Chapter 7
Botulinum Toxin Treatment in Multiple Sclerosis

Introduction

Multiple sclerosis is seen in 130–150/100,000 of the US population [1]. It affects over two million people world-wide and 400,000 people in the USA [2]. In US, the financial burden per person can be up to $52,000 per year [3]. In 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 and 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 the electrical signals flowing in them both away and towards brain. This sheath of tissue that covers the nerves has a fat composition and is called myelin. Multiple sclerosis is, therefore, considered one of the diseases that specifically destroy myelin (demyelinating). Loss of myelin leaves scars in the brain and/or spinal cord. These scars are easily detected by modern imaging techniques such as MRI. Currently, MRI is a major diagnostic device used to confirm or support the diagnosis of multiple sclerosis (Fig. 7.1). These scars or plaques are often multiple and occur at different levels of the central nervous system, 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 support the diagnosis of multiple sclerosis. Cerebrospinal fluid is made in the brain and runs inside the spinal canal between the bones 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 back bones in the lumbar area. In most patients with MS, examination of CSF shows an elevation of certain specific proteins.

Multiple sclerosis can cause a variety of symptoms depending on the location of the lesions. A large number of patients complain of motor symptoms, such as sudden weakness or even total paralysis of one limb. Others may have sensory

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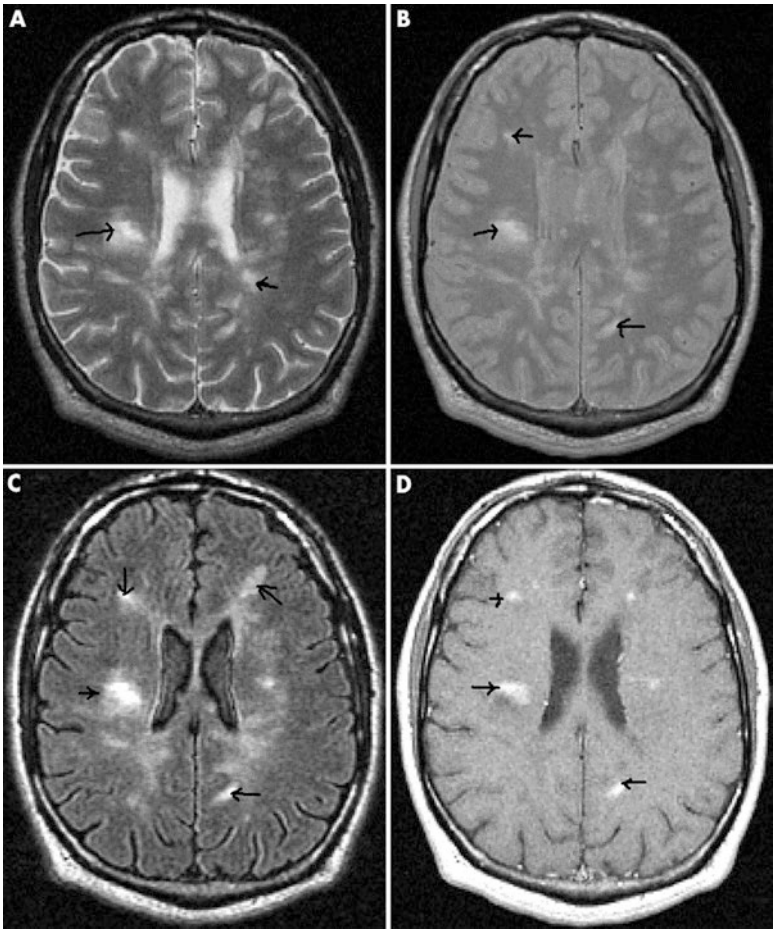

Fig. 7.1 Multiple brain lesions in a patient with multiple sclerosis. The lesions, white patches, marked by arrows in the brain slices on MRI, represent abnormal areas of the brain. From Trip and Miller 2005, reproduced with permission from publisher (BMJ group)

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, scars 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 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 the body. The damage to nervous system in multiple sclerosis is believed to be due to this immune reaction which is associated with a lymphocytic reaction (certain blood cells) in this area.

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. Several newly discovered drugs in this category have succeeded to slow the course of multiple sclerosis and prevent appearance of new brain lesions. Some of these drugs such as alemtuzumab and or daclizumab specifically work on the lymphocytes and the immune system. Unfortunately, despite these efforts, still a large number of patients with MS are left with permanent disabilities due to multiple damages sustained within the nervous tissue (brain and spinal cord) over years. Among these disabilities, stiffness of muscles (spasticity) and dysfunction of bladder can significantly impair the patients' quality of life. Research data and clinical experience have shown that both muscle spasticity and bladder dysfunction in MS, improve significantly with botulinum toxin injections into the involved muscles or into the bladder wall.

