Chapter 7
Botulinum Toxin Treatment in Multiple Sclerosis

Abstract According to the latest data from the National Multiple Sclerosis Society (2019) nearly one million people live in US with this disease annually. The disease process destroys the nerve fibers in the spinal cord and brain myelin substance resulting in motor and sensory problems. Injection of botulinum toxins into the stiff muscles of patients with multiple sclerosis reduces the muscle tone and improves muscle function. In patients with bladder dysfunction, injection of botulinum toxins into the wall of the bladder decreases abnormal urges to urinate and regulates bladder function. Involuntary and painful muscle spasms in MS patients, can be subdued by injection of botulinum toxin into the affected muscles.

Keywords Multiple sclerosis · Botulinum toxin · Overactive bladder · Neurogenic bladder · Spasticity · Muscle spasms

Introduction

World-wide, multiple sclerosis affects over three million people and is considered the most common cause of disability in the young [1]. In 2019, a study funded by National Multiple Sclerosis Society reported that approximately one million people affected by multiple sclerosis live in US [2]. The people in the north of US living in colder climates, women and whites are more affected than others. The estimated total economic burden of MS in US was $85.4 billion in 2019, with a direct medical cost of $63.3 billion and indirect and nonmedical costs of $22.1 billion. The average per-person annual medical costs was $65,612 [3].

In the late nineteenth century, a famous French neurologist by the name of Charcot was the first to describe, in detail, the symptoms and the pathology of multiple sclerosis. Multiple sclerosis damages both motor and sensory nerve fibers. Motor fibers originate from brain cells and go to the muscles while the sensory fibers convey sensations from skin to the brain. These nerve fibers normally have a protective sheath on their surface that enhances the conduction of electrical signals flowing in them both away and towards the brain. This sheath of tissue that covers

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the nerves is composed of a specific fat called myelin. Multiple sclerosis is, therefore, considered one of the diseases that specifically destroys myelin and, hence, called a demyelinating disease. Loss of myelin leaves scars in the brain and/or spinal cord and slows the nerve conduction. These scars (plaques) are easily detectable by modern imaging techniques such as Magnetic Resonance Imaging (MRI). Currently, MRI is the most useful diagnostic device used to confirm or support the diagnosis of multiple sclerosis (Fig. 7.1). The scars or plaques (areas of lost myelin) of MS are often multiple and occur at different levels of the central nervous system within the brain and/or spinal cord (multiple sclerosis). One can also use the changes that takes place in the composition of the cerebrospinal fluid (CSF) to confirm the diagnosis of MS. Cerebrospinal fluid is produced in the brain and flows inside the

