Chapter 6
Botulinum Toxin Therapy for Complications of Stroke

Introduction

Stroke is due to occlusion or rupture of a blood vessel in the brain. Occlusion of blood vessel acutely deprives a part of the brain from nutrients and oxygen, whereas rupture of a vessel destroys the brain tissue and replaces a part of the brain by a blood clot. Close to 90% of all strokes are caused by occlusion of a blood vessel. Brain's function is highly dependent on its blood supply which provides brain with oxygen. Brain uses oxygen more than any other organ in the body. Brain cells are very sensitive to lack of oxygen which can result in their death within a few minutes. Each year, over 800,000 people in the US suffer from stroke [1]. Stroke is the fourth cause of mortality world -wide and the first cause of adult disability in the US [2].

Acute impairment of brain function or lack of it leads to a variety of neurological deficits. The type of deficit depends on the region of the of the brain disabled by stroke. In small strokes recovery may be quick and sometimes complete. Unfortunately, most strokes result in a sizeable deficit with incomplete recovery despite the best medical treatment.

The most common and often the most disturbing of all mishaps after stroke is impairment of muscle function. Depending on the severity of the stroke, the aftermath of most strokes is some degrees of muscle paralysis. Our muscles function based on the nerve signals that they receive from the brain. In human, the brain is extremely well developed and has a larger size per body weight compared to much larger primates. Human brain contains approximately 86 billion nerve cells (neurons) and almost the same number of non-nerve cells (supporting cells-glia) [3]. The most superficial layer of human brain is called cortex. Cortex which is only 3–4 mm thick, consists of 26 billion nerve cells. Many of these cells are located in the motor region of the cortex which governs the motor function and controls the muscles (Fig. 6.1).

The large nerve cells that are located in the motor region of the cortex, send the motor command through their long processes (axons) to another motor cell in the

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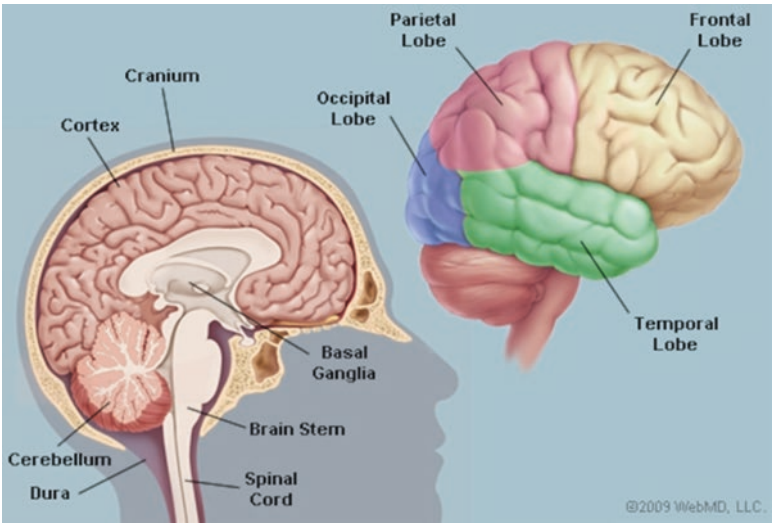

Fig. 6.1 The primary motor area is the most posterior and the primary sensory area is the most anterior part of frontal and parietal lobes, respectively. Reproduced with permission from WebMD

spinal cord and then to the muscle. This is unlike the cells in the sensory system, that covey the sensory signals from the skin to the brain. In the sensory system, at least two other sensory cells (one in the spinal cord and one higher up inside the brain) are contacted before the peripheral sensory signal reaches the sensory cortex. Each motor cell has one axon, a long fiber that conveys the message of the cortical nerve cell to motor cells in the spinal cord. The axons of the motor cells in the spinal cord convey the motor message to the muscle. Each axon of spinal cord motor cell when nears the muscle divides to several branches, each connecting to one muscle fiber. The point of contact between an axon and a muscle fiber is called neuromuscular junction. A neuromuscular junction has a axon part and a muscle fiber part with a cleft between the two structures (synaptic cleft) (Fig. 6.2). Since botulinum toxins relieve many muscle-related symptoms through their action on neuromuscular junction, the structure of neuromuscular junction and mechanism of muscle activation is described in more detail below.

