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Dystonia, Spasticity and Botulinum Toxin Therapy: Rationale, Evidences and Clinical Context

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1. Introduction

Perhaps among the central nervous system (CNS) conditions with muscle hyperactivity, dystonia and spasticity figure as those that are disabling and requiring therapeutic intervention. Dystonia is a neurological syndrome characterized by sustained muscle contractions usually producing twisting and repetitive movements or abnormal postures. The sustained movements of dystonia may have overlying spasms similar to tremor but have a directional preponderance. Three other important clinical features of dystonia are occurrences of pain, sensory trick phenomenon (i.e. touching “hot spots” in body surface that abolishes the dystonia), and changes in severity depending on activity and posture . Spasticity is typified by a velocity-dependent occurrence of a “catch” following passive limb movement. Recently, the scope of spasticity has been broadened in its definition as a disordered sensori-motor control resulting from an upper motor neuron (UMN) lesion presenting as intermittent or sustained involuntary activation of muscles(1-2) . Although their etiopathogenesis differ, both conditions overlap as regard the following: [a] occurrence of muscle co-contractions; [b] Overactivity involves not only extrafusal but also intrafusal muscles(3-4) [c] Intrinsic muscle changes in size and visceco-elastic properties (5-6); [d] contractures if left unattended (7);[e] muscular spread in synergy, “overflow” and compensatory muscles; [f] loss of dexterity; [g] occurrence of pain to varying degrees; [h] secondary bone and joint abnormalities; [i] may lead to “compensatory circuitry changes” at segmental and suprasegmental levels (4) ; [j] May lead to posturing and cosmesis issues, and [k] hygiene, quality of life and social impact . Another common thread between dystonia and spasticity is the reduction in muscle tone following botulinum neurotoxin therapy (BoNT), and effectively addressing the disordered sensori-motor control in both conditions. Intuitively, BoNT will be most efficacious in cases with a combination of spasticity and dystonia (i.e. spastic dystonia), such as in childhood spasticity(8). This chapter summarizes the clinical efficacy of BoNT in both dystonia and spasticity.

2. BoNT: Peripheral blockade and beyond

There are two kinds of BoNT (type A [BoNT-A: *onabotulinumtoxinA* or Botox®, *abobotulinumtoxinA* or Dysport® and *incobotulinumtoxinA* or Xeomin®], and type B [BoNT-B: *rimabotulinumtoxinB* or Neurobloc®/Myobloc®]) that have been proven to be safe and effective in treating various hyperfunctional cholinergic states. Their therapeutic applications range from various forms of muscle hyperactivity (e.g. dystonia, spasticity, spasms, tremors, and tics), autonomic hyperactivity (e.g. drooling, hyperhidrosis and bladder overactivity) and cosmesis (e.g. frown lines and “crow’s feet”). BoNT is more effective in blocking active neuromuscular junctions(9), and this effect can be enhanced by electric stimulation of the peripheral nerve(10). This toxin disrupts neurotransmission by cleavage of pre-synaptic vesicle fusion proteins; SNAP-25 for BoNT-A and synaptobrevin for BoNT-B, effectively blocking release of acetylcholine to the neuromuscular junctions and induce chemodenervation. The BoNT-A initially binds presynaptically (via the heavy chain attachment domain) and enters neurons by binding to the synaptic vesicle protein SV2(11). The toxin then undergoes internalization by vesicle endocytosis and translocation into the cytosol, to eventually exert its light chain proteolytic activity(12). After injection, the BoNT complex dissociates and diffuses into the target tissues. Toxin spread is a fast and active phenomenon that is driven by BoNT dose, dilution, needle size, and injection technique among others(13). Subclinical effects of BoNT on endplates far away from the injected sites can be demonstrated by increased jitter in single-fiber electromyography (SFEMG) in animals(3,14) and humans(15-16). Clinically not relevant for the moment and taken with a cautious stand because of the high animal doses applied, BoNT may undergo retrograde axonal transport, possibly transcytosed to afferent neurons, in which it cleaves its substrate SNAP-25. BoNT-truncated SNAP-25 appears not only at the injection site but also in distant regions that project to the infusion area. This retrograde spread was blocked by colchicine, pointing to a likely involvement of microtubule-dependent axonal transport(17). BoNT also affects the cholinergically mediated intrafusal fibers of muscle spindles, parallel to that of extrafusal fibers, implying an important functional effect (see a review on the subject by Rosales and Dressler, 2010[4]). In healthy, dystonic or spastic adults, the effect on muscle spindles appear to be more prolonged than that in extrafusal fibers, and whether one applies studies using the tonic vibration reflex (TVR)(18-19); or the transcranial magnetic stimulation(20). Since the gamma-motor-neurons are unable to activate the intrafusal fibers with BoNT-A, the muscle spindle output via the afferent axons will be reduced, and because muscle activity is supported by afferent feedback, there may be reduced alpha-motor-neuron drive(3). These events imply that there could be potential modulation of central motor programs following BoNT-A(21). In fact, recent BoNT-A studies in dystonia and spasticity have shown evidences of modifications in the cortical and subcortical levels(22-24); including plasticity changes(25).

