

# Contralateral Upper Limb Weakness Following Botulinum Toxin A Injection for Poststroke Spasticity



## Paresia do Membro Superior Contralateral Após Infiltração de Toxina Botulínica A para Espasticidade Pós-AVC

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### ABSTRACT

Botulinum toxin type A has been approved for spasticity management in poststroke patients. The adverse effects are generally of two types: those related to local injection; and those related to the systemic effects from spread of the toxin. Contralateral weakness after botulinum toxin A treatment is a rarely reported adverse effect. We report the case of a 33-year-old female who had been receiving regular injections of incobotulinum toxin A due to spasticity of the right limbs after a hemorrhagic stroke. A switch was made to abobotulinum toxin A with an overall conversion ratio of 1:3.83. The patient presented contralateral upper limb paresis, especially of the deltoid muscle, in the second week post-injection. The electroneuromyography showed neuromuscular block due to botulinum toxin A. She recovered completely after eight months. A switch between different formulations of botulinum toxin type A should prompt caution when carrying out unit conversions. Distant side effects may appear, including paresis in the contralateral limbs.

**Keywords:** Botulinum Toxins, Type A/adverse effects; Muscle Weakness/etiology; Upper Extremity

### RESUMO

A toxina botulínica A foi aprovada para o tratamento da espasticidade em doentes pós-AVC. Os efeitos adversos são geralmente de dois tipos: efeitos adversos relacionados com a administração local de toxina botulínica A; e efeitos adversos sistémicos relacionados com a difusão à distância da toxina. A paresia muscular dos membros contralaterais após tratamento com toxina botulínica A é um efeito adverso raro. Descrevemos o caso de uma mulher de 33 anos de idade que recebia infiltrações regulares de toxina incobotulínica A por espasticidade dos membros direitos pós-AVC hemorrágico. Foi feita uma troca para toxina abobotulínica A com um factor de conversão global de 1:3,83. A doente apresentou parésia do membro superior contralateral, especialmente do músculo deltóide. A electroneuromiografia foi compatível com bloqueio neuromuscular devido a toxina botulínica A. Recuperou totalmente após oito meses. A troca entre diferentes formulações de toxina botulínica A deve exigir precaução na conversão das unidades. Efeitos adversos à distância podem surgir, incluindo parésia dos membros contralaterais.

**Palavras-chave:** Fraqueza Muscular/etiologia; Membros Superiores; Toxinas Botulínicas Tipo A/efeitos adversos

### INTRODUCTION

Botulinum toxin A (BoNT-A) has been approved for spasticity management. The most serious adverse effect is related to systemic spread, manifested by generalized weakness.<sup>1,2</sup> We report a case of contralateral upper limb weakness in a patient who received BoNT-A injection for poststroke spasticity.

### CASE REPORT

A 33-year-old white female with a history of hemorrhagic stroke started a rehabilitation program that included BoNT-A in the right upper and lower limbs for spasticity management. Injections were performed at three-month intervals for five years, always with Incobotulinum toxin A (Inco/A) 400 U, except during the Tower study,<sup>3</sup> when she received one 600 U and one 800 U injection. Due to unavailability of Inco/A in our hospital, a switch to Abobotulinum toxin A had to be made. The new formulation injection was performed under ultrasonographic guidance. Approximately 10 days after injection, the caregivers noticed diminished muscle strength in the proximal left upper limb. The patient was assessed by her regular BoNT-A injector that found a paresis of the left shoulder flexors and abductors graded as 2 in the Medical Research Council scale; the left hemi-body sensitivity, reflexes and tonus were normal, as well as muscle strength in other muscle groups. The magnetic resonance imaging did not show any findings suggestive of acute lesions. The electroencephalography showed normal baseline electrogenesis. A cervical spine MRI did not show any significant findings. The electroneuromyography (EMG) findings at day 21 and week 16 after injection are described in Table 1 and Table 2, respectively. Eighteen months after the patient's last BoNT-A injection, the caregivers reported full recovery of her left shoulder flexors and abductors strength. It was decided to resume treatment with a switch back to 450 U of Inco/A. The patient has had good response to treatment, with adequate right hemi-body tonus control, and no further adverse effects.