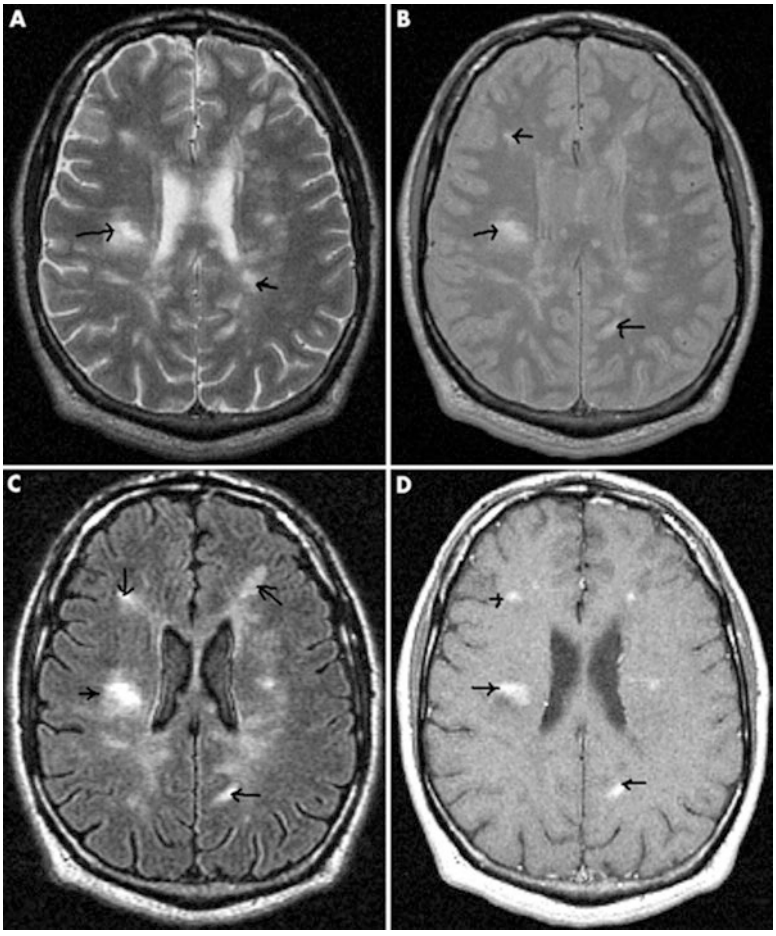

Fig. 7.1 Multiple brain lesions in a patient with multiple sclerosis. The lesions, white patches, marked by arrows in the brain slices on MRI, represent abnormal areas of the brain devoid of myelin. (From Trip and Miller 2005, reproduced with permission from publisher (BMJ group) [4])

spinal canal, all the way from the upper neck to the low back area. To test CSF, a small amount of this fluid is removed for examination by a procedure called spinal tap. For spinal tap, after numbing the skin, a needle is placed at midline between two low backbones (vertebral bodies) in the lumbar area. In most patients with MS, examination of CSF shows an elevation of certain specific proteins (immunoglobulins).

Multiple sclerosis can cause a variety of symptoms depending on the location of the lesions [5]. A large number of patients complain of motor symptoms, such as sudden weakness or even total paralysis of one limb. Others may have sensory symptoms, often described as tingling and numbness affecting some part of the body. Sudden onset of diminished or even total loss of vision in one eye is also a frequent complaint. Symptoms of MS fluctuate in intensity, disappear and reappear over time. In chronic cases, plaques accumulate in the brain or/and spinal cord and lead to permanent loss of function.

The cause of multiple sclerosis is still not fully understood. In current scientific thinking, multiple sclerosis is defined as an "autoimmune disease". Our immune system normally protects us against germs like viruses or bacteria. When body is exposed to foreign invaders, immune system sends a group of fighter cells to attack and destroy the invaders. Usually, the immune system can differentiate between one's own cells and foreign cells. In an autoimmune disease, the immune system mistakenly attacks the cells and organs of one's body. The damage to nervous system in multiple sclerosis is believed to be due to an immune disorder which is associated with an abnormal reaction of lymphocytes (certain blood cells).

In the past two decades, significant strides have been taken to find drugs that work against these immune reactions while aiming to arrest progression of MS and prevent appearance of new lesions in the brain and/or spinal cord. Several newly discovered drugs have succeeded to slow the course of multiple sclerosis and prevent appearance of new lesions in the central nervous system. The most successful of these are drugs known as disease modifying antibodies (DMA). Several of these drugs are now FDA approved; Alemtuzumab, Ofatuzumab and Ublitucimab seems to be the most effective among DMAs. These drugs can slowdown progression of MS and, in many cases, prevent appearance of new lesions in the brain and spinal cord. Unfortunately, DMAs are very expensive costing a sum of $ 34,000 per person per year [3]. Furthermore, despite their effectiveness, still a large number of patients with MS are left with permanent disabilities due to multiple damages sustained within brain and spinal cord over years. Among these disabilities, stiffness of muscles (spasticity) and/or dysfunction of bladder can significantly impair the patients' quality of life. As discussed in Chaps. 6 (stroke and spasticity) and 10 (botulinum toxin therapy in bladder dysfunction), botulinum toxin injections have a significant potential to improve spasticity and bladder dysfunction regardless of the cause.

Botulinum Toxin Treatment of Spasticity in Multiple Sclerosis

In multiple sclerosis, similar to other disease conditions that damage the brain and spinal cord (stroke, trauma), muscles gradually weaken and show increased tone, become stiff and spastic. In many patients with MS, this spasticity can be quite severe and can interfere with the activities of daily living. The spastic muscle often remains contracted resulting in impaired timing and precision of movements. Using fingers and hands for eating, washing, shaving, dressing and any other fine movements becomes exceedingly difficult. In the lower limbs, spasticity adds to weakness and impairs balance. Adductor muscles of the thigh (muscles that bring the thighs together) often show marked spasticity in multiple sclerosis [5]. As a result, sustained contraction of these muscles keeps the thighs stiffly together, a position that impairs normal leg movements and disrupts ambulation. The affected patients complain of poor balance and frequent falls. In women, severe adductor spasticity can lock the thighs together, interfere with sex and disrupt urination.