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), weakened muscles gradually show increased tone, become stiff and spastic. In many patients with MS, this spasticity can be quite severe and 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. As a result, sustained contraction of these muscles keeps the thighs always together, a position that impairs normal leg movements and ambulation. These patients complain of poor balance and frequent falls. 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 such as 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 expert 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 [4]. Spasticity of multiple sclerosis is more prominent in the lower limbs. The adductor muscles of the thighs that bring the thighs together are often involved. Increased tone of these muscles may lock the thighs together causing difficulty with hygiene and ambulation.

Botulinum toxin treatment (with Botox and other variants) provides a reasonable alternative to pharmacotherapy. In general, botulinum toxins have less side effects than anti-spasticity drugs and require a set of injections (usually into 3–5 muscles) every 3–4 months. The effect of botulinum toxin injection on the muscle becomes manifest in 2–5 days and peaks at 2–3 weeks. The muscle relaxing effect of the toxin can last 3–4 months; this effect, is to a large degree, dose dependent.

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 – in Europe Neurobloc). For detailed description of toxin types and information on toxin characteristics the reader is referred to Chap. 3 of this book. Although the units of these four toxins are not exactly comparable, in clinical practice the following approximations are used:

1 unit of Botox = 1 unit of Xeomin=2.5 to 3 units of Dysport = 40–50 units of Myobloc.

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: Fig. 7.2a), significantly reduced the spasticity and improved hygiene in 7 out of 9 patients studied [6]. A total of 400 units of Botox was shared with three thigh adductor muscles. Several, subsequent high quality studies with much larger number of patients (in hundreds) have supported this observation. Furthermore, longterm observations over several years have shown that repeated injections at every 3 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 in this setting. Comparative studies have shown that MS- related spasticity is as responsive as any other form of spasticity (stroke, trauma) 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 (stroke, trauma, etc). For this reason, botulinum toxin therapy is now among the first lines of treatment for spasticity in multiple sclerosis.

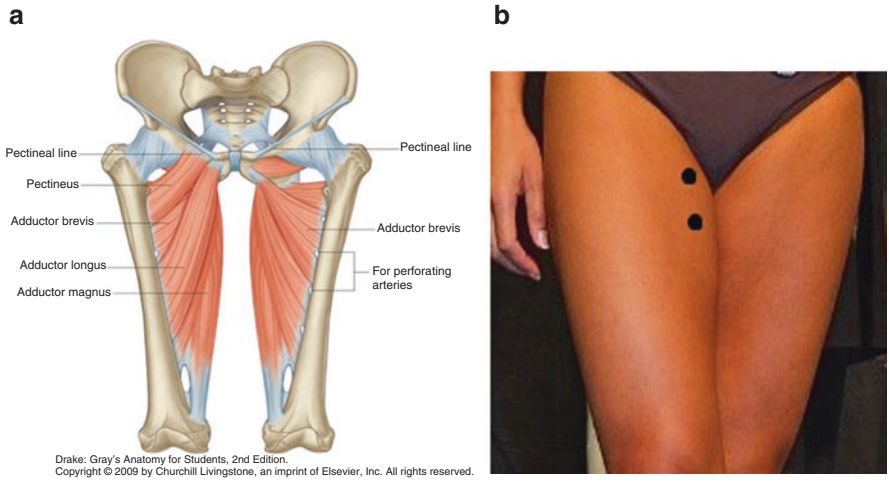

Fig. 7.2 (**a**) Three adductor muscles of the thigh that bring the thighs together; short (brevis), long (longus) and large (magnus). From Drake Anatomy for students printed with permission from elsevier. (**b**) A common site of botulinum toxin injection for adductor spasticity

Technique of Injection

The injection technique for thigh muscles of patients with multiple sclerosis is very similar to what has been described in Chap. 7 for stroke-related spasticity. The size of the muscle and the degree of tightness of the muscle determines the dose. The dose is delivered in units. In the upper limbs, for small muscles of the forearm and hand, the dose varies from 5–20 units per muscle, whereas larger muscles (i.e biceps) may require up to 100 units (Botox or Xeomin, for Dysport and myobloc, multiply the units by 2.5–3 and 40–50 units respectively). In the lower limb muscles, even larger doses can be used for instance up to 150–200 units for adductor muscles and even higher for large muscles in the back or front of the thigh that flex or extend the knee joint. The injecting needle is thin and short for upper limb muscles but longer for larger muscles of the lower limb. Injections are delivered at two or three sites into the each muscle, using anatomical landmarks for identifying nerve-muscle junctions (where injections are most effective). 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. 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 10–15% 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. Dose miscalculations can lead to serious side effects such as total paralysis and endanger patient's life.

