Sarcopenia, Cerebral Palsy, and Botulinum Toxin Type A

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Abstract

» Sarcopenia is common in both the elderly and children with cerebral palsy.
» Children with cerebral palsy have muscles that are much smaller than muscles in typically developing peers.
» Injections of botulinum toxin type A (BoNT-A) result in acute muscle atrophy in animal models and in human subjects.
» It is not known when or if muscles recover fully after injection of BoNT-A.
» These findings have implications for management protocols.

In 2016, sarcopenia was recognized as a disease entity in the International Classification of Diseases, 10th Edition, Clinical Modification (ICD-10-CM)[1]. The European consensus on the definition of sarcopenia, published in 2010, describes sarcopenia as "a loss of function (either walking speed or grip strength) associated with a loss of muscle mass."[1-3] Deren et al. used computed tomography (CT) to measure the cross-sectional area of muscle in patients who were >60 years old who presented with a closed fracture of the acetabulum[4]. They found that sarcopenia was common in elderly patients and was associated with lower-energy fractures and a higher risk of 1-year mortality[4]. Sarcopenia also has been reported to contribute to the inability of older patients to maintain weight-bearing restrictions following a hip fracture[5]. Sarcopenia and osteoporosis may develop insidiously and simultaneously[6]. Some of the factors that predispose to sarcopenia in the elderly, including malnutrition and type-2 diabetes, are potentially modifiable[6,7].

In children with cerebral palsy, muscle weakness is the predominant negative feature of upper motor neuron (UMN) syndrome and is a substantial determinant of gross motor function. It has been suggested that the negative features of UMN syndrome (weakness, loss of selective motor control, and impairments of balance and sensation) are stronger determinants of a child's ambulatory potential than the more obvious positive features (spasticity, hyperreflexia, and cocontraction). The positive and negative features of UMN syndrome can all be considered pathologic and have been discussed in detail previously[8]. In an attempt to delay the need for surgery, intramuscular injections of botulinum toxin type A (BoNT-A) have become popular as a focal treatment for spasticity in children with cerebral palsy, with reportedly few side effects[8]. Recent animal studies have shown that the use of BoNT-A may

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not be as benign as previously thought; prolonged decreases in muscle strength and contractile elements have been identified[9]. Furthermore, the best evidence to date suggests that the effects of BoNT-A are transient and have not resulted in long-term functional improvements[10].

The purpose of this review article is to consider the evidence of the effects of the BoNT-A injection on sarcopenia and muscle function in children with cerebral palsy and the implications for current and future functioning. Information relevant to this discussion comes from 3 principal sources: injection of BoNT-A in typically developing adult volunteers and patients, injection of BoNT-A in experimental animals, and injection of BoNT-A in children with cerebral palsy.

Muscle Morphology in Cerebral Palsy

Objective measurement of muscle morphology has been enhanced by the development of nonionizing axial imaging modalities, including 3-dimensional (3D) ultrasound and magnetic resonance imaging (MRI)[11-16]. Cerebral palsy is the leading cause of sarcopenia in children[8,17,18]. Injury to the descending pathways from the central nervous system (CNS) results in paresis or a reduction or failure of voluntary activation of skeletal muscle, as well as failure of inhibition, resulting in movement disorders such as spasticity, spastic dystonia, and spastic