3. BoNT for dystonia

3.1 Rationale

Dystonia is a multi-level system disorder where involvement spans from the peripheral (muscular) to the segmental and suprasegmental levels (brainstem, basal ganglia and cortex)(4,26). Muscle hypertonus/spasms in dystonia are relieved by chemodenervation procedures that include muscle-based injections (i.e. muscle afferent block [MAB] and

BoNT) and near nerve injections (i.e. phenol block). Although useful in near large nerve injections (e.g. obturator and femoral nerves), phenol has not been encouraging because of pain associated with the procedure and its unpredictable response (27). Hinged on the abolition of abnormal muscle spasms with “sensory trick” and MAB in dystonia (i.e. applying TVR[28]), it is believed that the BoNT does have sensory modulatory effects, apart from pure muscle relaxation (see a recent review on the subject by Kanovsky and Rosales[26]). In addition, BoNT-A may reduce pain comorbidity that occur in dystonia (see a recent review by Rawicki and cohorts[29]). The fact that BoNT injections are able to improve an individual’s occupational function and quality of life elevates the rationale for its applications. The latter is best exemplified by occupational dystonias (A separate chapter is dedicated to this end). Figure-1 depicts cases of focal hand dystonias with task-specificity and those with complex regional pain syndrome, being prepared for BoNT-A injections.



Fig. 1. Focal hand dystonias (upper panel: with task-specificity [Writer’s cramp and Barber’s cramp]); (lower panel: with complex regional pain syndrome)

3.2 Evidence-based medicine

Cochrane reviews summarized the evidences of BoNT superiority as a therapy for blepharospasm(30) and cervical dystonia(31). The American Academy of Neurology (AAN)(32) recommended that BoNT injections should be offered as a treatment option for cervical dystonia (established as effective) and may be offered for blepharospasm, focal upper extremity dystonia, adductor laryngeal dystonia (probably effective). A lower level of evidence was detected for focal lower limb dystonia (possibly effective). According to the European Federation of Neurological Societies [EFNS] version(33), BoNT-A is considered the first-line treatment for primary cranial (except oromandibular) or cervical dystonia; it is

also effective for writing dystonia; BoNT-B is not inferior to BNT-A in cervical dystonia. Despite the variety of trial formats, virtually all the trials individually, and each outcome measure (objective and subjective) separately, suggested that a single injection cycle of BoNT-A is effective and safe for treating cervical dystonia. Enriched trials (using patients previously treated with BoNT-A), suggest that further injection cycles continue to work for most patients. Appropriate injections of BoNT-A into cervical muscles at therapeutic doses are well tolerated, and although adverse effects occur these are transient and rarely severe(31). Furthermore, the available evidence suggests that BoNT-A injections provide more objective and subjective benefits than an anticholinergic drug (i.e. trihexyphenidyl) to patients with cervical dystonia(34).

An international consensus on the aftercare for cervical dystonia and other causes of hypertonia of the neck stated that the benefits following BoNT injection include increased range of movement at the neck for head turning, decreased pain, and increased functional capacity (Class I evidence, level A recommendation). The evidence for efficacy and safety in patients with secondary dystonia in the neck is unclear based on the lack of rigorous research conducted in this heterogeneous population (level U recommendation). Psychometrically sound assessments and outcome measures exist to guide decision-making (Class I evidence, level A recommendation). Much less is known about the effectiveness of therapy to augment the effects of the injection (Class IV, level U recommendation). More research is needed to answer questions about safety and efficacy in secondary neck dystonia, effective adjunctive therapy, dosing and favourable injection techniques(35).