Case Report

A 32 years-old female with multiple sclerosis was referred to the 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 legs constantly together. Oral medications provided modest relief. She had difficulty sitting up and ambulating. The legs pulled together further during walking and impaired her balance. On examination, one could feel very tight adductor muscles on the medial aspect of the thighs close to the groin (Fig. 7.2b). She was injected with Botox into adductor muscles- 150 units/side (Fig. 7.2). After a week, she reported marked improvement of several of her functions. Relaxation of thigh muscles allowed her to stand and walk better and with less fear of falling. Moving in bed became easier, she slept better. Movement of the thighs was no longer painful. Hygiene related tasks were carried out with more ease and comfort. The satisfactory effects of Botox injection lasted for 3 months. She experienced the same positive response with repeated injections, every 3–4 months, over a follow up period of 5 years.

Botulinum Toxin Therapy for Bladder Problems in Multiple Sclerosis

Patient 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 function of the bladder is called detrusor muscle (See Fig. 7.1 in Chap. 6, bladder dysfunction). This muscle that spread 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 spread from brain to the 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, bed wetting at night and 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. The 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.

Bladder symptoms are common in multiple sclerosis. A survey conducted by the North American Research Committee on Multiple sclerosis (NARCMS), found that 65% of patients with MS complained from moderate to severe bladder symptoms which include leakage, urgency, frequent urinations at night and urinary incontinence [7]. What happens to the bladder muscle in MS is somewhat similar to what happens to the neuromuscular junction leading to muscle spasticity as describd 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 as in other muscles of body with spasticity becomes overactive. 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 Chap. 2 on mechanism of function of botulinum toxins). The drugs that are used for control of bladder symptoms in MS anticholinergics- Ditropan, Detrol - also work by reducing or blocking the effects of acetylcholine. The frequent side effects of these drugs, anticholinergics, such as blurring of vision, impaired memory and dryness of the mouth make them hard to tolerate especially over 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. 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 showing their satisfaction with 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. In many patients with advanced MS, however, this was not problematic since they had already chronic urinary retention and were self-catheterizing themselves for months or years. Nevertheless, patients need to be alerted and trained for this side effect. Some recent studies have shown that with time, the incidence of urinary retention after Botox injection into the bladder goes down, 8% at third year and almost 0% by the fourth year of treatment. A recent analysis of 18 studies with 1553 MS patients in whom bladder dysfunction was treated with Botox injection into the detrusor muscle reported sustenance of positive results after repeated injections and a low incidence of side effects [8].

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 usually contain 100 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- Fig. 7.3) of the bladder. Currently, however, different protocols are used at different institutions with the number of injections ranging from 20 to 40, including or not including bladder's trigone.

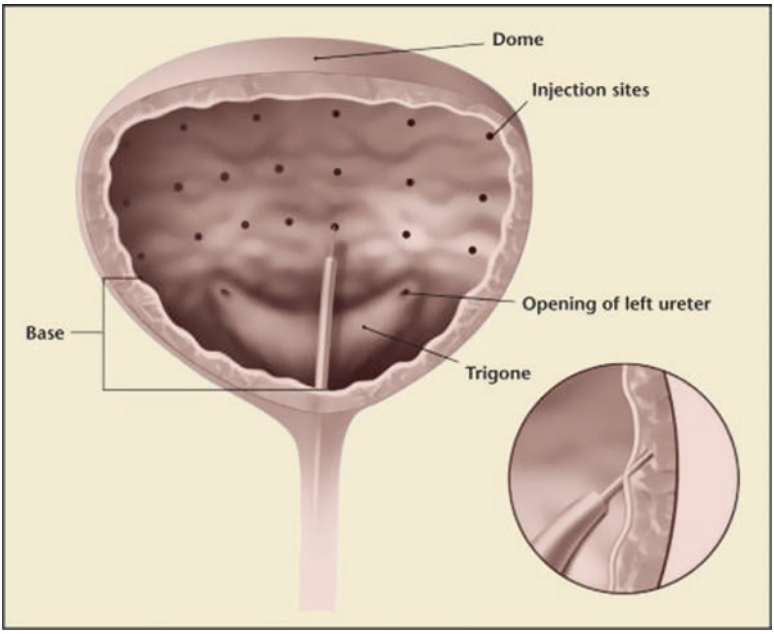

Fig. 7.3 Botox injection of bladder for overactive detruser muscle. From Obstetrics and gynecology 2014. With permission from publisher, Wolter Kluver. Original from Allergan http://www.allergancom/assests/pdf/botox/-pi.pdf

Treatment of Pain with Botulinum Toxins in Multiple Sclerosis

Pain is a common symptom in multiple sclerosis. In one study, 63% of the patients with multiple sclerosis complained of chronic pain [9]. Among several types of pain in MS, three types of pain are most frequent: neuropathic, pain associated with spasticity and tonic spasms.