The end of each axon (axon terminal) contains many vesicular structures, filled with a chemical called acetylcholine (Fig. 6.2). Acetylcholine is one of many chemicals that are considered neurotransmitters. This particular neurotransmitter's main function is conveying the nerve message to the muscle. The motor command from a cortical nerve cell travels along the axon to the periphery in form of an electric signal. When the nerve signal from the brain reaches the axon terminal next to the muscle, it activates a set of proteins in the axon terminal. Activation of these proteins ruptures the vesicular structures and releases their content (acetylcholine) into the synaptic cleft. The released acetylcholine attaches itself to muscle receptors (located on the surface of the muscle), excites, activates and contracts the muscle fiber.

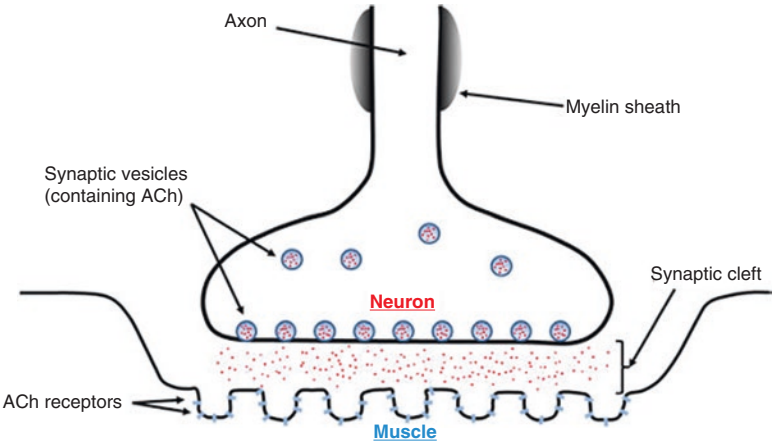

Fig. 6.2 Neuromuscular junction – The end of the motor axon (axon terminal) which faces the muscle fiber encompasses vesicles that contain acetylcholine (AC)

In stroke, in addition to paralysis which is the result of loss of nerve cells, degeneration and death of many axons and its terminal connections to muscle fibers results in a cascade of complicated events that leads to significant increase of tone in the weak muscle. This increased tone, leads to stiffness of the muscle and causes further functional disability. The increased tone of the muscle which is often associated with increased reflexes is called spasticity.

Spasticity After Stroke and the Role of Botulinum Toxins in Treatment of Stroke– Related Spasticity

Spasticity is a major handicap to patients who have suffered from stroke. Between 20 to 40% of patients with stroke develop spasticity within 1–6 weeks after the onset of stroke. Spastic muscles have limited range of motion and lack speed of function and precision. In the lower extremities, spasticity interferes with proper balance and ambulation.

Why the muscles of a weak limb after stroke gradually develop increased tone and become spastic has been the subject of extensive research. Brain both excites and inhibits the muscle activity through a set of complex mechanisms. Hence, enhanced excitation or reduced inhibition both can cause abnormally increased muscle tone and muscle spasticity. We have mentioned above the chemical acetylcholine that is present at nerve endings and upon release, excites the muscle. Inhibitory fibers that influence the muscle, work through their own inhibitory chemical (transmitter). Currently, there is strong evidence to support that disruption of these inhibitory fibers via tissue damage caused by stroke, plays a major role in development of spasticity.

Spasticity is not a benign complication of stroke. In addition to impairing balance and interfering with ambulation, spastic muscles can continue to harden and end in a state of continued contraction (contracture) leading to pain and immobility if not properly treated (Fig. 6.3).

Aggressive physical therapy, such as induced movement therapy, stretching, dynamic elbow-splinting and occupational therapy offer some help and can delay development of contracture to some extent. A large number of medications are used for reducing the tone in the spastic muscles, among which, baclofen, benzodiazines (valium), tizanidine and dantrolene are the most commonly used. These medications, although partially effective, are beset by undesirable side effects which limit increasing their dose to the optimal level (Table 6.1).

