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Case Report
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Intra Detrusor Botulinum Toxin and Lower Limbs Motor Deficit: About 2 Clinical Cases

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Abstract

Objective: To demonstrate how a single intra detrusor botulinum toxin injection could be responsible for lower limbs proximal motor deficit.

Results: Two women-37 and 38 years old-presenting with secondary progressive multiple sclerosis, having received intra detrusor botulinum toxin injections (400 BOTOX® U and 750 DYSPORT® U) due to major neurogenic detrusor over activity with high-pressure and risks of uro-nephrologic complications despite an efficient-dose anticholinergic bi-therapy (DITROPAN®/CERIS®). Few days in post-injection they present heavy tiredness, instability of the pelvis, and a major reduction of the walking distance. Those symptoms last for several months. During the emergency neurology consultation set up in the event of a new relapse, an aggravation of the paraparesis at the proximal level is observed. This deficit accounts for the realization of a corticosteroids bolus, the effectiveness of which is questioned by the patient. A cerebral and medullary MRI is performed in order to certify the appearance of new lesions. The MRI doesn't objectify any new lesions or any pathological contrast enhancement.

Discussion: Ramirez-Castaneda et al. describe three means of dissemination of the BoNT: migration by systemic or neuronal transport, propagation/spread and diffusion.

Conclusion: The retrograde migration of the botulinum toxin via hypo-gastric nerves seems to prevail. It could be followed by axonal anterograde transport causing a deficit on the hip flexors via the L2 nerve root.

Keywords: Detrusor hyperactivity; Botulinum toxin; Adverse effects; Muscle fatigability; Motor deficit; Diffusion; Migration

Introduction

Multiple sclerosis is a chronic demyelinating and inflammatory disease of the central nervous system, characterised by a spatio-temporal dissemination of the lesions, source of a polymorphous clinical presentation. It's the first cause of non-traumatic handicap in France. Handicap is evaluated thanks to the Kurtzke EDSS scale (Expanded disability status scale) which allows to rate from 0 (no handicap) to 10 (death) [1,2].

Bladder disorders are extremely frequent in MS (prevalence of 87% with an average occurrence around 6 years in the evolution of the disease). They can be inaugural in 0-10% of the cases. Over activity and obstruction symptoms can be associated in 1 patient out of 2, with little clinical and urodynamical correlation. The most often found cystomanometric board is a neurogenic detrusor over activity (NDO) (median of 65 %) [3].

The main objective of the treatment is to ensure continence and a complete vesical emptying in low pressure. It can be ensured in a first attempt with a parasympatholytical treatment. Botulinum toxin A (BoNTA) is proposed in a second attempt in case of failure or intolerance of the parasympatholytics at an efficient dose (in mono or bi-therapy) in patients with intermittent catheterization or having accepted to do them [4,5]. It's following Brigitte Schurch's work that this new indication of BoNT developed [6]. In France, only BOTOX® (Onabotulinumtoxin A) was granted marketing authorization with 200 IU maximum dosage after a placebo vs 300 IU comparative study [7]. Intra detrusor use of DYSPORT® (Abobotulinumtoxin A) is currently being evaluated.

The treatment of NDO by BnTA is considered to be efficient and often well tolerated. The main side effects as described in the literature are classified as local secondary effects (hematuria, urinary tract infections, injection site pain…) and as general (asthenia, generalized muscle fatigue, digestion troubles, flu-like syndrome, cephalia…) [8].

A local motor deficit being observed at the root of lower limbs in two of our BoNT intra detrusor injected female patients, made us consider its diffusion beyond the injection site.

Observations

Clinical case 1

A 37-year-old woman presenting with secondary progressive MS (SPMS) and an EDSS at 6, having received, between April 2010 and August 2012, intra detrusor injections of 300 BOTOX® U due to major NDO with high-pressure and risks of uro-nephrologic complications despite an efficient-dose anticholinergic bi-therapy (DITROPAN®/CERIS®). In August 2012, six weeks after the injection, urodynamics unmasked numerous uninhibited contractions of the detrusor. Following a multidisciplinary meeting, it was agreed that the posology should be raised to 400 BOTOX® IU/40 ml of physiologic serum, injected on 40 points. The raise in BoNT injection dose did not allow a pharmacologic disconnection of the detrusor, remaining

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hyper-active and hypo-compliant (non-inhibited detrusor contraction from a 100 ml filling at 50 cm H_20). A VESICARE® 10 mg treatment is associated for about 5 months (maximal cystometric capacity of 400 ml with no detrusor contraction). After this period, the patient adds one DITROPAN® a day.

