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Botulinum toxin for the management of adult patients with upper motor neuron syndrome

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ABSTRACT

The upper motor neuron (UMN) syndrome is a collection of interactive positive signs (associated with spastic hypertonia) and negative signs, such as muscle weakness and loss of voluntary control. In clinical practice, the distinction between active and passive functions allows identifying appropriate treatment objectives. During the last decades, many studies have evaluated the possibility to treat UMN syndromes with botulinum neurotoxin (BoNT). They have shown that BoNT is effective in controlling upper limb spasticity in adults. The clinical improvement is more consistent in the distal joints and the reduction of muscle hypertonia is dose-dependent. The functional efficacy of BoNT for lower limb spasticity has not been documented as well, as some series report efficacy in reducing muscle tone in the lower limb, but not in improving walking.

The functional benefit arising from the reduction of spasticity is often difficult to judge in the context of the complex phenomenology of the UMN syndrome. Certain data indicate that some disabilities related to passive and active function in the upper limb can improve with treatment. However, to date, the functional improvement after BoNT treatment in patients with UMN symptoms remains a point of ambiguity in the literature.

BoNT is overall well tolerated and must be regarded as a safe treatment intervention. Safety data are abundant in the literature for type-A toxin and scant for type-B toxin. There is no clear evidence to suggest the best time to introduce BoNT injections in the management of UMN syndromes. A common sense approach would be to introduce BoNT treatment as early as possible, in order to prevent further complications including contractures.

1. Upper motor neuron syndrome and spasticity

Since the seminal observations of Hughlings Jackson (1875), clinicians have characterized the upper motor neuron (UMN) syndrome as a collection of interactive positive and negative signs. UMN symptoms and signs include loss of selective voluntary movement, dexterity and control, stretch sensitive (spastic) phenomena such as increased phasic and tonic stretch reflexes, spastic co-contraction and spastic dystonia, and non-stretch sensitive phenomena such as released flexor reflex afferent activity, and associated reactions (Sheean, 2002; Mayer and Herman, 2004). In general terms, positive signs are characterized and generated by involuntary muscle overactivity; negative signs such as weakness are related to loss of voluntary control over muscles. In the clinic, these phenomena interact to produce a functional impairment characteristic of the UMN syndrome (Table 1).

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Table 1
Upper motor neuron syndrome: positive and negative signs

Positive signs	Negative signs
• Phasic and tonic stretch reflexes (Gracies, 2001; Mayer and Esquenazi, 2003)	• Muscle weakness (Mayer and Esquenazi, 2003)
• Co-contraction (Mayer and Esquenazi, 2003)	• Loss of finger dexterity (Mayer and Esquenazi, 2003)
• Released flexor reflexes (Mayer, 1997; Mayer and Esquenazi, 2003)	• Loss of selective control of limb movement (Mayer and Esquenazi, 2003)
• Associated reactions (synkinesia) (Mayer and Esquenazi, 2003)	
• Spastic dystonia (Mayer and Esquenazi, 2003)	
• Increased muscle stiffness that may contribute to contracture (Mayer, 1997; Mayer and Esquenazi, 2003)	

Table 2
Functional goals of treatment in UMN syndrome

Passive function	Active function
• Increased range of motion*	• Improved upper limb use: reaching, grasping, releasing*
• Improved positioning*	• Improved mobility*
• Increased ease of hygiene*	• Improved gait
• Improved cosmesis*	• Decreased energy expenditure*
• Decreased spasm frequency	
• Improved orthotic fit*	
• Decreased pain*	

Modified from Brin (1997). *, BoNT can help reaching this goal.

Patients with an UMN syndrome may complain of one or more types of problems including symptomatic issues, loss of passive function and loss of active function (Mayer and Esquenazi, 2003). UMN syndrome motor problems can be classified in four types that recognize the main clinical issues (Mayer et al., 2007). In type I, symptomatic issues include such complaints as stiffness, pain, clonus and spasm as some of the presenting problems; in type II, issues of passive function typically refer to the passive manipulation of limbs to achieve functional ends, typically performed by caregivers, though patients may also manipulate their limbs passively with their non-involved limbs; in type III, active functions refer to patient's direct use of the limb to carry out a functional activity. For example, a patient who walks with equinovarus during stance phase may fall because of an unstable base of support. A patient who walks with spastic hip adductor may have difficulty maintaining balance or advancing the uninvolved leg. Type IV is a mixed form, combining two or more of them.