As time goes by, the spastic muscles become painful to move. The ensuing immobility leads to replacement of muscle fibers by non-elastic tissue, a condition that is termed contracture. Muscles affected by contracture are often shortened and non-functional.

The drugs that treat spasticity including baclofen, tizanidine and valium often have undesirable side effects such a confusion and sedation. In severe cases of spasticity, especially if it predominantly involves the legs, baclofen can be delivered to the body through a baclofen pump. Use of baclofen pump is an involved procedure requiring insertion of a catheter into the spinal canal through which baclofen is continuously delivered into the spinal fluid. The procedure requires collaboration between an expert neurosurgeon, neurologist and a trained nurse who could do careful titration of the drug. Miscalculations can lead to overdosing, leading to serious complications such as suppressed level of consciousness and seizures. Other severe cases of spasticity can be treated by injection of phenol into the nerve that supplies the tight and spastic muscles. Phenol injections are effective but reserved for very severe cases when all other means fail since such injections destroy the nerve permanently. Pharmacological treatments of spasticity are usually combined with physical therapy that includes passive and active exercises. It is believed that 80% of the patients with multiple sclerosis will experience spasticity of muscles some time during their lifetime. In a large US registry of patients with multiple sclerosis, 72% of the patients demonstrated moderate to severe spasticity on examination [6].

Currently, four globally marketed botulinum toxins are approved by FDA for use in the US. Three of these toxins are type A (Botox, Xeomin and Dysport) and one toxin is type B (Myobloc-called Neurobloc in Europe). For detailed description of toxin types and information on toxin characteristics, the reader is referred to Chaps. 2 and 3 of this book. Although the units of these four toxins are not exactly comparable, the following approximations are used in clinical practice and clinical research: 1 unit of Botox = 1 unit of Xeomin=2.5 to 3 units of Dysport = 40–50 units of Myobloc.

Botulinum toxin treatment (with Botox and other toxin brands) provides a reasonable alternative to pharmacotherapy for moderate to severe spasticity of multiple sclerosis. In general, botulinum toxins have less side effects than anti-spasticity drugs. As described in more details in Chaps. 2 and 3 of this book, botulinum toxins decrease the tone of the muscle and relax it via blocking the release of acetylcholine at the junction of nerve to muscle. Acetylcholine is a chemical that upon reaching the muscles allows the electrical nerve signal enter to the muscle and activate it.

In 1990, Dr. Snow, a Canadian investigator and his colleagues reported that injection of Botox into the adductor muscles of the thigh (muscles that bring the thighs together) significantly reduced the spasticity and improved hygiene in seven out of nine patients with multiple sclerosis [7, 8]. A total of 400 units of Botox was divided among three thigh adductor muscles. Following this pioneering observation, several subsequent high quality studies with much larger number of patients (some in hundreds) have supported the value of intramuscular injection of botulinum toxins in reducing spasticity of muscles in multiple sclerosis [9–14]. Furthermore, long-term observations over several years have shown that repeated injections at every 3–4 months are well tolerated and the satisfactory effects continues over months and years of treatment. These studies have also shown the safety of botulinum toxin therapy for treating of MS-related spasticity. Comparative observations have shown that MS-related spasticity is as responsive as any other form of spasticity to the botulinum therapy and the effective dose per muscle in multiple sclerosis is comparable to that used for spasticity caused by medical conditions other than MS such as stroke, spasticity after brain and spinal cord trauma. For this reason, botulinum toxin therapy is now among the first lines of treatment for spasticity in multiple sclerosis.