Following the 400 U BOTOX® injections, the patient presents heavy tiredness, instability of the pelvis, increased distal muscle tone and major reduction of the walking distance. Those symptoms appeared 7 days in post-injection and lasted for several months. During the emergency neurology consultation set up in the event of a new relapse, an aggravation of the paraparesis at the proximal level is observed, with an iliopsoas rated at 0/5 on both sides. This deficit accounts for the realization of a corticosteroids bolus on 3 occasions, the effectiveness of which is questioned by the patient. A cerebral and medullary MRI is performed, in order to certify the appearance of new lesions, in June 2013 after the first 2 boluses. The MRI doesn't objectify any new lesions or any pathological contrast enhancement.

Clinical case 2

A 38-year-old woman presenting a SPMS with an EDSS at 6 with vesicle hyper-activity responsible for a major degradation of her quality of life because of episodes of incontinence. Urodynamic in pre-toxin again shows a hyper-active hypocompliant detrusor limiting the cystometric capacity to 76 ml. the emptying is done in high pressure up to 80 cmH_2O (despite a VESICARE® treatment). From October 2012 to July 2014, she was treated with intra-detrusor BoNT injections with a dosage of 750 DYSPORT® IU on 30 points (as part of a clinical research protocol). Those injections allowed a pharmacological disconnection of the detrusor as is demonstrated by the different control urodynamic performed (maximal cystometric capacity higher than 300 ml in low pressure). The efficiency duration was estimated at 15 months. 15 days after the injections, the patient complained about an increase of her asthenia, a reduction of her walking distance (dropping from 40 m to only a few steps) with steppage difficulties, instability of the pelvis, an increase in the extremities hypertonia and a proximal muscle weakness. Unfortunately, we do not have any analytical testing to authentificate the deficit. However, the similarity of the symptoms between the two patients, the role of the iliopsoas muscles in the stabilization of the pelvis in the coronal plane and the complaint about a proximal hypotonia suggest the presence of a motor deficit on this muscle.

Discussion

The presence of a muscle fatigue in the striated skeletal muscles remote to the site of BoNT injection has been reported for more than 20 years [9,10]. It is observed in more than 10% of the patients after a therapeutic use of BoNT (according to the Food and Drug Administration) [11]. Ramirez-Castaneda et al. describe three means of dissemination of the BoNT remote to the site of injection: migration by systemic or neuronal transport, spread secondary to a physically active movement and diffusion corresponding to a microscopic phasic movement of the BoNT [12].

Migration by systemic transport

Systemic manifestations in the migration of BoNT are many and most often subclinical: asthenia, global muscle fatigue. They are not always associated with the injected dose [13]. They are confirmed in the striated skeletal muscle by single-fiber electromyography (SFEMG) that reveals the presence of a reversible conduction delay in the distant muscles [14]. The electromyogram (EMG) highlights an increase in latency and a decrease of the contraction time [15]. The absence of clear physical signs could be explained by a migration rate not sufficient enough to inhibit the potential for action triggered by the release of AcH at the neuromuscular junction level. To our knowledge, only one study with neurophysiological record has been made after an injection of 300 BOTOX® IU in the detrusor of a spinal cord injury patient. It is a prospective pilot study including 21 patients, 7 of whom present with a general asthenia. The EMG on distant muscles (orbicularis oris muscle of tetraparetic patients, extensor muscles of the fingers of paraparetic patients) shows conduction abnormalities in 4 of the 21 included patients. Only one patient presenting with an asthenia shows an increase of the conduction time [16]. This study suggests, when compared to the results on the striated skeletal muscles, a lower rate of the systemic migration of the BoNT with a therapeutic dose, after injection in the detrusor vs striated skeletal muscle. This lower rate of systemic migration can be related to the bio muscular structure. The latter having an impact on the efficacy of BoNT [17], it could therefore play a role in the spread but also in the migration. Schnitzler et al. study also suggests no correlation between fatigue and systemic diffusion of the BoNT [16] after injection in the detrusor. This assumption is supported by a retrospective study by Ruet et al. carried out after a BoNT injection in the striated skeletal muscles and in the detrusor and identifying no significant difference on SFEMG parameters between the patients presenting asthenia (n=15) and control subjects (n=17) [17,18]. In the MS female patients, the presence of a general asthenia is even less attributable to the systemic migration of BoNT as it is a very frequent functional sign in MS (53%-92%) probably of multi-factorial origin (conduction or nerve cell excitability troubles, neuro-muscular anomaly, the role of immunological factors) [19].