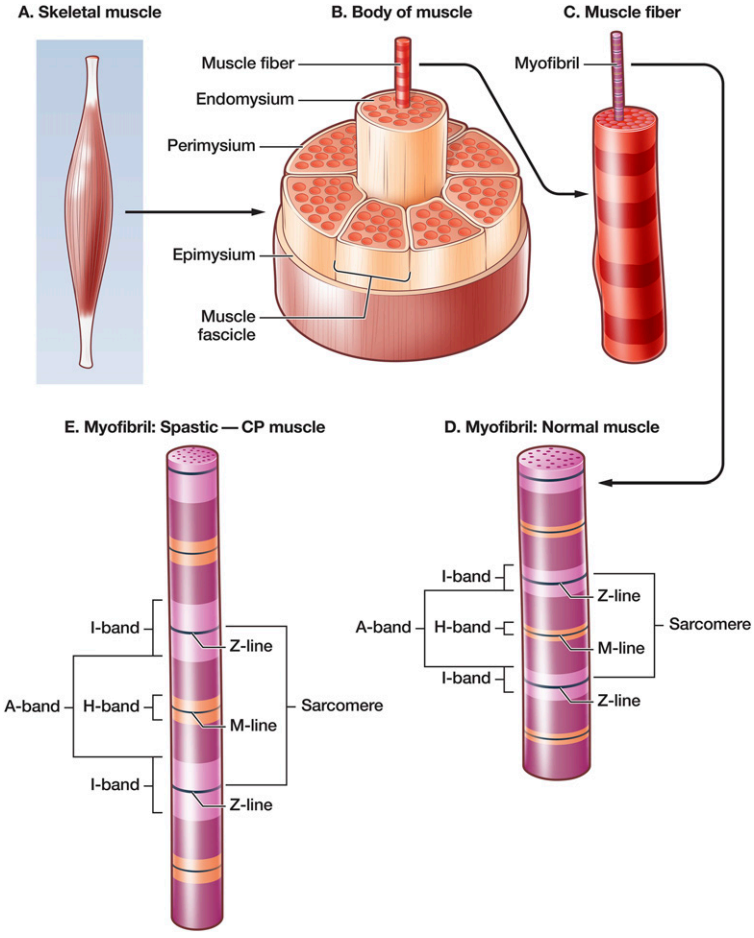

Fig. 1

Figs. 1-A through 1-E Muscle morphology. **Fig. 1-A** A generic muscle tendon unit is depicted. **Fig. 1-B** Surrounded by the epimysium, the whole muscle belly comprises bundles of muscle fibers known as fascicles. Each fascicle is surrounded by the perimysium with its collagen-based matrix. **Fig. 1-C** Muscle fibers are comprised of bundles of myofibrils, and each fiber is surrounded by endomysium. Epimysium, perimysium, and endomysium are collagen-based noncontractile elements that are increased in children with cerebral palsy and may contribute to fixed muscle contractures. **Fig. 1-D** Myofibrils are subcellular organelles of sarcomeres that are arranged longitudinally in series. These are the basic contractile units of muscle, each containing actin and myosin myofilaments that slide over one another during muscle contraction. Under microscopy, sarcomeres are delineated by alternating "bands," with the A-band containing the thick myosin myofilaments, the H-band where there is no actin-myosin overlap, and the I-band containing the actin myofilaments alone. The M-line is a dense zone in the center of the A-band. The Z-line bisects the I-band, delineating the sarcomere. In this illustration, the H-band is narrow, suggesting increased actin-myosin overlap and a shortened sarcomere (as occurs during muscle contraction). Not shown are satellite cells (muscle stem cells that are responsible for regeneration of myotubules and thus muscle repair), which are known to be decreased in number in children with cerebral palsy. **Fig. 1-E** In spastic muscle, sarcomere length is increased, and there is less overlap between actin and myosin with broader I-bands and H-bands. Overstretched sarcomeres are a major contributor to the weakness of muscle in children with CP (cerebral palsy).

cocontraction[18]. In recent years, there has been an increasing emphasis on the changes in skeletal muscle, which is envisaged as the "end organ" that is affected by the CNS lesion of cerebral palsy[17,18]. In children with cerebral palsy, abnormalities in skeletal muscle include decreased muscle thickness and volume[8], decreased moment-generating capacity[19,20], and weakness[21]. Barrett and Lichtwark reported reduced muscle-belly length, muscle volume, and cross-sectional area in paretic muscles when compared with nonparetic muscles[22]. Mathewson and Lieber published an extensive review on the pathophysiology of contractures in patients with cerebral palsy, including detailed descriptions at both the macroscopic and microscopic levels in terms of structure and muscle biomechanics[23]. Key findings included changes in sarcomere length, fiber type, bundle stiffness, extracellular-matrix (ECM) concentration, and stem-cell numbers[23]. The reasons for muscle weakness in children with cerebral palsy may be grouped into 3 main categories: loss of muscle mass, reduced contractile material with more connective tissue and fat, and overstretched sarcomeres[8,17,21-23].

Reduction in muscle volume may be recorded as early as age 15 months in the gastrocnemius of toddlers with cerebral palsy[24]. In early development, the volume of the calf muscle in children with cerebral palsy can be up to 22% smaller by preschool age, increasing to a deficit of 45% in young adults[25]. With time and growth, substantial volume deficits have been recorded in 9 major lower-limb muscle groups, with greater deficits in distal muscles compared with proximal muscles[25]. Coupled with consistent findings of reduced muscle-belly length, cerebral palsy can be described as "short/small muscle" disease[8,24,25]. Despite this evidence, management of spasticity commands a higher priority than management of weakness in most cerebral palsy management programs[8,18,26,27].