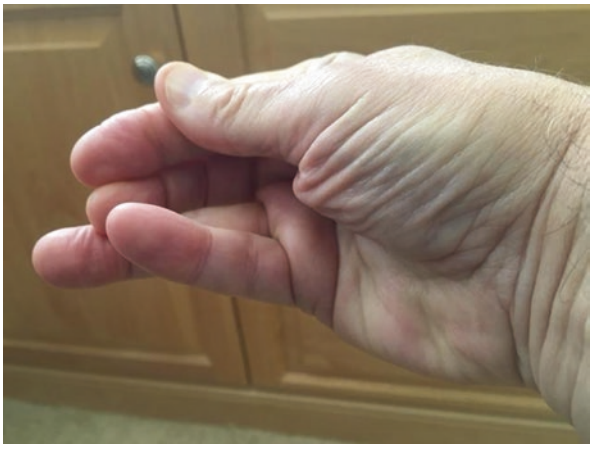

Fig. 6.3 Contracted and spastic muscles leading to contracture and loss of fingure function

Table 6.1 Medications commonly used for treatment of spasticity

Medication	Dose	Side effects
Valium	2–10 mg;3–4 times daily	Drowsiness, sedation impaired balance. Drop in blood pressure
Baclofen	Initial dose 5 mg, two to three times daily. Can be increased	Drowsiness, nausea, muscle weakness, confusion, seizures
	Every 2 to 3 days by 5 mg increments up 50-60 mg daily	
Tizanidine	Initial dose: 2–4 mg orally every 6–8 h	Sedation, drop in blood pressure, liver toxicity
	Maximum dose: 36 mg/day (12 mg, three times daily)	
Dantroline	Initial dose 25 mg once daily	Drowsiness, weakness, fatigue, liver toxicity
	Maximum dose: 100 mg, three times daily	

In severe lower limb spasticity, pharmacological treatment is often not very effective. Insertion of baclofen pump can reduce lower limb spasticity. This is an involved procedure that requires insertion of a small pump surgically into the abdominal wall. A catheter that emerges from the pump delivers a carefully titrated amount of baclofen into the cerebrospinal fluid (flowing inside that spinal canal) of the patient. This treatment requires facilities with experienced surgeons to insert and titrate the dose of baclofen in the pump. Inappropriate titrations can lead to severe side effects such as seizures and depressed level of consciousness. Other non-pharmalogical treatments of spasticity include repetitive electrical stimulation of the nerves and magnetic stimulation of the motor cortex with a specially designed magnet. Both procedures have a modest effect and are uncomfortable for the patient.

Botulinum Toxin Treatment of Spasticity

Botulinum toxins inhibit the release of acetylcholine from nerve ending, an agent that normally activates the muscle and in abnormal conditions may intensify the muscle contraction. This unique function makes the botulinum toxins effective therapeutic agents for treatment of hyperactive muscle disorders including spasticity. The commercially available toxin preparations are now used widely for treatment of a variety of neurological disorders [4].

As described earlier in Chap. 3, of the seven recognized serotypes of botulinum toxins, only types A and B are of clinical use due to their long duration of action (3–6 months). This long duration of action after a single injection is an advantage over oral medications which need to be taken daily. Three type A toxins are approved by FDA for use in the US with the trade names of Botox, Xeomin and Dysport. One type B toxin, Myobloc, is approved by FDA and is currently available in the US Market. The doses of these toxins are not comparable or interchangeable but in clinical and comparative studies the following approximations are used:

1unit of Botox = 1 unit of Xeomin = 2–3 units of Dysport = 40–50 units of Myobloc.

Spasticity not only pertains to stroke but can also be seen after brain and spinal cord trauma, in association with multiple sclerosis and in children with cerebral palsy. Following a large number of animal studies that showed reduction of muscle tone in animal models of spasticity after intramuscular injection of botulinum oxins, significant interest has developed among neuroscientists, neurologists, physiatrists and pediatricians for investigating the role of botulinum toxins in human spasticity. Early investigations focused on the role of botulinum toxin therapy in upper limb spasticity. These investigations looked at many facets of upper limb spasticity and aimed to answer many questions:

Can injection of Botulinum toxin (Botox, Xeomin, Myobloc, Dysport) into spastic muscles reduce muscle tone in human and improve the patient's quality of life?

Does reduction of spasticity of hand, forearm and shoulder muscles relieve the burden of caregivers and help physical therapy?

In other indications of botulinum toxins therapy such as involuntary, hyperactive muscles of face and neck, improvement lasts 3–4 months after muscle injection(s). Is this the case with spasticity?

Because of the size of muscles (considerably larger than face or neck muscles), larger doses of botulinum toxins are needed for injection into the affected muscle. Is injection of these higher doses in one session (for Botox up to 500 units for upper extremities) safe and devoid of serious side effects? How high of the dose can be used when both arm and leg muscles are injected?