1-Neuropathic Pain Neuropathic pain has a burning, searing and jabbing quality and 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 face pain in MS. The trigeminal nerve, the fifth of 12 nerves that exit the brain, provides sensation of 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) without MS due to age related degeneration of this nerve. Trigeminal neuralgia is very rare in young individuals, but can be seen in one out of 300 young patients with multiple sclerosis. Therefore, in a young person, especially when the facial pain affects both sides, the diagnosis of multiple sclerosis should be strongly suspected. Treatment of trigeminal neuralgia is difficult; most patients are not happy with oral medications. High quality studies 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 the common, late onset form of trigeminal neuralgia [11]. No studies are available with botulinum toxins for treatment of TN in multiple sclerosis. However, case reports suggest that injections of botulinum toxin into painful areas of the face is also effective for MS -related trigeminal neuralgia (see below).

How injection of botulinum toxin inside and under the skin can help neuropathic pain has been the subject of many investigations. It is now common knowledge from both animal and human studies that BoNTs not only inhibit the function of acetylcholine (nerve-muscle chemical transmitter) but also diminish the effect of variety of chemicals that are essential for transmission of pain signals from the skin to brain. Though still not approved by FDA (except for chronic migraine), BoNTs injection into and under the skin is now used by many clinicians for a variety of neuropathic pains such as pain associated pain with shingles, pain after limb trauma and so forth based on the published data from high quality studies [10].

Case Report

A 42 year-old women, with history of multiple sclerosis since age 18 with intermittent paralysis, and sensory loss and visual symptoms complained of intermittent severe facial pain. The pain involved the left side of the face and recurred many

timers 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 medications including the commonly used drug for trigeminal neuralgia; tegretol and gabapentin that "did not help much". On the scale of 0 to10, 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 and 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.

2- Pain Associated with Spasticity As was discussed earlier, stiff muscles of patients with multiple sclerosis are often painful. Muscle pain interferes with rest and sleep and deteriorates the patients' quality of life. In majority of patients with spasticity, botulinum toxin injection into the tight muscles improves muscle pain along with spasticity.

3- Tonic Spasms Tonic spasms are intermittent muscle spasms often affecting wrist and foot, toe and fingers. The result is painful twisting of wrist 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 found that these spasms improved significantly when Botox, 80–120 units was injected into forearm or leg muscles of five affected patients [12].

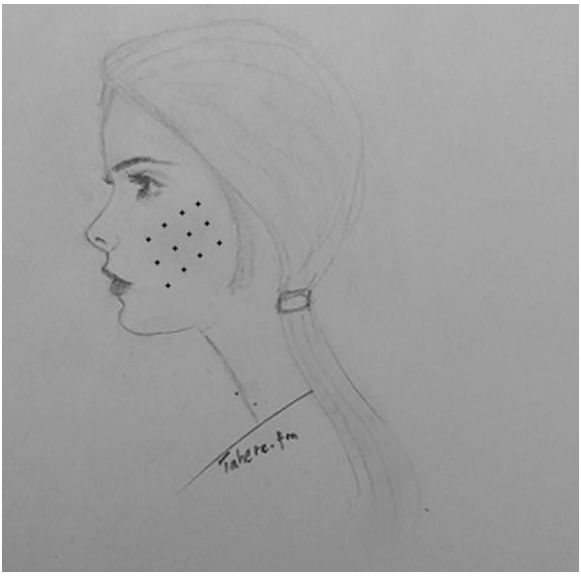

Fig. 7.4 Case report. Sites of Botox injections in a patient with multiple sclerosis and trigeminal neuralgia. Injections are carried out using a thin and short needle and under the skin. Drawing courtesy of Dr. Tahereh Mousavi

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 which acts via inhibition of nerve muscle chemical transmitter, acetylcholine (described earlier). Two of these movements are discussed briefly here:

1. Facial myokymia: this is fine twitches of small muscle fibers of the face seen in some patients with multiple sclerosis. It is not painful but a nuisance, esthetically unpleasant and often a cause of social embarrassment. Injection of small amount of Botox 1 to 2 units into the areas of the muscle twitch (barely under the skin of the face) can reduce or stops the movements for 3 to 4 months.
2. Tremor: a special form of tremor, called cerebellar tremor, sometimes, is a disabling symptom in multiple sclerosis. Cerebellar tremor unlike Parkinson tremor increases in amplitude during the hand and forearm motion. Cerebellum (called by some the little brain), is located under 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 normal movements and causes a coarse limb tremor. There are some reports that claim injection of Botox into different muscles involved in cerebellar tremor can diminished this high amplitude tremor to a level that is manageable by the patient.

Treatment of Difficulty with Swallowing (Dysphagia)

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 which had unusually high tones [13].

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 face pain and muscle spasms and the swallowing difficulties in MS is also encouraging and expands the utility of BoNT therapy in multiple sclerosis.

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