Technique of Injection

The injection technique for spastic muscles in multiple sclerosis is very similar to what has been described in Chap. 5 for spasticity in stroke. The size of the muscle and the degree of tightness of the muscle determine the dose. The dose is delivered in units. In the upper limbs, for small muscles of the forearm and hand, the dose varies from 5 to 20 units per muscle, whereas, larger muscles (i.e. biceps) may require up to 100 units (for Botox or Xeomin, multiply by 2.5–3 for Dysport and by 40–50 for Myobloc.) Large muscles of lower limb (s) may require larger doses. For instance, severe spasticity of hamstring (the large muscle in the back of the thigh that flexes the knee) may require 150–200 units (Botox). The injecting needle is thin and short for upper limb muscles but longer needles may be required for larger muscles of the lower limb. Injections are delivered at two or three sites into the larger muscles, using anatomical landmarks for identifying nerve-muscle junctions where injections are most effective. For small muscles of the forearm (flexors of fingers or wrist) the muscle may need to be identified by electromyography (recording electrical activity of muscle), nerve stimulation or ultrasound.

Recent studies have shown that larger doses of Botox or Xeomin of up to 800 units, can be injected in one session (into 3–5 muscles), without any serious side effects [15, 16]. Side effects include local pain at the site of injection for a few minutes, minor transient bleeding, and a mild, transient flu like reaction experienced in 5–10% of the patients. It should be remembered that toxin preparation needs to be done by trained personnel and injections should be carried out by experienced injectors familiar with the muscle anatomy and proper technique of injection. Dose miscalculations can lead to serious side effects such as total paralysis and may endanger patient's life. The effect of botulinum toxin injection into spastic muscles becomes evident in 2–5 days and peaks at 2–3 weeks. The muscle relaxing effect of the toxin can last 3–4 months, and then, needs to be repeated for sustainability. This effect is to a large degree, dose dependent considering the size of the muscle and degree of muscle tightness. Long-term data, up to 15 injection cycles (every 3–4 months) are now available and attest to the safety of botulinum toxin therapy in multiple sclerosis [11, 14].

Case Report A 32 years-old female with multiple sclerosis was referred to the Yale Botulinum Toxin Clinic for treatment of severe spasticity of the thigh muscles. For several years, she had suffered from severe tightness of her thigh muscles, the overactivity of which pulled her thighs constantly together. This issue worsened during walking, and impaired her balance. Over years, she had also noticed more difficulty in urination. Oral medications provided modest relief.

On examination, the adductor muscles of the thigh, close to the groin (Fig. 7.2a) very very tight. She was injected with Botox into adductors—150 units/side at two points (Fig. 7.2b). After a week, she reported marked relaxation of her thigh

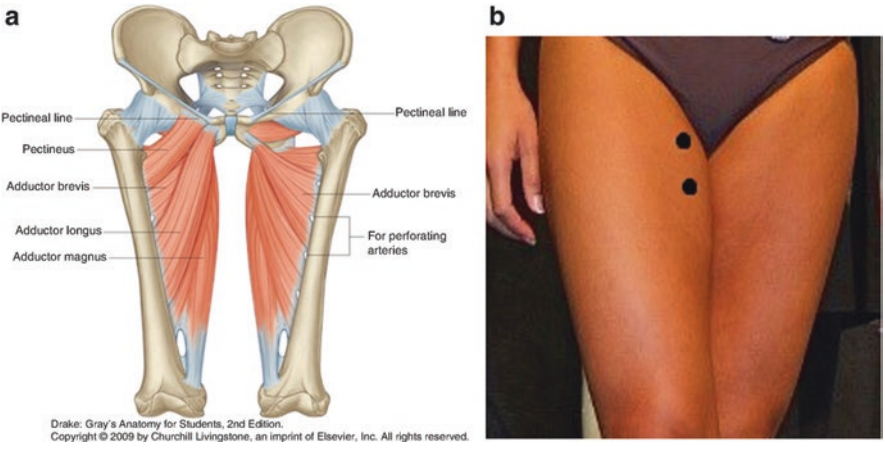

Fig. 7.2 (**a**) Three adductor muscles of the thigh that bring the thighs together; short (brevis), long (longus) and large (magnus) (From Drake Anatomy for students reproduced with permission from Elsevier). (**b**) Common sites of botulinum toxin injection for adductor muscle spasticity

muscles allowing her to stand and walk better with less fear of falling. Moving in bed became easier and she slept better. Movement of the thighs was no longer painful. Hygiene related tasks were carried out with more ease and comfort and her urination improved. The satisfactory effects of Botox lasted for 3 months. Repeated injection 3–4 months sustained relaxation of thigh muscles over a follow up period of 5 years.