At the ultrastructural level, skeletal muscle is composed of both contractile (actin and myosin) and noncontractile tissue (mainly collagen)[18,28]. The contractile tissues, or muscle fibers, are responsible for generating moments that result in the movement of joints and functional activities such as gait. These fibers are comprised of bundles of myofibrils: subcellular organelles of long serially arranged sarcomeres, each containing actin (thin) and myosin (thick) myofilaments that slide over one

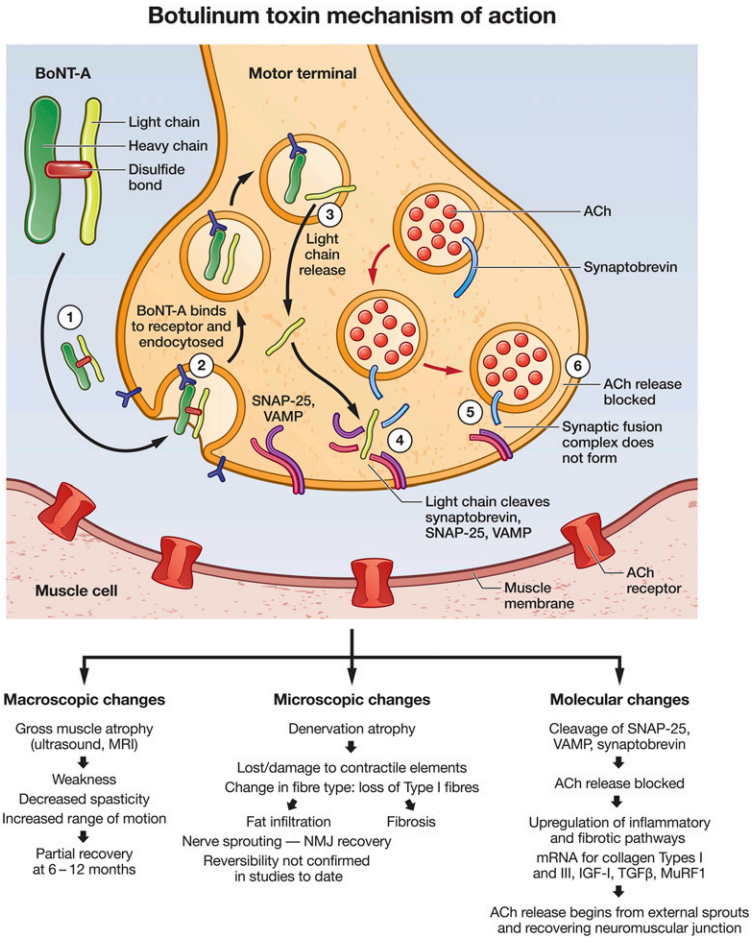

Fig. 2

BoNT-A is a potent neurotoxin comprised of a heavy chain and a light chain that are linked by a disulfide bond (1). The heavy chain binds with high affinity to receptors on the cholinergic nerve terminal, and the intact neurotoxin molecule is endocytosed (2). The disulfide bridge bond is broken and the light chain is released (3), affecting a series of intrasynaptic proteins. SNAP-25 (synaptosomal nerve-associated protein 25) is cleaved first (4), destabilizing the SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) complex (including synaptobrevin, SNAP-25, and VAMP [vesicle-associated membrane protein]) (5), which is responsible for mediating the fusion of neurotransmitter-containing vesicles with the synaptic membrane. This effectively blocks the release of the neurotransmitter acetylcholine (ACh) (6), resulting in "chemodenervation" of skeletal muscle. The recovery of neurotransmission occurs gradually with axonal sprouting and partial recovery of the original neuromuscular junction (NMJ). IGF-I = insulin-like growth factor 1, TGFβ = transforming growth factor beta, and MuRF1 = muscle RING-finger protein-1. (Reproduced, with permission, from Multani I, Manji J, Hastings-Ison T, et al. Botulinum toxin in the management of children with cerebral palsy. Pediatr Drugs. Epub 1 July 2019. https://doi.org/10.1007/s40272-019-00344-8).