Local dissemination of BoNT by diffusion or spreading

The presumption of a local diffusion due to contiguity is to be interpreted with caution. The bladder, organ of the lesser pelvis, has direct muscle links with the levator ani muscles, the obturator internus muscles and the rectus abdominis muscles (most often untested muscles in current practice) (Figures 1 and 2). The presence of a motor deficit on those muscles in post BoNT injection in the detrusor therefore cannot be excluded. Psoas muscles insertion points are located between T12 and L4 vertebrae, being directly linked to the kidneys and the ureters via the renal fascia and the fascia transversalis. Iliacus muscles cover the whole of the internal iliac fossa in contact with the ureters. Yaraskavitch et al. [20] brought to light the capacity of BoNT to disseminate through the muscle fasciae. The assumption of a vesicoureteral reflux of BoNT

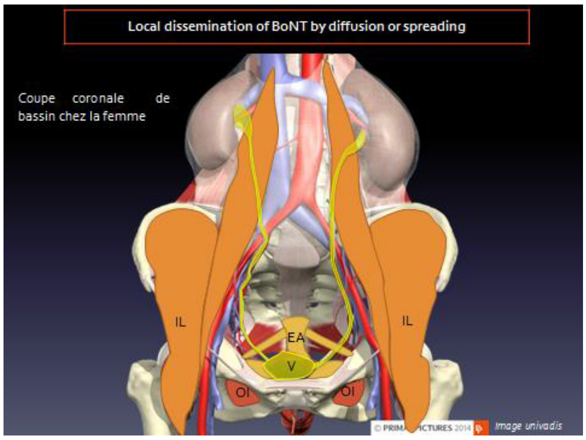

Figure 1: The bladder, organ of the lesser pelvis, has direct muscle links with the levator ani muscles, the obturator internus muscles and the rectus abdominis muscles (most often untested muscles in current practice).

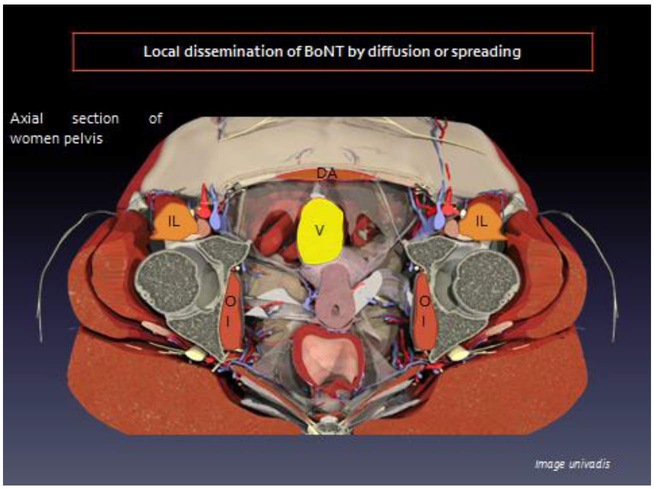

Figure 2: (IL) ilio psoas, (EA) elevator muscle of anus, (V) bladder, (OI) obturator muscle.

occurring during the medical gesture on a painful hyperactive bladder cannot be excluded. That reflux could be followed by an active local spreading of the BoNT, going past the different fasciae and towards the iliopsoas muscles [21], and even more so when the psoas present a low resistance fascia [22].

Migration by axonal transport

A mechanism mentioned since the 1970's [23]. Since then, other animal model studies have been published and they confirm the axonal transport-retrograde but also anterograde-of BoNT [24,25]. Torii et al. study is also to be mentioned, proving the migration of active BoNT/A from the injected limb to the contralateral limb in rats, by immunolabelling of the SNAP-25 protein cleaved by BoNT and by the use of the grip test showing a loss of contralateral strength. The absence of migration of an active form of BoNT in control rats having undergone a neurotomy of the ipsilateral brachial plexus, and in control rats for which the neuro-axial transport is blocked via the ipsi and contralateral use of colchicine, confirm the neuronal nature of the migration [25]. However, the mechanisms of internalisation of BoNT in intramedullary are still not fully explained. That is why, in order to confirm that assumption, we refer to Matak et al. work on pain (formalin animal experimental study). That research highlights the presence of BoNT-cleaved SNAP-25 (immuno-histochemical labelling) on the posterior horn of the spinal cord (trigeminal nucleus caudalis). No direct study on human subjects proving the axonal transport of BoNT has ever been made. However, the assumption of a neuronal transport was made as early as the 1960's by Tyler who had noticed the presence of an H-Reflex in a patient with botulism. A recent study by Marchand-Pauvert et al. supports the hypothesis of a central action of BoNT on humans, after axonal transport of its active form: it suggests a decrease of the reciprocal inhibition of the Renshaw cells (located on the anterior horn of the spinal cord) between the agonist and antagonist muscles after BoNT injection in the plantar flexors [26-28].