Botulinum Toxin Therapy for Bladder Problems in Multiple Sclerosis

Many patients with multiple sclerosis develop a variety of bladder problems as the disease progresses. Bladder, as the organ of urine storage and emptying, functions mainly with three muscles. The major bladder muscle that controls storage and emptying functions of the bladder is called detrusor muscle. This muscle that spreads over nearly all of the bladder wall can expand during urine storage. When the volume of urine in the bladder reaches a certain level, sensory nerves of the bladder signal the bladder centers located in different parts of the brain (there are more than one) to tell the detrusor muscle to contract. Detrusor muscle contraction propels the urine against the hole in the lower part of the bladder through which the urine leaves the bladder. Two circular muscles, called sphincters, control the opening and closing of this hole. The one closer to the inside of the bladder is called inner and the one further out is called outer sphincter. Inner sphincter automatically relaxes after contraction of detrusor muscle. This relaxation is not under conscious control. The outer sphincter is under conscious control and can be relaxed by will, letting the urine out in an appropriate setting. A complex network of nerve cells located in the brain and spinal cord control the bladder function. As spinal cord nerve cells and nerve fibers are major contributors to the innervation of bladder, damage to the spinal cord in multiple sclerosis (with lesions similar to those seen in the brain), (Fig. 7.1) results in erratic and poorly timed contractions of the detrusor muscle with subsequent development of bladder symptoms. These symptoms include frequent urge to urinate and frequent urination as well as bed-wetting at night and urinary incontinence during the day. Poor emptying of the bladder predisposes the patient to development of bladder infections. In more severe cases, the urine can back up toward the kidney and cause kidney damage. This type of bladder dysfunction in MS is called neurogenic bladder i.e. a bladder problem that is related to damage to the nerve supply of the bladder.

According to National Multiple Sclerosis Society, bladder dysfunction occurs in at least 80% of patients with multiple sclerosis during the course of illness [17]. The symptoms of bladder dysfunction in MS include leakage of urine, urinary urgency, frequent urinations at night and urinary incontinence. What happens to the bladder muscle in MS is somewhat similar to what happens to the neuromuscular junction leading to muscle spasticity as described earlier in this chapter. The muscle (in this

case detrusor muscle of the bladder), after being weakened by damage to its nerve supply, gradually develops increased tone, and becomes overactive as in other muscles of body with spasticity. Since acetylcholine is also the chemical transmitter (from nerve ending) to the muscular layer of the bladder, injection of botulinum toxins into the bladder wall will subdue the bladder overactivity by reducing the effect of acetylcholine (see Chaps. 2 and 3 on mechanism of botulinum toxins function). The drugs that are used for control of bladder symptoms in MS are anticholinergics—Ditropan, Detrol—also work by reducing or blocking the effects of acetylcholine. The frequent side effects of these drugs such as blurring of vision, impaired memory and dryness of the mouth make them hard to tolerate especially when used for a long period of time.

In 2013, FDA approved the use of Botox for treatment of neurogenic, overactive bladder in multiple sclerosis based on the positive results of two large high quality, multicenter studies (DINGY studies) that investigated close to 700 patients with MS and spinal cord injury [18, 19]. A majority of the patients in these studies had multiple sclerosis. These studies have shown that injection of 200 units of Botox at multiple points into the bladder wall significantly improves the patients' urgency and incontinence as well as their quality of life. Patients also scored highly on a post-treatment satisfaction questionnaire confirming their satisfaction with the treatment.

The main side effect of botulinum toxin injections for bladder symptoms in MS is retention of urine which occurs in 25% of treated patients and may require daily, clean self-catheterization. For many patients with advanced MS, however, this is not problematic since they already have chronic urinary retention and have learned to catheterize themselves for months or years. Nevertheless, patients need to be alerted and trained for this side effect. However, some studies have found that with repeated injections of Botox (every 4–6 months) the incidence of urinary retention improves as time goes by. An analysis of 18 studies on 1553 MS patients in whom bladder dysfunction was treated with Botox injection into the detrusor muscle found sustenance of positive results after repeated injections and a low incidence of side effects [20].