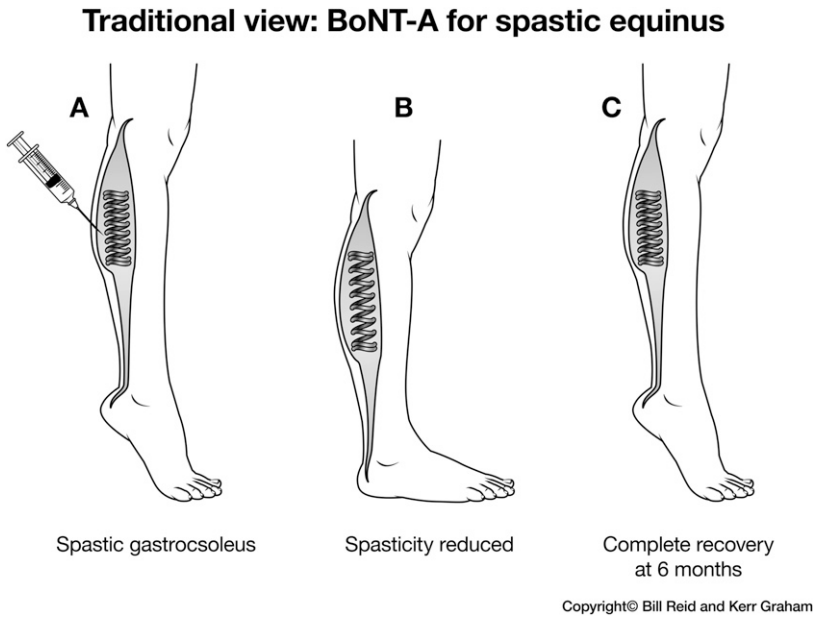

Fig. 3

Figs. 3-A, 3-B, and 3-C The traditional view of an injection of BoNT-A for spastic equinus. **Fig. 3-A** The ankle is in equinus because of spasticity in the gastrocnemius-soleus complex muscle, illustrated graphically with the muscle containing a tight spring. In patients with cerebral palsy, muscles can be described as being "spring-loaded" because of spasticity and increased stretch reflexes. **Fig. 3-B** After injection, the muscle/spring is relaxed. This is usually accompanied by a reduction in the Modified Ashworth Scale (MAS) measurement and sometimes improvements in ankle dorsiflexion. **Fig. 3-C** After 3 to 6 months, the effects of the injection wear off completely, and the muscle returns to the preinjection size and level of spasticity (as shown, the spring is tight again). The injection of BoNT-A is repeated until fixed contracture develops. (Reproduced, with permission, from Multani I, Manji J, Hastings-Ison T, et al. Botulinum toxin in the management of children with cerebral palsy. Pediatr Drugs. Epub 1 July 2019. https://doi.org/10.1007/s40272-019-00344-8).