The distinction between active and passive functions allows to identify appropriate treatment objectives (Sheean, 2001). Active function relates to the capacity to move the body or its parts actively and can range from simple active movements at a specified joint to complex movements and even complex actions; it is impaired when spasticity interferes directly with voluntary movement. Passive function relates to the ability to integrate a body part in activities passively (Platz et al., 2005); it is impaired when there is little or no residual voluntary movement due to severe weakness. As far as active function is concerned, the goal of spasticity treatment is to reduce motor overactivity in order to improve movement; for passive function, instead, the main goal is to reduce pain during passive mobilization, painful spasms and attain better hygiene or prevent contractures (Table 2).

In everyday life, bi- or multi-directional joint motion is the rule and fixed positions are not typically maintained for extended periods of time. However, for patients with an UMN lesion, control over individual degrees of freedom of joint motion becomes impaired and, consequently, positive sign activity promotes unidirectional movements that often persist as postures because of the loss of voluntary movement in the return direction. The combined effect of recurring positive and negative signs leads to a net imbalance of muscle torques across individual joints that favor movement stereotypy and postural persistence (Fig. 1). By forcing joints into undesired static positions or into poorly controlled and stereotyped dynamic movements, the combined effects of positive and negative signs lead to limb deformity in patients with UMN syndrome (Fig. 2). Spasticity leads to exaggerated reflexes, posturing (so-called "spastic dystonia"), and flexor or extensor spasms, which are often painful. The terms "muscle hypertonia" and "muscle overactivity" are often used to describe the tone-dependent component of spasticity, which is most apparent in these patients.

Traumatic brain injury, embolic and hemorrhagic stroke, and common types of acquired brain injuries frequently result in motor dysfunction of the UMN type.

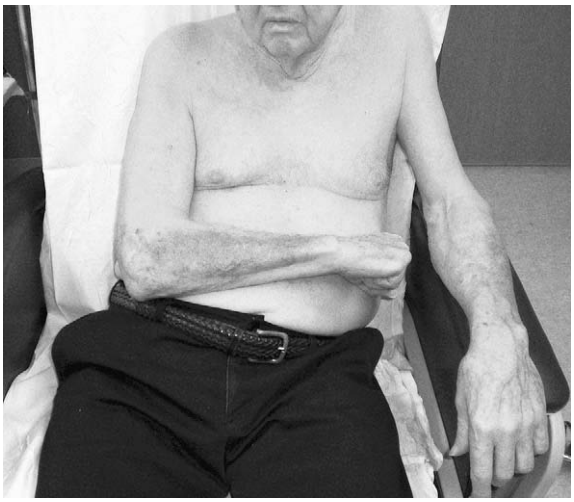

Fig. 1. The adducted, internally rotated shoulder is a common pattern of UMN dysfunction. Patients complain of stiffness, difficulty with passive range of motion especially needed for washing the axilla and dressing the upper limb. Sometimes a passive stretch of adductors is painful. The hyperextended shoulder, especially accompanied by elbow extension, is a problem during gait (e.g., knocking into doorways or furniture) and many patients are uncomfortable with the way they look (Esquenazi et al., 2008).

Fig. 2. Muscles that may contribute to the flexed elbow pattern include *brachioradialis*, biceps, *pronator teres* and brachialis. If the wrist is fixed in flexion, even *extensor carpi radialis* can contribute to flexor torque across the elbow because of its relationship to the elbow joint's axis of rotation. A severely flexed elbow, persistent in its posture, can lead to ulnar neuropathy because of ulnar nerve stretching in the cubital tunnel. Such a lesion severely weakens hand intrinsics, causing some patients with a wrist flexion deformity (stretching finger extensors) to distribute dynamic and static muscle forces across fingers, resulting in a claw hand.

The clinical expression of motor dysfunction in the UMN syndrome is strongly influenced by three factors: spasticity and other forms of muscle overactivity, contracture and impaired motor control. The time elapsed between the acute event leading to UMN signs and the comprehensive management of the patient (particularly physical treatment) significantly influences the long-term clinical picture.

A limb with UMN dysfunction is vulnerable to loss of range of motion, skin, bone and joint problems, impairment of activities of daily living and body image disturbance. Evaluation of a patient with UMN movement dysfunction requires a thorough comparison of needs and perceptions reported by the patient and the caregiver with the objective physical examination and laboratory evaluation. Voluntary capacity and spastic reactivity are examined and interpreted in light of clinical and functional complaints. Not surprisingly, several outcome measures are available to evaluate spasticity, pain, function and disability in patients with UMN problems. The Ashworth rating scales (Ashworth, 1964; Bohannon and Smith, 1987) are typically applied to measure the tone perceived across a joint; passive range of motion (de Jong et al., 2007) allows measure variation of joint angles; other measures include the spasm frequency scale (Penn et al., 1989) and the analysis of postures (Biering-Sorensen et al., 2006). In addition, functional scales estimate the patients' functional status regardless of the specific underlying impairment (Cohen and Marino, 2000). Many studies of spasticity treatments have used other generic measures of disability, such as the functional independence measure (FIM) or the Barthel index, and generally they have not demonstrated changes directly related to variations of spasticity (Hinderer and Gupta, 1996). The selection of outcome measures to assess the functional impact of spasticity is not straightforward and this is probably the reason why in most spasticity studies disability and functioning have been evaluated using a heterogeneous collection of outcome measures.