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## DISCUSSION

### Previously described case reports

Muscle weakness contralateral to the injected side was found to be extremely rare in a systematic review.<sup>1</sup> There are only three other case reports of patients who received BoNT for post-stroke spasticity and presented with contralateral upper extremity weakness.<sup>4,5</sup> In the first described case, a 53-year-old woman received 800 U and 500 U of Ona/A, and developed contralateral weakness and fatigue two weeks after treatment. No electrophysiological testing was done in this case. In the following case, a 43-year-old woman received 700 U of Ona/A, and three weeks later presented with contralateral upper extremity weakness. Upon electrophysiological testing, she revealed on slow (3-Hz) repetitive nerve stimulation of the left axillary nerve a 23% decrement in amplitude. EMG revealed abnormal spontaneous activity and polyphasic motor unit potential (MUP) with reduced recruitment in the left deltoid, biceps brachii, and infraspinatus (the only muscles tested for comfort). On the 2-month follow up visit, she had improved, but was still recovering. In the third case, a 21-year-old woman, who had suffered a stroke when she was two years old, received 700 U of Ona/A, and developed contralateral upper limb weakness six weeks posttreatment. A 2-Hz repetitive stimulation of the spinal accessory nerve revealed a 16% decrease in amplitude. EMG showed mild abnormal spontaneous activity and small polyphasic motor unit potentials with reduced recruitment in the deltoids, biceps, infraspinatus and supraspinatus (the only muscles tested for patient comfort). In the 4-month follow up visit she had improved, but was still recovering. In the 5-month follow up visit she was reinjected and started to receive subsequent injections of 500 U of Ona/A, without injection of any muscle proximal to the elbow, and did not present further contralateral upper limb weakness.

### Similarities to our case report

In accordance with these three case reports, our patient was also female and presented with contralateral upper limb weakness (there was no weakness noted in the lower limb) in the second week following treatment. Electrophysiological testing was suggestive of dysfunction at the level of the motor endplate, showing, in slow (3-Hz) repetitive stimulation, a 45% – 48% decrease in amplitude. The EMG findings of fibrillations and/or positive waves in the left deltoideus and infraspinatus muscles, with decreased recruitment, and small amplitude polyphasic MUPs have been described in botulism and are attributed to severe blockade of the neuromuscular junction.<sup>6</sup>

### Adverse events

Systemic adverse effects reported after BoNT limb muscles injection include muscle weakness *distant* to the injection site, dysphagia, and dry mouth, among others.<sup>1</sup> Absorption of free BoNT may occur through the capillary system. It is also possible that a combination of vascular and neural spread occurs. Limited evidence exists of retrograde axonal spread in humans. Most evidence of this mechanism is derived from animal studies,<sup>1</sup> and it is still unclear if the transported BoNT remains enzymatically active.<sup>7,8</sup> Taking all into account, we believe that the most probable cause for contralateral weakness in our patient was 'hematogenous spread'. Although BoNT can travel through muscle fascia, as hypothesized by Thomas and Simpson,<sup>5</sup> we do not believe this to be the most plausible explanation, because: (1) the most proximal muscle injected in our patient was the biceps brachii (injected at half distance between the shoulder and the elbow); (2) there was no weakness in the muscles present in the hypothetic subcutaneous or trans-fascial trajectory of BoNT until it reached contralateral deltoids (namely, there was no weakness of the coracobrachialis or any of the pectoralis muscles); (3) the ipsilateral deltoid muscle showed a smaller decrease in amplitude than the contralateral deltoid to low-frequency stimulation which would probably not have happened if we consider local diffusion gradients (higher proximal to the injection site); (4) if it was not osmotically but mechanically induced movement, it should not have affected the contralateral upper limb, because the trajectory that would have to be made was against gravity. Our hypothesis is that saturation of BoNT receptors occurred in one or more of the injection sites, and that unbounded BoNT was washed away from that/those regions by the circulatory system, specially the capillary system. Why did it affect predominantly the contralateral deltoid muscle (and not other muscles, such as the orbicularis oculi or swallowing muscles) we do not know and it is a question that could be addressed in further studies. Perhaps it can have something to do with the deltoid muscle having a high blood flow,<sup>9</sup> which could increase the probability of circulating unbound BoNT binding to the motor endplates at that anatomical region (increased number of unbounded BoNT molecules present at that site per unit of time) and not binding sufficiently in other muscles in order to produce clinical symptoms.