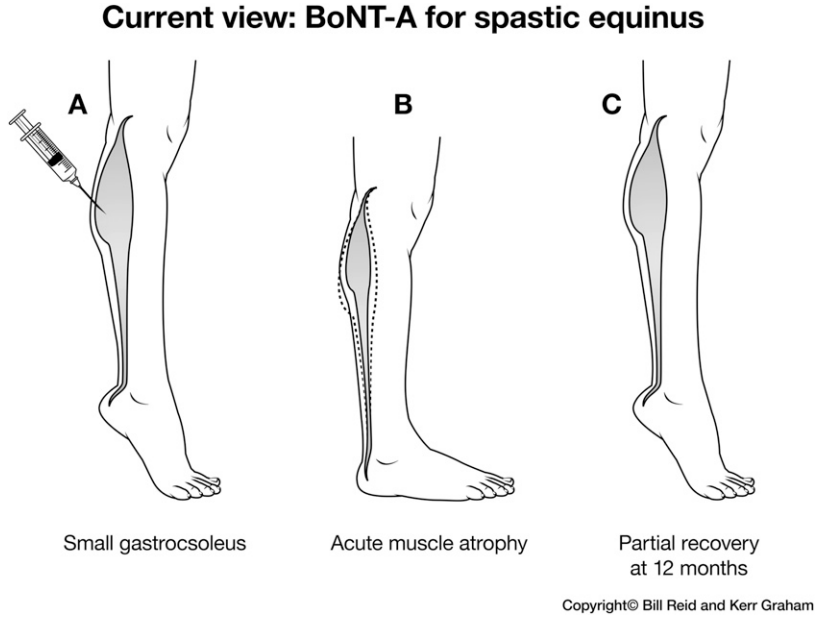

Fig. 4

Figs. 4-A, 4-B, and 4-C The current view of injection of the gastrocnemius-soleus complex for spastic equinus. **Fig. 4-A** As part of the natural history (from studies that are based on ultrasonography), before the injection, the gastrocnemius-soleus complex is small and atrophic. Injection of BoNT-A results in acute chemodenervation and further muscle atrophy. **Fig. 4-B** The muscle atrophy and weakness results in a reduction in the MAS measurement and sometimes an increase in ankle dorsiflexion. **Fig. 4-C** At 12 months after injection, there is incomplete recovery in muscle size, morphology, and function. The duration of the effects of a single injection cycle and the upregulation of fibrotic pathways at the molecular level are not known in either experimental animals or children with cerebral palsy. (Reproduced, with permission, from Multani I, Manji J, Hastings-Ison T, et al. Botulinum toxin in the management of children with cerebral palsy. Pediatr Drugs. Epub 1 July 2019. https://doi.org/10.1007/s40272-019-00344-8).

another during muscle contraction[29]. The contractile elements are highly metabolic and contribute to metabolic balance in the body. The noncontractile tissue, including the ECM, is mostly collagenous, both within the muscle structure and condensed into aponeuroses and tendons (Fig. 1). Collagen-based ECM has been implicated as one of the primary factors that is associated with the development of static muscle contractures in patients with cerebral palsy[30-35]. Given that children with cerebral palsy often reach adult life with substantial impairments in the volume and functional capacity of important muscles, they are at greater risk of developing age-related sarcopenia than typically developing individuals, and they have a concomitant loss of functional capacity at an earlier age[8,18,26]. Up to 75% of individuals with cerebral palsy who were mobile as children eventually stop walking as adults[36]. Information from gross motor curves and Gross Motor Function Classification System (GMFCS) descriptors also show age-related functional decline that is typified by an increased need for assistive devices and wheeled mobility[37]. These observations have led to the adoption of the term "accelerated musculoskeletal aging" as a hallmark of the phenotype of individuals with cerebral palsy over their life span[8,17,18,26].

The Effects of Injection of BoNT-A in Mammalian Skeletal Muscle

Injection of BoNT-A in mammalian skeletal muscle is followed by rapid binding of the heavy chain to cholinergic nerve terminals with internalization of the light chain into the muscle cell[38] (Fig. 2). Once inside, the light chain cleaves a series of intrasynaptic proteins that are responsible for mediating the fusion of neurotransmitter-containing vesicles with the synaptic membrane. This effectively blocks the release of the neurotransmitter acetylcholine, resulting in a "chemodenervation" of skeletal muscle[38-41]. Individual muscle fibers are unable to contract during the effects of BoNT-A-induced paralysis. However, the course is partly reversible by 2 processes: axonal sprouting resulting in reinnervation of the muscle and eventual recovery of the "poisoned" neuromuscular junction[39].

The recovery of skeletal muscle following injection of BoNT-A was widely studied in animal models 20 to 30 years ago, and, at that time, it was considered to be fully reversible[39] (Fig. 3). Therefore, BoNT-A was widely promoted as a safe and effective focal spasticity treatment that, even if not effective, would do no harm[8,41,42]. Unfortunately, more recent studies have suggested that this is not the case and that muscle recovery following injection of BoNT-A is partial and incomplete (Fig. 4). Furthermore, there is little evidence for a specific "antispastic" effect. The primary effect of BoNT-A is to promote chemodenervation and acute muscle atrophy[43].

Sarcopenia and Muscle Atrophy Following Injection of BoNT-A in Typically Developing Adults

In 2009, a randomized clinical trial (RCT) on the effects of BoNT-A injection into the calf muscle in typically developing adult volunteers was reported. The lateral head of the gastrocnemius was injected either with a standard clinical dose of BoNT-A or with normal saline solution[43]. The outcome was studied with MRI scans at 3, 6, 9, and 12 months after injection and a muscle biopsy at 12 months after injection. At 3 months after the injection, an abnormality of the high signal intensity pattern (HSIP) in the MRI STIR (short tau inversion recovery) sequence and a reduction of muscle cross-sectional area were identified, which ranged from 81% to 86% of the initial cross-sectional area when compared with the contralateral control muscle. These changes also were apparent at 6, 9, and 12 months following the injection. Histopathology revealed neurogenic atrophy of small groups of muscle fibers that amounted to 30% in the BoNT-A-injected muscle. There also were increases in the number of perimysial fat cells and the amount of connective tissue surrounding the atrophic muscle fibers[43].