Treatment aims at alleviating symptomatic issues related to passive and active functions. The UMN syndromes associated with spasticity and muscle overactivity may lead to abnormal limb posturing that interferes with active function such as the ability to use the limb for a functional task and passive function, when the limb cannot be assisted either by the uninvolved limb or a care taker (Mayer and Herman, 2004). There is no evidence to suggest when to introduce antispasticity treatments in patients with UMN syndrome. Certainly, BoNT therapy should be given when spasticity causes a functional problem (Ward, 2002) and likely well before then, as a means to prevent functional impairment. If patients with UMN syndrome remain untreated for a long time following the acute injury, they may also develop limb contractures, pain or limb deformity due to uncorrected loss of balance between agonist and antagonist muscles acting across joints.

With current comprehensive management strategies, the improvement in the acute medical care of acquired brain injuries has resulted in a dramatic increase of the survival rate of these patients that will frequently present residual functional deficits, estimated to be related to spasticity and muscle overactivity in about 40% of cases (O'Brien et al., 1996). In parallel the continuing growth of the elderly population in developing nations has significantly increased the number of stroke survivors. This combination has resulted in a very significant number of patients with UMN syndrome residual, characterized by symptoms of UMN syndrome and its secondary complications (Kotila et al., 1984; Watkins et al., 2002). Current standards of care indicate that a comprehensive treatment should be introduced before the occurrence of secondary orthopedic and neurological complications that may worsen over time to become irreversible. Early management is the most effective approach to prevent some spasticity from developing and complications from arising (Ward, 2002). Once a patient has developed residual from the UMN syndrome, treatment is aimed primarily at improving symptoms, hygiene, and passive function and in selected cases restoring active function. Table 3 summarizes the available treatments for early and late stage complications of UMN syndromes.

Table 3
Treatment options and goals of UMN syndrome treatment according to time following acute injury

Stage	Treatment options
• Early or intermediate	• Physical management • BoNT (spasticity, improve active functions)
• Late and UMN syndrome residuals	• BoNT (hygiene, pain, improve passive functions) • Pharmacological treatments • Surgery

2. Botulinum neurotoxin treatment of spasticity

During the last 15 years, botulinum neurotoxin (BoNT) has been widely used to reduce muscle overactivity that occurs in a number of neurological and non-neurological conditions. The first usage in patients with UMN syndrome dates back to almost 20 years ago (Das and Park, 1989). In this early paper, the symptomatic efficacy of BoNT was not only assessed on spasticity, the most prevalent positive sign of UMN syndrome, but also on other features observed in the syndrome, such as the range of active and passive joint movements, pain and functional abilities. The second paper for this indication used the Ashworth scale to measure spasticity (Dengler et al., 1992) and set a standard that has been since followed by later studies.

Several research and clinical reports support the concept that chemodenervation with BoNT is an excellent intervention for treatment of focal muscle overactivity and spasticity related to UMN syndrome. Aside clear evidence of efficacy on functional outcomes, a number of unsettled issue still relate to the usage of BoNT treatment in the management of patients with UMN syndrome. These aspects will be briefly reviewed here within the frame of the above-mentioned complexity of the UMN syndrome.

Two recent evidence-based reviews have evaluated the efficacy of BoNT treatment in patients with spasticity. A report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (Simpson et al., 2008) evaluated the available literature on the use of BoNT in disorders with spasticity, whereas another meta-analysis (Elia et al., in press) evaluated the available randomized controlled trials on the use of BoNTs in adult post-stroke spasticity. Both reports concluded that BoNT is an effective treatment of upper limb spasticity in the adult population, where it reduces muscle overactivity in a dose-dependent manner.

In the North-American review, reduction of tone was evaluated considering the upper limb as a whole, regardless to the injection sites, whereas in the European review an individual analysis was performed for each upper limb joint. The latter study concluded that single BoNT/A treatments reduce hypertonia in the elbow, wrist and finger flexors 1 month after treatment; 3 months after treatment, the effect of BoNT/A is less evident at the elbow.