More recently, high quality studies (double-blind and placebo-controlled) with other type A botulinum toxins (Dysport and Xeomin) have also shown efficacy in management of bladder dysfunction due to multiple sclerosis and traumatic spinal cord injury [21, 22]. It is likely that Dysport will soon receive FDA approval for treatment of the type of bladder dysfunction (neurogenic bladder) that occurs in patients with multiple sclerosis.

Injection Technique

Botox is marketed in a powder form stored in small vials. For all indications, it needs to be mixed with normal saline (salt water) before injection. Botox is very heat sensitive so it requires refrigeration. Botox vials marketed as 50, 100 and

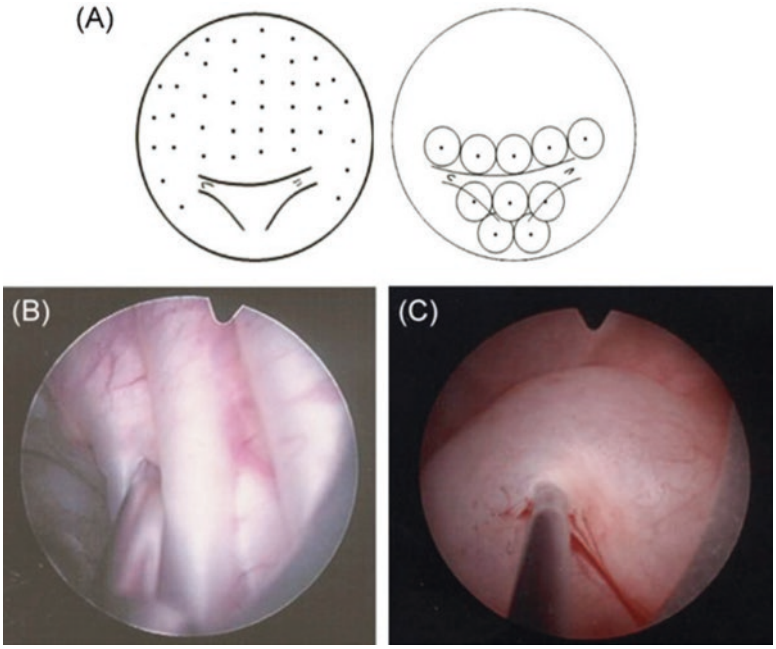

Fig. 7.3 Technique of bladder injection: (**A**) (top left) 30 injections for patients with severe symptoms, (top right) 10 injections for patients with mild symptoms (From Da Silva and coworkers. Toxicon 2015. Reproduced with permission from the publisher Elsevier). (**B** and **C**) site of injection just under the mucosa of bladder surface

300 units. A total of 200 units is recommended for treatment of overactive bladder in multiple sclerosis. Injections are carried out through a special instrument, cystoscope, that after entering the bladder can visualize inside the bladder via a small light. A hollow needle is attached to the cystoscope through which the injections are performed. The original FDA approved protocol calls for 30 sites of injections sparing the trigone (the lower, triangular par of bladder). Currently, however, different protocols are used at different institutions with the number of injection sites ranging from 20 to 40, including or not including bladder's trigone. Some authors, in patients with mild symptoms, only 10 sites including the tigone that is right in sensory nerves (Fig. 7.3).

Treatment of MS-associated Pain with Botulinum Toxins

Pain is a common symptom in multiple sclerosis. In one study, 63% of the patients with multiple sclerosis complained of chronic pain [13]. Among several types of pain in MS, three types are most frequent: neuropathic, pain associated with spasticity and tonic spasms.

Neuropathic Pain

Neuropathic pain has a burning, searing and jabbing quality; the most severe form of it involves the face in multiple sclerosis. Irritation of damaged nerve fibers that provide sensation to the face is believed to be the cause of facial pain in MS. The trigeminal nerve, the fifth of 12 nerves that exit the brain, provides sensation for the face, inside the mouth, the tongue and the throat. The pain is called trigeminal neuralgia (nerve pain related to the trigeminal nerve). Patients complain of severe bouts of pain lasting for seconds but recurring many times during the day. The most common type of trigeminal neuralgia, however, is seen in older individuals (>50 years of age) due to age related degeneration of this nerve. Trigeminal neuralgia is rare in young individuals. When it occurs in young individuals, one should think of MS. It can be seen in 1–3% of patients with multiple sclerosis [23].