Summary

A mechanism of systemic diffusion cannot alone account for the existence of an isolated motor deficit on our two patients' hip flexors. The assumption of a local dissemination of BoNT towards the iliopsoas cannot be excluded but seems compromised in the absence of a direct link between the hip flexors and the bladder. The hypothesis of a retrograde migration of BoNT via the thoracolumbar sympathetic fibres (in the hypogastric nerves) thus seems to prevail. It would be responsible for the internalisation of active BoNT in intramedullary (T10 to L2 levels), followed by a bilateral anterograde axonal transport on the motoneurons, generating a deficit on the iliopsoas and on the accessory muscles of the hip flexion (adductor, pectineus, sartorius muscles) via the L2 root. That migration could also be possible via the pelvic and pudendal (sacral plexus) nerves, the internalisation would then affect the S2 S3 S4 roots generating a deficit by anterograde propagation on the hamstrings whose innervation originates from the sciatic nerve (L4 L5/S1 S2 S3 lumbosacral plexus). Furthermore, the lumbosacral trunk abandons the superior inferior gluteal nerves (L5 S1 S2) which innerve the gluteal muscles.

We could then assume that there would be a deficit of the muscles in the event of a retrograde diffusion. The patients both presented axial hypotonia and an instability of the pelvis that could be due to the aggravation of a pre-existing deficit of the muscles mentioned above. The EMG could have confirmed or overturned the formulated hypothesis. It would have been of interest in the search of a systemic diffusion that would be responsible for increased fatigue. In this particular case, it will be performed at a distance from the injection site. Concerning our two patients, it would be best on the upper limbs with no deficit. About retrograde migration, the EMG will concern the gluteal muscles for the superior and inferior gluteal nerves, the hamstrings for the four nerve branches of the sciatic nerve reaching the semitendinosus, the semimembranosus, the short head and long head of the biceps femoris. The psoas being difficult to access with the EMG, a scanner must be used for the exploration. The onset of a localized muscular deficit following a BoNT injection in the detrusor appears to be rare, as an example the literature review by Soljanik et al. which includes 2301 patients identifies only two cases of a localized muscle fatigue [7,29]. For our patients, the onset of that deficit on the hip flexors could be explained by the specificities of their injections: The first one gets 400 IU of BOTOX®, on 40 points, in 40 mL. But a volume effect on the diffusion of BoNT is reported (an increase of BoNT efficacy is highlighted by an EMG test on animals when they receive an injection with a higher volume for the same dosage. On human patients, an increased surface action of BoNT is highlighted when a higher volume is injected for the same dosage [30,31]. The dose effect on migration is uncertain and remains highly controversial [7,13]. The second patient is included in the DYSPORT® BoNT protocol, the migration of which seems higher. On a retrospective study by Roche et al. including 187 patients receiving intramuscular BOTOX® or DYSPORT® BoNT injections, only 5 of them (who had received DYSPORT® Abobotulinumtoxin A) had shown signs of distant diffusion.

Conclusion

BoNT injections in the detrusor in the context of a NDO refractory to anticholinergic are now routine procedures. Reported side effects seem to be less frequent than in the striated skeletal muscles. However, there are very few specific researches studying their onset, even if the increase of a motor deficit in already severely disabled patients is not without. Consequences in terms of functional prognosis and quality of life. Having a reference motor testing in pre-injection is essential in order to confirm or refute its aggravation in the event of a change in the neuro-functional status in post-injection. It is even more significant when the aggravation reported by the patients is of a more subjective nature. The presence of an onset is to be excluded in this context but we must always keep a possible diffusion of the BoNT in mind particularly when a higher dose than the one validated by the different studies is used. The use of a toxin, other than BOTOX (the only toxin granted marketing authorisation in that indication) necessitates the same rigour.

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