To date 17 high quality studies have been published on Botulinum toxin effect on the spasticity of upper limb muscles, some of them including a sizeable number (in hundreds) of subjects [5, 6]. These studies collectively demonstrated that botulinum toxin injections into the tense and high tone muscles of stroke subjects reduced muscle tone, eased physical therapy and improved the patients' quality of life. Most patients were satisfied with botulinum toxin therapy and preferred this mode of treatment over taking large doses of daily medications. Serious side effects in spasticity studies were extremely rare and the toxin therapy was considered, in general, safe and practical. Based on the positive results of these studies, FDA first approved the use of Botox for treatment of upper limb spasticity in 2010. Subsequently, with availability of further studies, FDA approved the other two type A toxins, Xeomin and Dysport for treatment of upper limb spasticity in 2015.

One of the most feared complications of spasticity after stroke is development of muscle contracture. Contracture is loss and shortening of muscle fibers and replacement of muscle by non-elastic connective tissue. Contracture leads to total loss of muscle function and joint deformity.

There are some preliminary reports indicating that injection of botulinum toxin into the spastic muscle shortly after development of stroke can delay development of contracture. Further and higher quality studies are necessary to support these positive observations.

Muscle pain is another disturbing complaint of patients who develop spasticity after stroke. Pain is often measured on a scale of 0–10 (visual analogue scale). A value of over 4 is considered to represent a pain severe enough to interfere with daily activities. Patients with spasticity often have muscle pain. In a recent Canadian study Dr., Shaikh and his colleagues found that 65% of their patients with post-stroke spasticity had associated muscle pain[7]. The pain was more noticeable during movements. Most patients (80%) believed that their muscle pain was related to their stiff, spastic muscles. Following Botox injections, 62% of the patients reported pain relief within days after injection.

Lower limb spasticity after stroke can be very disabling. Spasticity adds to muscle weakness in stroke patients, limits leg movements and adds to difficulty with ambulation. High quality studies in lower limb spasticity, although fewer in number (six), also have shown reduction of tone and improvement of quality of life after botulinum toxin therapy. Some studies have clearly demonstrated that botulinum toxin injections into the leg muscles of patients with stroke improve ambulation.

Based on availability of these high quality studies, FDA approved the use of Botox and Dysport for adult lower limb spasticity in 2014 and 2017, respectively. Currently, Dysport is the only form of botulinum toxin approved for lower limb spasticity in children (FDA approval 2016).

Lower limb includes large muscles of the thighs that require more units of botulinum toxins in order to relax compared to hand or forearm muscles. Investigators wondered if injection of doses larger than that usually used for the upper limb muscles (up to 400–500 units of Botox or Xeomin), are safe to be given in one session to the lower limb muscles or in conditions that require treatment of both arms and legs. Furthermore, it is known that the larger the dose of the toxin, the higher the chance of antibody formation against the toxin, which upon development may nullify the toxin's therapeutic effect. Antibody formation is also enhanced by repeated injections which in case of spasticity are required to maintain the reduced tone in the spastic muscles of the stroke patients over time.

In regard to safety of larger doses, Dr. Wissel and his colleagues has recently published the result of a combined European- American investigation on 155 patients in whom doses of Xeomin (a botulinum toxin A with units similar to Botox) were escalated over months from 400 to 600 and then ultimately to 800 units per session of treatment [8]. Increasing the dose was more efficacious in reducing spasticity but did not increase the percentage or severity of side effects. Main side effects were diarrhea and minor throat infections, noted in 5% of the patients.

Several investigators have researched development of antibodies in patients who received large doses of botulinum toxin A over several years. These studies either did not find any antibodies or found antibodies in a very small percentage of the patients (< 0.4%) [5, 9]. The antibody research, therefore, indicates that with the latest formulation of botulinum toxins, antibody formation is not an issue of significance when botulinum toxin therapy is used for spasticity.

Technical Issues in Botulinum Toxin Treatment of Stroke Spasticity

All four of FDA approved botulinum toxins in the market (Botox, Xeomin, Dysport, Myobloc) have shown efficacy in treatment of post stroke spasticity, though the data on myobloc (type B toxin) is small compared to the other three toxins. In case of Botox, Xeomin and Dysport, the powder form of the toxin (provided in a small vial) needs to be mixed with salt water– saline, usually 2 ccs before injection. Myobloc is marketed in an already prepared solution form. Injections are often guided by electromyography, a device that identifies muscles by their electrical pattern. Also, location of the muscle can be identified by nerve stimulation. A nerve stimulator, stimulates a nerve which is known to serve a certain muscle and by doing so identifies the muscle (muscle moves in response to the stimulation). Ultrasound is a more precise way to localize and clearly visualize the muscles [10]. The technique however, requires a fair amount of expertise.