In a more recent study using serial MRI scans, 46% to 48% atrophy of the procerus muscle was demonstrated after a single dose of BoNT-A, which was still present at 12 months after injection, long after the clinical effect had worn off[44]. In another study using serial MRI scans, changes to the piriformis muscle were studied prospectively following injection of BoNT-A for piriformis syndrome. Serial MRI scans showed muscle atrophy and fatty infiltration[45]. All 3 of these studies share a common finding: intramuscular injection of BoNT-A in standard therapeutic doses resulted in acute muscle atrophy with deficits that were evident on MRI scans at the 12-month follow-up, long after the clinical effects had worn off[43-45].

Sarcopenia and Muscle Atrophy in Experimental Animal Studies

A number of small mammals have been studied to elucidate the effects of injection of BoNT-A[46]. In 2011, Fortuna et al. reported changes in the contractile properties of the quadriceps muscles in New Zealand white (NZW) rabbits following injection of BoNT-A[47]. Their principal findings included an acute reduction in muscle mass to 80% and 64% at 3 and 6 months after injection, respectively, with contractile material replaced largely by fat. Similar but less-pronounced results were reported in the contralateral noninjected limb[47]. In 2013, the same research team investigated whether skeletal muscles recover following repeated injections of BoNT-A[48]. They reported that neither the injected nor the contralateral noninjected muscles had recovered by 6 months after injection[48]. In 2015, the same research team reported that muscle strength and contractile material had not recovered by 6 months after BoNT-A injection. In addition, the messenger (m)RNA expression phenotype remained altered in favor of fibrotic response molecules[9]. The authors concluded that BoNT-A-induced weakness and muscle atrophy

lasts much longer than had been previously thought. As such, they advised caution in treating the skeletal muscles of children with cerebral palsy, which are already grossly abnormal. In 2018, this same team reported mRNA elevation for inflammatory molecules, proteinases, adipokines, and mesenchymal stem cells (MSCs) after BoNT-A injection, theorizing that these molecules and cells contributed to a lack of muscle recovery and promoted the development of fatty tissue infiltration[49] (Fig. 2). In addition, the extent of mRNA expression increased as the number of injections increased, suggesting a dose-dependent response. Given these findings, the authors expressed additional concern regarding the long-term effects and possible complications after BoNT-A injections in children with cerebral palsy.

In 2017, another research team injected the triceps surae in Sprague Dawley rats[50]. BoNT-A was injected into the medial gastrocnemius, the lateral gastrocnemius, and the soleus. The rats were studied extensively with a combination of techniques, including gait pattern analysis, image analysis (including synchrotron-radiation x-ray tomographic microscopy [SRXTM]), and molecular studies (including RNA extraction and real-time polymerase chain reaction [PCR] analysis with complementary cDNA synthesis). The effects of the injection included a deterioration in the gait pattern of the rats at 3 weeks after injection, characterized by external rotation of the ankle joint, a flat-footed gait, and a decreased stride length. At the ultrastructural level, damage was noted to both fibrillar and nonfibrillar structures. The volume fraction of fibrillar (i.e., contractile) tissue was reduced significantly, while the nonfibrillar (i.e., mostly collagen-based) tissue was significantly increased and was accompanied by a loss of linear structure of muscle tissue ($p < 0.05$). Upregulation of the inflammatory marker interleukin-6 (IL-6) further suggested the presence of an acute inflammatory response following muscle injury. The authors' interpretation of the results was that molecular changes reflected increased collagen synthesis as a result of BoNT-A-induced muscle damage rather than denervation. They speculated that repeated injections with BoNT-A may have unwanted and irreversible effects that potentially outweigh any positive benefits[50].

In 2015, Minamoto et al. reported a 50% reduction in muscle torque after a single injection of BoNT-A in a rat model and a 95% reduction in torque after a second injection 3 months later[51]. The same group reported recovery of muscle size but not contractile function at 12 months after a single injection of BoNT-A[52].

Despite targeting different muscles in different animal models and using different combinations of biomechanical, morphological, imaging, and molecular techniques, the results of the 3 research teams described above are broadly similar. Injection of BoNT-A results in acute muscle atrophy, reduction in torque, damage at the ultrastructural level, and loss of contractile function and induction of fibrosis[47-52] (Fig. 2). It is not known how long the gross morphological changes or the molecular changes last, but the changes would seem to exceed the expected clinical duration of benefit by a substantial margin. These studies should raise concerns for clinicians who inject BoNT-A and for all clinicians who counsel parents of children who are affected by cerebral palsy[8,18,26].