On the issues of BoNT-A application in secondary dystonia as well as for oromandibular dystonia, an applied example is the case of x-linked dystonia-parkinsonism (XDP), a type of heredo-degenerative disorder . In the large cohort of oromandibular and lingual dystonias found in XDP, BoNT-A was shown to be safe and effective as one carefully navigates through recommended technical considerations(36). In XDP as well, BoNT-A targeted in cervical and limb dystonias, indicated its superiority over MAB(37). Interestingly, BoNT-A may also be combined with pallidal deep brain stimulation (DBS) in XDP(38), when the former eventually fails as the only treatment, or when toxin doses increase due to body area spread of dystonia, or even in certain instances after DBS .

3.3 Clinical context

BoNT is a safe and targeted treatment approach suited for focal dystonia where certain muscles are clearly involved during co-contraction and in which injections can be modified for the changing dystonia patterns, including segmental and overflow muscles involved (4,13,26). Depending upon factors such as muscle bulk, severity of muscle spasm and whether one may want/avoid contiguous muscles in a clinical context, BoNT-A in dystonia may be tailored in certain instances. A “high potency, low dilution” of BoNT-A may best be applied in the cranio-cervical (i.e. injections in the peri-ocular, facial, oromandibular, lingual, laryngeal and neck muscles) and distal limb regions, where BoNT-A is expected to be maximized in a targeted (usually smaller) muscles through 1–2 injection sites, and where spread is best avoided. Whereas, in dystonias of the abdominal, paraspinal, and proximal limb muscles, a “low potency, high dilution” BoNT-A injection protocol could best be applied, since spread may be desirable for very large muscles, when multipoint muscle

injections is utilized (36). In view of its “dual effects” on the extrafusal and intrafusal muscles, the clinical benefit in practice may “outstrip” the weakness induced by the BoNT(4,39) . Interestingly in cervical dystonia, discrepant and time-related effects vary between relief of muscle hypertonus, associated pain and head posture(31) . These findings underscore the BoNT effects far beyond simply blocking muscle spasms in dystonia. For instance, the head posture may be related to muscle spindle changes among other factors(4) and the associated pain relief having perhaps an independent mechanism(29) . The role of BoNT-A in pain pathophysiology is beginning to be understood, however, larger studies in neuropathic pain, joint pain, and myofascial pain syndrome are needed to fully ascertain robustness of BoNT therapy in those areas(40-41).

4. BNT for spasticity

4.1 Rationale

Arguably only one component of UMN, spasticity in both children (e.g. cerebral palsy, see Figure-2) and adults (e.g. post-stroke, traumatic brain/spinal injuries and multiple sclerosis; see Figure-3), may impair one’s motor control, quality of life and may eventually lead to economic and care-giver burden. More than one third of patients develop spasticity within



Fig. 2. Childhood spasticity (thigh adductor spasms or “scissoring” and equinovarus foot deformity)



Fig. 3. Spasticity “plus” (Post-stroke with spastic dystonia-left panel; Multiple Sclerosis with spastic dystonia-middle panel; Traumatic brain injury with spasticity and dynamic contracture-right panel)

12 months after stroke(42-43) and a proportion of these patients will develop disabling spasticity requiring intervention(44). Even in the early phases of stroke (“evolving spasticity”[45]) about 19% of patients(46) or possibly more(47), develop spasticity within 3 months after the ictus. In fact, as many as 80% of patients without useful functional arm movement after the ictus, develop spasticity (measured by muscle activation recording) within 6 weeks of first stroke(48).

Strokes in the middle cerebral artery region occur in three quarters of patients, hence, the upper limb is affected in a large number of them. In regard to therapeutic intervention, differences may arise between the hemiplegic upper and lower limbs, and these are(49): (a) functional recovery of an arm that enables grasping, holding, and manipulating objects,