Upper limb, spasticity more often involves muscles that flex the joints. For instance, involvement of biceps muscle leads to abnormal flexion of the arm, a position that can interfere with dressing and use of the arm for other activities of daily living. This is often associated with wrist spasticity (flexed wrist) and sometimes with forced flexion of fingers causing "clenched fist." The latter two, when severe enough, can make the involved hand non- functional. In the lower limb, abnormal flexion of the knee or foot interferes with standing and ambulation. Flexion of the knee results from spasticity and high tone in the large hamstring muscles located on the back of the thighs. Botulinum toxin injections are usually carried into two to three points into the large muscles (Fig. 6.4). The units of toxin used per muscle depend on the size of the muscle (Table 6.2). The effect of botulinum toxin injection, appears in 3–7 days (muscles loosen) and the effect peaks in 2–3 weeks. The effect usually lasts for 3–4 months. Reinjections are required every 3 to 4 months to keep the spastic muscle in the state of reduced tone.

In clinical practice, in order to achieve best results, botulinum toxin therapy is often combined with physical therapy. Concurrent pharmacological therapy with anti-spastic drugs such as baclofen or tizanidine (see Table 6.1) may be required in cases of severe spasticity. Unfortunately, in elderly patients, these medications often cause undesirable side effects, the most disturbing among them are sedation and depressed level of consciousness. On the contrary, Botulinum toxin injections do not cause sedation or depress the level of consciousness (Fig. 6.4).

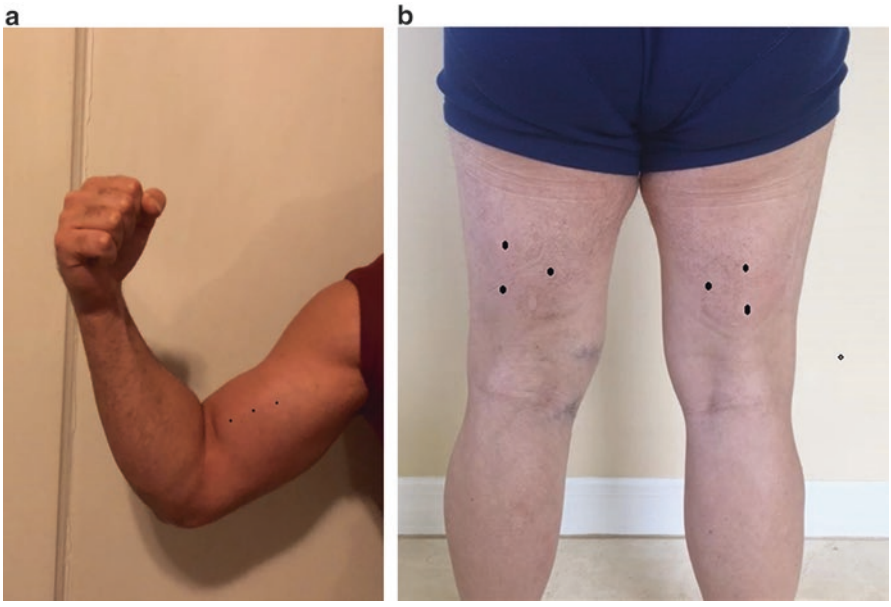

Fig. 6.4 Botulinum toxin injection of biceps (**a**) and hamstring (**b**) muscles. Each muscle is injected in three points. Courtesy of Dr. Damoun Safarpour

Table 6.2 Dose of Botox or Xeomin per muscle per side for some of the commonly injected muscles in stroke spasticity. For Dysport the dose can be multiplied 2.5–3 times and for Myobloc multiplied by 40 to 50 times

Muscle	Dose in units (Botox or Xeomin)
Biceps	60–100 Per muscle, per side
Triceps	60–100
Wrist flexors	40–60
Hamstring (knee flexor- back of the thigh)	60–200
Quadriceps (knee extensor- front of the thigh)	60–100
Gastrocnemius (foot flexor-back of the leg)	60–80