Sarcopenia and Muscle Atrophy in Children with Cerebral Palsy

The introduction of BoNT-A as a therapeutic agent may be unique in the history of drug development in that the majority of clinical trials have been conducted by clinical investigators, with a dearth of relevant clinical data provided by the manufacturers of the various BoNT-A preparations[27,53]. For example, experimental work in animals suggesting a functional recovery of endplate function by 6 to 12 weeks after injection led to early recommendations supporting repeat BoNT-A injections for various clinical conditions every 3 months[54]. In the only 2 RCTs to date of injection frequency in children with cerebral palsy, both studies confirmed that injection of the gastrocnemius-soleus complex for spastic equinus was as effective when performed once per year compared with 3 times per year (every 4 months)[55,56].

Despite the widespread use of BoNT-A injections in ambulant children with cerebral palsy, the study of changes after injection has largely been confined to measures of spasticity, such as the Modified Ashworth Scale (MAS) or the Modified Tardieu Scale (MTS). In a recent large international multicenter trial, the MAS was used as the primary outcome measure[57]. The MAS is a surrogate outcome for the measurement of spasticity. It should not be accepted as a primary outcome measure because of its poor correlation with meaningful functional measures such as gait and function[58]. Fewer studies have reported functional outcomes (including changes in gross motor function and gait) after BoNT-A injection[58,59]. Similarly, very few studies have investigated changes in muscle volume, changes in muscle strength, or changes in muscle ultrastructure or molecular events after BoNT-A injection in children with cerebral palsy. The historical context is important. The ability to image muscles in children without ionizing radiation had not been developed when BoNT-A was first released[12,13]. Knowledge regarding the small size of muscles in children with cerebral palsy at that time also was rudimentary. Muscles in children with cerebral palsy were known to be short, but little was known about size[8,25,26].

BoNT-A and Acute Changes in Muscle Morphology in Children with Cerebral Palsy

In 2013, using serial MRI scans, Van Campenhout et al. demonstrated 20% atrophy of the psoas muscle following injection of BoNT-A. Six months after injection, the muscle atrophy was still present on the final MRI scan. Given the short-term follow-up, it is not known if

or when the muscle atrophy might have resolved[60].

Also in 2013, Williams et al. demonstrated a 5% reduction in gastrocnemius volume with serial MRI scans in children with cerebral palsy after a single injection of BoNT-A in the gastrocnemius[61]. However, this decrease was accompanied by a 4% increase in the volume of the soleus muscle, which may have been a compensatory phenomenon. In 2018, the same group reported a 7% reduction in gastrocnemius muscle volume after injection of BoNT-A at 25 weeks after injection[62]. Although the volume of the plantar flexors was maintained by hypertrophy of the soleus, this cannot be taken as reassuring. Injections for equinus gait in many centers include the injection of the gastrocnemius and the soleus, with injections repeated every 4 to 6 months[18,53]. With a combination of small numbers and short-term follow-up, these studies do not provide robust evidence for safety.

The reduction in muscle volume in these clinical studies is much less than in both previously described groups (typically developing adults and animal models). Nevertheless, given that children with cerebral palsy are subjected to intramuscular injections of BoNT-A several times per year throughout childhood, the smaller degree of acute muscle atrophy cannot be taken as completely reassuring[18,53].

The traditional view of BoNT-A therapy was that injection resulted in a reduction in spasticity in the injected muscle, with full recovery of muscle function at 3 to 6 months following the injection (Fig. 3). Unfortunately, the effects of BoNT-A are much less precise. The current view, supported by the evidence in this review, is that injection of BoNT-A is followed by acute muscle atrophy, reduction in hypertonia and strength, decreased muscle stiffness, and increased range of motion in the distal joints (e.g., ankle dorsiflexion) (Fig. 4). Most studies report improvement in measures of spasticity with the MAS or the MTS[57]. However, these are surrogate measures rather than valid or reliable measures of gait or function[18,27,56,58]. In terms of outcome measures that are meaningful to patients, the desired effects are both temporary and small[59]. When gold standard measures of function such as the Gross Motor Function Measure (GMFM) are utilized, some RCTs report no improvements[63]. In studies utilizing gait analysis, improvements in targeted muscle function are frequently recorded, including increased ankle dorsiflexion and improved foot contact following BoNT-A injection for spastic equinus[64,65]. However, most studies have relied on observational gait analysis or video recordings of gait (supplemented by rating scales such as the Physician Rating Scale [PRS] or the Edinburgh Visual Gait Score [EVGS]) rather than a full 3D gait analysis (3DGA)[66,67]. There are a relatively small number of studies utilizing 3DGA and, to our knowledge, only 1 study in which an overall measure of gait function, the Gait Profile Score (GPS), has been reported[58]. Selective reporting of gait parameters such as increased ankle dorsiflexion is not sufficient given that this may be achieved at the expense of diminished knee extension (i.e., impaired plantar flexion, knee extension coupling).