requires the recruitment and complex integration of muscle activity from the shoulder to the fingers. In contrast, a minimal (or less complex) amount of recovery of a hemiplegic leg may be sufficient to obtain functional ambulation; (b) the ability to reach and grasp is a necessary component of many daily life functional tasks, hence reduced upper limb function is likely to reduce independence and increase burden of care. Moreover, muscles in the affected ankle cannot be efficiently recruited in a timely manner to overcome reaching task impairment in stroke patients (50); (c) left uncorrected, secondary complications such as inferior subluxation of the glenohumeral joint, shoulder-hand syndrome, soft tissue lesions, and painful shoulder further hinder rehabilitation of the hemiplegic arm; (d) there is a lack of spontaneous stimulation when performing upper limb functional activities that “assist” in recovery, compared to lower limb activities. Bilateral activity in the legs is often required whenever a patient attempts to transfer, stand or walk, whereas, in performing upper limb activities, the patient may opt to simply use the non-affected side exclusively(51); and, (e) the “protective effect” of spasticity applies more to the lower limbs, and not necessarily for the upper limbs. For example, lower limb spasticity may be beneficial by enabling patients to stand despite the co-occurrence of lower limb weakness. When it does cause harm, however, treatment is required(51-52). Spasticity in the upper limbs (ULS), with these inherent characteristics, may lead to compensatory central nervous system adaptations and changes after stroke such as the “learned non-use” of the affected upper limb. As a form of maladaptive plasticity, the frequent assistance of the non-affected limb may prove to be disadvantageous in the efforts to improve functional recovery(45). Not all patients with ULS will have spasticity-related symptoms (i.e. *symptomatic spasticity*), but those with functional impairment can be categorized into: (a) those relating to passive function, e.g. hand hygiene, wearing of upper garment, application of splints; (b) pain; (c) associated reaction, and (d) those relating to impaired active function(53). Therefore, it is not unusual that a large majority of BoNT randomized and systematic spasticity intervention studies have been performed on the upper limbs(54). Having its effect in the neural component of spasticity(2,55), the rationale for BoNT-A use is hinged on its reduction of muscle tone via chemodenervation of injected overactive muscles, and potentially prevent, through early injection protocols, eventual complications brought about by the non-neural components (e.g. contracture in spasticity, Fig-3)(45). In fact, BoNT-A is likewise able to address muscle overactivity in spasticity with associated reactions and dystonia (spastic dystonia; Fig-3) (45). The current state of knowledge on the application of BoNT-A in the management of spasticity is depicted in Figure-4.

4.2 Evidence-based medicine

Based on meta-analysis derived from well-conducted, randomized controlled clinical trials(54) BoNT-A proved to be safe and efficacious in treating upper and lower limb spasticity, as measured by lowering the Modified Ashworth Score (MAS) that clinically assesses hypertonicity during passive range of motion across a joint(56). A contemporary review on ULS also indicated robust efficacy of BoNT-A, over other pharmacologic therapies(57). Systematic reviews from the AAN (58), Royal College of Physicians (UK-RCP)(59), European Consensus (60) and Movement Disorders Society (MDS)(61) lead to formulation of therapeutic guidelines for the application of BoNT-A in the over-all

management of spasticity. In parallel, international consensus statements were made on the use of BoNT-A over a wide range of indications for adult and childhood spasticity(62-65). The benefit from BoNT-A is maintained after repeated treatment cycles(66-67) and thus, BoNT-A has been thought to be a first line treatment in focal/multifocal spasticity(68). In addition, BoNT treatment has been shown to improve associated reactions in ULS(69) reduce predetermined disability parameters (including pain) (70-73), reduce carer burden(70,73-74), improve person-centered goals(75) and self-reported efficacy with safety(76). However, efficacy of BoNT-A for improvement of motor control and active functions have not been attained(77). While spasticity is an important component of reduced upper limb function, Shaw and colleagues(71) argue that motor weakness is the most important factor. Likewise, their study did not demonstrate improved active function (despite an improvement in muscle tone in favor of intervention), arguably suggesting that spasticity is of less importance. To date, most of the studies show that BoNT-A injection has been applied in the chronic stage(78-80) (i.e. more than 6 months after stroke; average of 2.5 years) wherein spasticity has been established(45) and wherein non-neural, rheologic changes have set-in. Early intervention with BoNT-A (i.e. less than 3 months post-stroke) has been performed in two Phase II trials (designed to estimate sample sizes)(81-82) and in a Phase III trial(83). The first Phase II study by Cousins and associates(81) indicated some functional recovery at 20 weeks in the groups that received *onabotulinumtoxinA*, following a subanalysis of patients with no arm function (employing Action Research Arm Test) in the baseline assessment (i.e. 3 weeks post-stroke). Interestingly, the second Phase II study by the German group(82) failed to demonstrate improvement in motor control with the Fugl-Meyer arm score, despite a reduction in finger flexor stiffness, 6 months after injecting *incobotulinumtoxinA*. The Asian Botulinum Toxin Clinical Trial Designed for Early Post-Stroke Spasticity (ABCDE-S) was a Phase III study (83) that demonstrated reduction in muscle tone (MAS) at week 4, and which was sustained to 24 weeks, despite a single cycle, uniform injection of 500units *abobotulinumtoxinA*. In the latter cohort of patients that enrolled patients 2 -12 weeks post- stroke, significant pain reduction (i.e. weeks 4 and 24) was demonstrated among those that had initial spasticity-related pain, but showed no motor control improvement (using the Motor Assessment Scale).

