------------------------------------|--------------------------------|
| 1   | M      | 32          | TBI                                                            | 4 limbs                                   | 5                        | 3                                  | ABTA 1500 IU                     |
| 2   | F      | 56          | Hypertensive hemorrhage                                        | 4 limbs                                   | 5                        | 3                                  | OBTA 600 IU                      |
| 3   | F      | 33          | HIE                                                            | 4 limbs                                   | 5                        | 4                                  | ABTA 1500 IU                     |
| 4   | M      | 25          | TBI                                                            | 4 limbs                                   | 5                        | 3                                  | OBTA 600 IU                      |
| 5   | F      | 21          | TBI                                                            | 4 limbs                                   | 5                        | 3                                  | ABTA 1500 IU                     |
| 6   | F      | 51          | Left frontal subarachnoid hematoma due to cavernous angioma rupture | Left hemibody                             | 4                        | 2                                  | OBTA 400 IU                      |
| 7   | F      | 80          | Ischemic stroke secondary to TTP                                | Left hemibody                             | 5                        | 3                                  | OBTA 400 IU                      |
| 8   | M      | 34          | HIE                                                            | 4 limbs                                   | 5                        | 4                                  | OBTA 600 IU                      |
| 9   | M      | 35          | TBI                                                            | Left hemibody                             | 5                        | 4                                  | OBTA 600 IU                      |
| 10  | M      | 54          | SCI                                                            | Upper limbs                               | 4                        | 1                                  | OBTA 400 IU                      |
| 11  | F      | 54          | HIE                                                            | 4 limbs                                   | 5                        | 4                                  | OBTA 600 IU                      |
| 12  | M      | 76          | SCI                                                            | Upper limbs                               | 5                        | 2                                  | OBTA 600 IU                      |
| 13  | M      | 36          | SCI                                                            | Upper limbs                               | 4                        | 2                                  | OBTA 600 IU                      |
| 14  | M      | 53          | Brain hemorrhage secondary to carotid procedure                | 4 limbs                                   | 5                        | 3                                  | OBTA 600 IU                      |

F female, M male, TBI traumatic brain injury, HIE hypoxic-ischemic encephalopathy, TTP thrombotic thrombocytopenic purpura, SCI spinal cord injury, ABTA abobotulinumtoxinA, OBTA onabotulinumtoxinA
associated with elevation of the production of carbon dioxide that depletes aerobic metabolism and increases anaerobic metabolism, leading to an imbalance of intracellular and extracellular ionic interchange that results in damage to the myocytes [12, 20]. The interruption of the active transport across the cell membrane consumes energy due to the high exchange of adenosine triphosphate (ATP); this exchange may be responsible for the temperature elevation in EHS [13] and MH [21]. There are also situations where other states of sustained muscular activity, such as dopaminergic withdrawal malignant syndrome, which is associated with rigidity, can cause fever regardless of whether they cause muscle damage [14]. To our knowledge, there are no reports of fever associated with spasticity.

Sustained muscle contraction has been considered as a cause of hyperpyrexia [1]. This complication first appears in the intensive care setting but may persist for months [22].

MH is treated with dantrolene, which inhibits the release of calcium from the sarcoplasmic reticulum with muscle relaxant action. Importantly, dantrolene does not have any action on the neuromuscular junction [23], but BoNTA does [24]. BoNTA acts as a metalloproteinase with a peripheral cholinergic effect on nerve endings; this effect causes reversible inhibition of presynaptic acetylcholine (Ach) [24] release without motor neuron loss [25]. After BoNTA is applied directly into the muscle, it passes through the endosomal membrane and causes a reversible but persistent inhibition of neurotransmitter release due to intracellular endopeptidase activity against the proteins necessary for Ach release [25]. How spasticity potentially causes fever is unclear. We hypothesize that, if the muscle contraction is the cause of fever, BoNTA could reduce the energy imbalance of ATP in myocytes caused by severe spasticity and directly decrease body temperature. However, we cannot rule out other sites of action for BoNTA.

BoNTA may be a good treatment alternative for refractory fever in patients with spasticity.

More studies should be done in patients with similar characteristics and should emphasize the causes of fever, as well as how BoNTA decreases body temperature in these subjects. This finding may also be extended to cases of dystonia and rigidity.

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**Compliance with Ethics Guidelines.** The project was presented to the ethics and research committee of our hospital and was approved.

**Data Availability.** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. We confirm that Table 1 is original and was produced by the authors for this particular publication.

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