### Dose equivalence

The conversion ratio between Ona/A and Abo/A is still debated. Even if the most commonly quoted conversion ratios are 1:3 or 1:4,<sup>10</sup> they range from 1:1<sup>11</sup>; to as high as 1:11.<sup>12</sup> However, in studies where the conversion ratio is higher than 1:3, Abo/A showed higher efficacy and longer duration of action compared to Ona/A, but with more adverse events.<sup>13</sup> In our case the mean conversion factor of Inco:Abo was 1:3.83, which could have led to systemic BoNT diffusion.

## CONCLUSION

Weakness of contralateral muscles to the injected side with BoNT is extremely rare and reported in very few studies. Physicians should be aware that a number of factors influence efficacy, diffusion and spread. In our patient, a global conversion ratio of 1:3.83 was used, which seemed to be the determinant factor that caused system spread of BoNT.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

## DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

## PATIENT CONSENT

Obtained.

## CONFLICTS OF INTEREST

All authors report no conflict of interest.

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Table 1 – Electroneuromyography at day 21 (third week post-toxin injection)

Sensitivity conduction study	Left median nerve (fingers 1 and 3)		Normal
	Left ulnar nerve		Normal
	Left radial nerve (superficial branch)		Normal
	Left lateral antebrachial cutaneous nerve		Normal
	Left medial antebrachial cutaneous nerve		Normal
Motor conduction study	Bilateral axillary nerve	Marked reduction of the left axillary nerve motor potential by comparison to the right axillary nerve. Normal latencies on left and right sides, without any significant asymmetries.	
	Bilateral musculocutaneous nerve	Normal, without any significant asymmetries.	
	Left median nerve	Normal, including the F waves.	
	Left ulnar nerve	Normal, including the F waves.	
	Left radial nerve	Normal, including the F waves.	
Repetitive stimulation testing	Low frequency stimulation (3 Hz) (at rest)	Left deltoideus	45% – 48% decrement in amplitude; 57% – 64% decrement in area
		Left anconeus	7% – 8% decrement in amplitude; 9% – 10% decrement in area
		Right deltoideus	6% – 13% decrement in amplitude; 14% – 19% decrement in area
		Right biceps brachii	No decrement
		Right trapezius	No decrement
		Right abductor digiti minimi	No decrement
		Abductor pollicis brevis	No decrement
	High frequency stimulation (20 Hz and 50 Hz)	Left deltoid	No increment
		Left anconeus	No increment
Electromyography	Fibrillations and/or positive waves in the left deltoideus and infra-spinatus muscles, with decreased activation, polyphasic PUM with small amplitude. Very sparse fibrillations in the left brachioradialis and biceps brachii, with normal recruitment pattern. Left pronator teres, flexor carpi radialis, triceps brachii, extensor indicis, first dorsal interosseous and cervical erector spinae muscles without pathological findings.		

Table 2 – Electroneuromyography at week 16th post-toxin injection

<b>Repetitive stimulation testing</b>	Low frequency stimulation (3 Hz) (at rest)	<b>Left deltoideus</b>	20% – 27% decrement in amplitude; 26% – 29% decrement in area
		<b>Left anconeus</b>	No decrement
		<b>Right deltoideus</b>	No decrement