The European meta-analysis identified a distal-to-proximal variation in outcome, whereby clinical improvement is more consistent at distal joints, possibly due to the smaller size of the distal muscles or to insufficiency of doses injected into the larger proximal muscles.

Published evidence for the functional efficacy of BoNT for lower limb spasticity is limited. The European study reported no significant improvement in walking or spasticity following injection in the gastrocnemius muscle. This evidence is derived from just one trial on post-stroke spasticity. The North-American study, which had wider inclusion criteria, reported efficacy in reducing lower limb muscle tone, but no improvement in walking. Overall, there is a need for further good quality studies on lower limb spasticity.

The North-American review concluded that BoNT should be offered as a treatment option to improve passive function in adults with spasticity, and should be considered to improve active function. The European study did not provide recommendations, but argued that the quality of functional improvement after BoNT treatment remains a point of uncertainty, that needs to be specifically addressed by future studies.

Many muscles differing in size, shape, location and function have been injected in the published series. The two systematic reviews indicate that the efficacy of BoNT is better established for upper than for lower limb spasticity. Clearly, BoNT/A can reduce spastic muscle tone if a sufficient dose is given. This may probably also be proven true for BoNT/B once a sufficient number of controlled trials become available (the only one available so far has failed to show an effect (Brashear et al., 2004). The functional benefit arising from the reduction of spastic tone is more difficult to judge. There are data to indicate that certain disabilities related to upper limb passive and active function can improve. However, it remains to be proven whether voluntary movement can be improved. The duration of action was not specifically addressed by the available studies, although some trials suggested that efficacy may be appreciated 6 weeks after injection and for up to 9–12 weeks (Elia et al., in press). The exact timing between repeated treatments may vary between individual joints, and requires to be assessed by specific studies.

Some clinically valuable information can be derived from experience in other movement disorders, particularly dystonia. In stroke patients the interval between treatments is approximately 3–5 months, after which BoNT is re-injected; it is likely that the duration of effect may increase over time. Similarities of treatment paradigms need to be emphasized, because it is unlikely that future controlled trials will be able to answer all the still open practical questions on the management of UMN syndrome.

Overall, BoNT/A is well tolerated and must be regarded as a safe treatment. No study reported more adverse events in the treated than in placebo arm. Published data on the safety of BoNT/A in patients with dystonia and other movement disorders also indicate a good safety profile (Naumann and Jankovic, 2004). A recent pooled analysis of BoNT/A safety in patients with post-stroke spasticity concluded that nausea was the most frequent problem with BoNT/A, affecting only 2.2% of cases (Turkel et al., 2006). BoNT/B may have more side effects than BoNT/A, particularly on autonomic function. In the BoNT/B trial on post-stroke spasticity, dry mouth was more common in the treated group than in controls (Brashear et al., 2004).

3. Outlook: BoNT treatment of UMN syndrome

Since spasticity is only one among several clinical signs of UMN syndrome (Mayer and Esquenazi, 2003), treatment with BoNT may not be sufficient to produce a demonstrable improvement in motor function, due to the persistence of the remaining features not addressed by this treatment intervention. BoNT treatment is only one out of several treatment strategies in the comprehensive management of upper motor neuron syndrome which, commonly is associated with physical therapy (Ward, 2002). Since rehabilitation is efficacious on UMN symptoms (Anonymous, 2003), future BoNT trials should consider patients receiving “standard

rehabilitation'' programs. Ideally, an appropriate rehabilitation management program should be in place already before starting BoNT treatment (Ward, 2002), and it should continue thereafter. Future placebo controlled research studies should consider the same rehabilitation treatment in both arms. Furthermore, inclusion criteria should not only consider spasticity, but also its presenting pattern, clearly identified functional goals and the ability to meet such goals.

In studies evaluating spasticity treatments, functional improvement has been rarely considered a primary outcome measure. Earlier studies have mainly assessed activities of daily living, which attempt to measure the ability of an individual to perform activities required in daily chores, such as bathing, dressing, using the toilet, moving around the house and eating. The lack of validated functional outcome measures is surprising, particularly because functional recovery is the primary goal of spasticity treatment in clinical practice.

Finally, there is no evidence to suggest an ideal time to introduce BoNT treatment following the acute onset of an UMN syndrome. Dealing with this aspect, the time lag between the acute event and BoNT treatment also needs to be stratified in future trials; the available series report BoNT treatments starting from 3 months to 8 years after a stroke (Elia et al., forthcoming). We wait for a large trial comparing early vs. late BoNT treatment, with reasonably high doses, in patients with UMN syndrome to be evaluated with functional primary outcome measures as a primary outcome and spasticity as a secondary outcome. This type of study will probably allow the establishment of new standards in clinical practice.

Conflict of interest

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