Given that the benefits of BoNT-A injection are so small and so short-lived, it would be reasonable to question its therapeutic value. From very early childhood, skeletal muscles in the ambulant child with cerebral palsy are smaller than in typically developing peers, and progressive sarcopenia is noted by early adult life[17,25]. Any intervention that further increases sarcopenia and reduces skeletal muscle reserves must be viewed with concern[26]. In this regard, the clinical study designs have been lacking by focusing almost entirely on a single BoNT-A injection cycle. This may be the reason for the false sense of safety in the literature to date[60-66]. Sarcopenia and injection-related fibrosis will only become clinically apparent at long-term follow-up. To our knowledge, there are no such studies in the literature to date, and they are urgently needed. Until then, BoNT-A should be used with caution and there should be consistent monitoring of muscle volume and strength until it can be demonstrated that the long-term benefits outweigh the risks. As a simple starting point, injection frequency should be reduced to once every 12 months rather than the current widely used 4 to 6 monthly injection protocols, as supported by the only 2 clinical RCTs to date[55,56]. This approach is also in accordance with the animal studies that have been discussed above.

If there is a persistent small but cumulative deficit in skeletal muscle volume, morphology, and function with each repeat injection of BoNT-A, there is the possibility that a slow and insidious reduction in function in key muscle groups (e.g., the gastrocnemius-soleus complex) will surface. More than 50% of gastrocnemius-soleus complex moment-generating capacity is required during normal gait, and the deficits in older children with cerebral palsy have been shown to be nominally in the region of 40% to 60%[25,26]. Thus, there is no reserve available to allow for any additional deleterious effects on muscle function to occur. Accordingly, in the effort to achieve "foot flat" during gait by injection of BoNT-A for spastic equinus, an increase in dorsiflexion at the ankle may be accompanied by an increase in knee flexion, crouch gait, and a decrease in overall gait function as measured by a global kinematic index (e.g., the GPS)[58].

Sarcopenia Is Accompanied by Osteopenia in Animal Models

The relationship between muscle and bone has been extensively explored in recent years, and injection of BoNT-A has become a standard model in animal studies to investigate disuse osteopenia. Animal studies utilizing this disuse model demonstrate that BoNT-A-induced paralysis precipitates an acute profound catabolic effect on the neighboring bone, with prolonged and incomplete recovery of bone density following the return of muscle function[68-70]. The

cause-and-effect relationship between muscle and bone is based on 2 consistent findings in recent studies. First, loss of bone mass is preceded by the onset of BoNT-A-induced muscle paralysis, and, secondly, return of bone mass is preceded by recovery in muscle function. Thus, any factor that compromises muscle function, such as injection of BoNT-A, will confer a deleterious effect on adjacent bone in animal models. We are not aware of any clinical studies on BoNT-A-associated osteopenia in children with cerebral palsy, but these are clearly needed.

Overview

We should focus on interventions that increase the volume, the strength, and the reserves of skeletal muscle in children with cerebral palsy. These may include strengthening programs, enhanced nutrition, and novel molecular therapies that have not yet been developed[17,26,71]. In the meantime, children with cerebral palsy will develop fixed contractures with or without prior injections of BoNT-A, and surgical correction of fixed deformities will be needed for the foreseeable future. In 1 study, gastrocnemius recession was associated with an increase in calf muscle volume at 12 months after surgery[72].

Given the short-term follow-up in studies to date, it is not known if complete muscle recovery ever occurs after injection of BoNT-A in terms of gross muscle morphology[60-62]. The corresponding duration of the upgraded inflammatory and fibrotic pathways in both children with cerebral palsy and in experimental animals is also unknown at this time[47-52]. Additional studies are required, and caution is needed with the administration of BoNT-A. We acknowledge the role of BoNT-A as a temporizing measure. However, therapeutic benefit must be balanced against long-term sarcopenic effects, and the necessity of BoNT-A injections must be reviewed continuously throughout treatment. For children who are enrolled in regular injection programs, we suggest that measurement of muscle volume at baseline and at intervals throughout the injection schedule should be performed to identify and limit potential loss of muscle function[73,74]. Novel therapies to limit contracture development also are required, and injections of collagenase have been proposed as one such therapy[75].

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