Treatment of trigeminal neuralgia (TN) is difficult. Most patients are not happy with taking daily oral medications. High quality studies (double-blind, placebo-controlled) have shown that injection of Botox and other type A toxin (Chinese type A toxin: Prosigne) with a small and thin needle into skin of the face can alleviate the pain in classic trigeminal neuralgia that occurs in older patients [24–26]. Although no high quality studies are available with botulinum toxins for treatment of TN in multiple sclerosis, a retrospective observation in 31 patients with MS treated with Botox injections disclosed positive results [27]. In this observation, 52% of patients with MS and TN reported relief of facial pain after Botox injections versus 45% of the patients with primary TN (older individuals with no known cause).

How injection of botulinum toxin into and under the skin can help neuropathic pain (TN as an example) has been the subject of many investigations. It is now common knowledge based on both animal and human studies, that BoNTs not only inhibit the function of acetylcholine (nerve-muscle chemical transmitter), but also diminish the effect of a variety of chemicals that are essential for transmission of pain signals from skin to the brain [28–35]. Several of these neurotransmitters, such as substance P, glutamate, and calcitonin gene related peptide (CGRP) are now well known. Though still not approved by FDA for pain disorders (except for chronic migraine), botulinum toxin injection into and under the skin is now used by many clinicians for a variety of neuropathic pains such as pain associated with shingles, pain after limb trauma, heal pain of plantar fasciitis (common among runners) and other pain problems based on the published data from high quality studies [36–40].

Case Report

A 42 year-old women, with history of multiple sclerosis since age 18 with intermittent paralysis, sensory loss and visual symptoms, complained of intermittent severe facial pain. The pain involved the left side of the face and recurred many times daily. The episodes of pain were brief (lasting only seconds) but “brought tears to her eyes.” The pain was described as jabbing and burning. She was treated with several

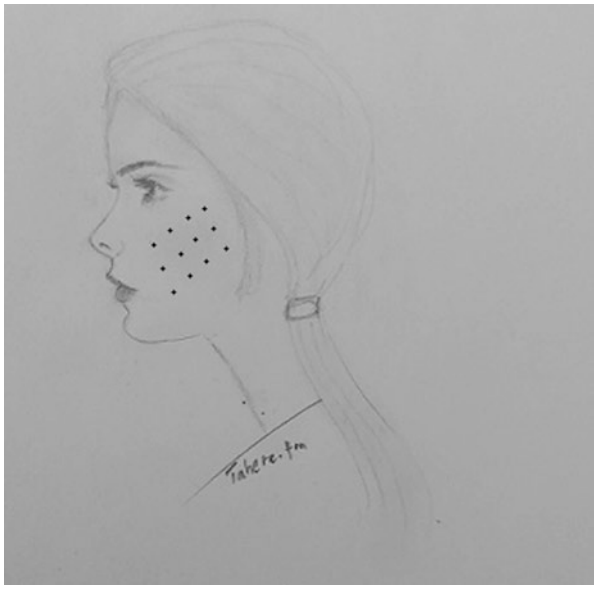

Fig. 7.4 Case report. Injections were carried out using a thin (gauge30), short needle and under the skin. (Drawing courtesy of Dr. Tahereh Mousavi)

medications including the commonly used drugs for trigeminal neuralgia; tegretol and gabapentin—that "did not help much". On the scale of 0 to 10, most of her pain episodes were described as 9 or 10 in severity. The pain occurred as many as 30 times per day. The MRI of her brain showed no abnormality to explain her facial pain. A neurological examination revealed no motor or sensory deficits. The affected area of the face was injected with Botox in a grid-like pattern, using a small thin needle. Injections were under the skin, 2.5 units per site at 12 sites (Fig. 7.4). She reported marked pain relief in a week post injection with the pain intensity dropping to 1–3 on a 0–10 scale. Repeated injections every 4 months had the same positive effect. No side effects were reported.