4.3 Clinical context

Spasticity has been shown to inhibit active upper limb function(84) mainly because the prime mover is not fully able to overcome the resistance of the spastic (antagonist) muscle. BoNT-A should be used to address specific functional limitations resulting from focal spasticity (i.e. muscle over-activity confined to one or a group of muscles that contribute to a specific functional problem). However, BoNT-A is not always expected to fully or partially recover lost function, except perhaps when that function has been lost primarily due to antagonist muscle over-activity(59). The effect of BoNT-A on muscle tone and muscle strength is dose-dependent (85). It is therefore important to titrate the dose in patients with an "incomplete" UMN lesion to reduce muscle tone sufficiently without inducing excessive weakness (and loss of function)(86). The appropriate time to initiate BoNT-A therapy in ULS should not be dependent on post- stroke duration, but rather on the goals initially set forth. In established spasticity, treatment should be based on the occurrence of impediments to occupational therapy or physiotherapy, or when the disability has reached a plateau or

when the disability continues to worsen despite such therapies (62). Predefined goals are ideally smart, achievable and person-centered, in order to optimize BoNT-A effects in areas of muscle tone, pain, active/passive functions, burden of care, cosmesis, among others(87). However, in early BoNT-A injection protocols, when spasticity is evolving, goals are likely different, as these are largely for prevention of contracture or possibly improvement in arm function in the long run. Finally, there are generally a couple of ways for which improvements in function can occur. Pre-morbid movement patterns may be regained first because of true motor recovery, and second, because of the redundancy in the number of degrees of freedom of the body(88). In the latter, actions can be accompanied by substitution of other degrees of freedom for movements of impaired joints. Such alternative movements or motor compensations(89) have also been observed in primates recovering from experimental stroke(90). Therefore, targeting specific muscle groups with BoNT-A, without affecting others, has the theoretical potential to unmask selective voluntary movement in situations where this is over-ridden by mass patterns of spasticity in antagonistic muscle groups(91). This underscores the interaction and complexity of proper (or improper) selection/targeting and accidental (or intentional) spread in achieving treatment goals. Last but not least, BoNT should not be administered alone, and its effects are best optimized in concert with a good rehabilitation program and an inter-disciplinary team.

5. Conclusion

Backed by robust clinical trials, we have undoubtedly reached a stage where the roles of BoNT in the management of dystonia and spasticity have been historically etched. This is paralleled by a BoNT safety profile that withstood the test of time over 20 years of application in hypertonic muscular disorders. The clinician is placed in a state to choose the best individualized approach to patients with dystonia and spasticity, bearing in mind that for BoNT, the evidences exist, as one negotiates through management issues related to benefit, harm and cost.

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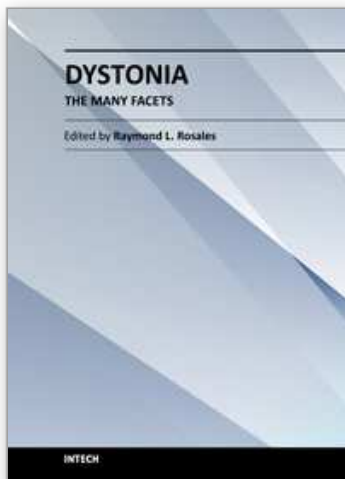
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Dystonia has many facets, and among those, this book commences with the increasingly associated genes identified, including a construct on how biology interacts with the dystonia genesis. The clinical phenomenology of dystonia as approached in the book is interesting because, not only were the cervical, oromandibular/lingual/laryngeal, task-specific and secondary dystonias dealt with individually, but that the associated features such as parkinsonism, tremors and spasticity were also separately presented. Advances in dystonia management followed, and they ranged from dopaminergic therapy, chemodenervation, surgical approaches and rehabilitation, effectively complementing the approach in dystonia at the clinics. A timely critical pathophysiologic review, including the muscle spindle involvement in dystonia, is highlighted at the book's end.

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