TREATMENT WITH BOTULINUM TOXIN FOR REFRACTORY FEVER CAUSED BY SEVERE SPASTICITY

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INTRODUCTION

Spasticity is described as a motor dysfunction in which there is increased muscular tone with an augmented stretch reflex.
Spasticity can be severe in patients with brain injury (BI) or spinal cord injury (SCI).
Muscular activity is a major factor in the production of heat under physiological conditions.
There are various pharmacological treatments for spasticity, but botulinum neurotoxin type A (BoNTA) is among the most efficient and safe treatments for this condition.
Sustained muscle contraction states have been reported to cause fever.
To our knowledge, spasticity has not been described as a direct cause of fever.

CASE REPORTS

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 studied with cultures, laboratory and imaging studies (Table 1). We also ruled out fever of central origin.
The patients included 6 women (42.86%) and 8 men (57.14%) aged from 21 to 81 years (mean 45.71 years).
All patients received were treated with BoNTA.
All patients exhibited improvement of their spasticity and, fever resolved in a period no greater than 48 hours; at the two month follow-up no recurrence was reported.

DISCUSSION

Fever treatment should be etiologically specific whenever possible and not just targeted toward the symptom. Nevertheless, all patients received treatment with antipyretics, muscle relaxants and physical methods without an adequate control. Infectious, inflammatory or central etiology was ruled out.
In all cases, there was improvement of spasticity after application of BoNTA, which facilitated neurorehabilitation.
Fever resolved in no more than 48 hours without any recurrence. Application of BoNTA is an accepted treatment for spasticity and, to our knowledge, BoNTA has not been reported for the treatment of fever associated with spasticity.
BoNTA has a peripheral cholinergic effect on nerve endings
This effect causes reversible inhibition of presynaptic acetylcholine (Ach) release without motor neuron loss.
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.
This constitutes its action as a muscle relaxant.

How spasticity potentially causes fever is unclear.
We hypothesize that 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 patients with fever associated 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.

TABLE. Patients` General Information

No.	Gender	Age	Diagnosis	Spasticity Anatomical Area	Spasticity Initial Score	Spasticity Score 2 Months Follow-Up	BoNTA 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	Subarachnoid hematoma	Left hemibody	4	2	OBTA 400 IU
7	F	80	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 400 IU
13	M	36	SCI	Upper limbs	4	2	OBTA 300 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
IU: International Units

REFERENCES

1. Sneed RC. Hyperpirexia associated with sustained muscle contractions: an alternative diagnosis to central fever. Arch Phys Med Rehabil. 1995; 76: 101-103.

2. Mandac RB, Hurvitz EA, Nelson VS. Hyperthermia associated with baclofen withdrawal and increased spasticity. Arch Phys Med Rehabil. 1993; 74: 96-97.

3. Heiman-Patterson TD. Neuroleptic malignant syndrome and malignant hyperthermia. Med Clin North Am 1993.77: 477-492.

4. Dressler D, Bhidayasiri R, Bohlega S, Chahidi A, Chung TM, Ebke M, et al Botulinum toxin therapy for treatment for spasticity in multiple sclerosis: review and recommendations of the IAB-Interdisciplinary Working Group for Movement Disorders task force. J Neurol. 2016; 264: 112-120.

5. Dressler D. Clinical applications of botulinum toxin. Curr Opin Microbiol. 2012; 15:325–336.

6. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther. 1987; 67: 206-207.

7. Kumar R, Ghaliwal HP, Kukreja RV, Singh BR. The Botulinum Toxin as a Therapeutic Agent: Molecular Structure and Mechanism of Action in Motor and Sensory Systems. Semin Neurol. 2016; 36: 10-19.