Pain Associated with Spasticity

As discussed earlier, stiff muscles in patients with multiple sclerosis are often painful. In a study of 1171 adult patients with MS and spasticity, moderate to severe pain was reported in 47% of the patients [41]. Muscle pain associated with spasticity can interfere with rest and sleep deteriorating the patients' quality of life. A literature review of this issue in 2022 assessed the efficacy of botulinum toxin injections for relieving pain associated with spasticity of MS [42]. In this review, seven of eight studies that used standard pain scales such as visual analogue scale (VAS), reported significant pain relief after botulinum toxin injections.

Tonic Spasms

Tonic spasms are intermittent muscle spasms often affecting wrists, feet, toes and fingers. The result is painful twisting of wrists or feet and flexion of toes or fingers. The cause of these painful spasms in MS is not clear, but it is generally attributed to irritation of damaged nerve fibers that travel from brain to muscles. Dr. Restivo and his coworkers reported that these spasms improved significantly when Botox, 80–120 units, was injected into forearm or leg muscles of five affected patients [43].

Movement Disorders in Multiple Sclerosis

Multiple sclerosis can cause involuntary movements of the muscle due to the disruption of muscle control at the brain level. In general, involuntary movements respond well to injection of BoNTs into the muscle through inhibition of nerve-muscle chemical transmitter, acetylcholine (described earlier). Two of these movements are discussed briefly here:

1. Tremor: a special form of tremor, called cerebellar tremor, is sometimes a disabling symptom in multiple sclerosis. Cerebellar tremor, unlike Parkinson tremor increases in amplitude during hand and forearm motion and can interfere with eating and writing. Cerebellum (called by some the little brain) is located below cerebrum—main part of the brain—in the back of the head, and through its extensive connections provides muscle coordination. Multiple sclerosis, via disruption of cerebellar connections, impairs the normal movements and causes a coarse limb tremor. In a double-blind, placebo controlled study of 23 patients with multiple sclerosis related forearm tremor, injection of Botox into the forearm muscles improved the tremor as well as witting of the patients significantly [44]. The drawback was development of some degree of weakness of forearm muscles that ceased within 6 weeks.
2. Facial myokymia (FM): FM is characterized by fine continuous twitching of small muscle fibers of the face seen in some patients with multiple sclerosis. It is due to disruption and irritation of nerve fibers at the base of the brain (brain stem). FM is not painful but a nuisance, esthetically unpleasant and often a cause of social embarrassment. Injection of a small amount of Botox (1 to 2) units (barely under the skin of the face) and into the twitching muscles can reduce or stops the movements for 3–4 months [45, 46].

Treatment of Difficulty with Swallowing (Dysphagia) and Difficulty in Phonation (Dysphonia)

Muscles of swallowing, like other muscles of the body in MS, develop increased tone and stiffness as the disease progresses. This stiffness associated with increased muscle reflexes results in difficulty in swallowing. A well-designed study assessed the effects of Botox injection into the muscles of esophagus (the tube connecting the mouth to the stomach) in 14 patients with MS and difficulty in swallowing. Patients were followed carefully at 1, 4, 6, 12, 16, 18 and 24 months. Difficulty in swallowing improved in all patients following injection of Botox into muscles of the back of the throat that initially had unusually high tones [47].

Dysphonia or spasmodic dysphonia is impaired phonation due to disturbed function of the vocal cords. Most of the affected patients have a shrill voice due to overactivity of the adductor muscles of the vocal cord (muscles that bring the vocal cords together during phonation). Spasmodic dysphonia may occur during the course of a variety of disease conditions including MS. Injection of small amounts of Botox into adductor muscles of vocal cords is an established treatment for management of persistent spasmodic dysphonia [48]. Observations in small number of patients with MS and spasmodic dysphonia have shown that this mode of treatment is also effective in MS-related spasmodic dysphonia [49].

Conclusion

Botulinum toxin therapy is useful for several disturbing symptoms of multiple sclerosis. Treatment of tight and stiff muscles (spasticity) and bladder symptoms (inappropriate urge to urinate, leaking and urinary incontinence) are the two most widely used indications which have shown to improve the patients' quality of life. Emerging data on treatment of facial pain, tonic muscle spasms as well as swallowing and phonation difficulties in MS are also encouraging and expand the utility of BoNT therapy in multiple sclerosis. The role of botulinum toxin therapy in multiple sclerosis is detailed in recent reviews on this subject [50, 51].

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