Botulinum Toxin Therapy of Persistent Drooling after Stroke

Drooling becomes an annoying problem in some patients after stroke. This is often due to paralysis of the face muscles which become unable to clear the saliva from the mouth. In such patients, reduction in saliva production would be desirable. It has been shown in both animals and human that injection of Botox and other botulinum toxins into the glands that produce saliva (parotid, sub-maxillary) reduces the production of saliva. This is also the case in patients who have drooling after stroke [11]. Injections are done with a very small needle. In case of parotid gland that are barely under the skin, a few milimeter penetration is sufficient. Usually 2 to 3 sites are injected within the gland, preferably under ultrasound visualization. Many clinicians inject without using the ultrasound machine since even without direct visualization of the gland, the yield of procedure is high and satisfactory to the patient. Injections take less than a minute and are associated with only mild discomfort. Numbing the skin is not necessary. Injections need to be repeated every 4–6 months. The chemical that conveys the nerve signal to the gland to initiate secretion of saliva is acetylcholine – the same chemical that activates the muscle. As was discussed earlier, botulinum toxins inhibit the release of acetylcholine at the nerve endings. Details of saliva secretion, anatomy of salivary glands and effects of botulinum toxins on saliva production are presented in chapter 13.

Botulinum Toxin Treatment of Joint Pain after Stroke

Immobility of the joints after stroke, caused by muscle paralysis, often leads to joint degeneration with subsequent chronic joint pain. As described in Chap. 5, botulinum toxins in addition to acetylcholine, also inhibit the function of a variety of pain transmitters. This inhibition of pain transmitters occurs in the peripheral nervous

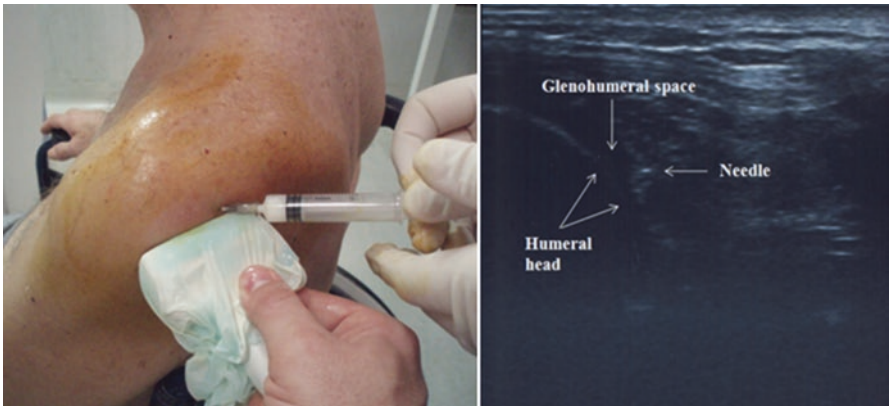

Fig. 6.5 Method of the shoulder joint injection in a patient with paralysis of the left arm after stroke and shoulder joint pain. The right side of the figure shows an ultrasound image that demonstrates the position of the injecting needle and the head of the long bone of the arm. From Castiglione and co-workers, printed with permission from Elsevier

system as well as in the central nervous system as the molecule of the toxin from the site of injection travels to the spinal cord and influences the sensory cells that convey pain to the brain. Injection of Botox (and other toxins) into the joints has been shown to alleviate joint pain in several of kinds of joint problems (Chap. 10 of this book, orthopedic indications). Chronic joint pain after stroke, specially pain in the shoulder joint, also responds to botulinum toxin injections into the involved joint (Fig. 6.5).

Movement Disorders After Stroke

A variety of involuntary movement can develop after stroke either due to damage to critical brain areas or damage to muscles that receive their nerves from the brain. Many patients with stroke demonstrate weakness of half of the face on the side of limb weakness. The weak eyelids or facial muscles sometimes develop bothersome and persistent involuntary twitches. Injection of small amounts of Botox into these muscles with a fine needle often suppresses the lid or facial movements for 3–4 months.

Dystonia is a movement disorder characterized by twisting and turning, flexion or extension of a joint leading to abnormal postures. Dystonia is a common movement disorder that may develop after stroke affecting the muscles opposite to the side of brain damage. In stroke patients, dystonia is often mixed with spasticity. Dystonia is one of the most responsive movement disorders to botulinum toxin therapy. Figure 6.6 shows dystonia of the neck and shoulder muscle developed after a stroke involving deep brain structures. The patient demonstrates head tilt to the

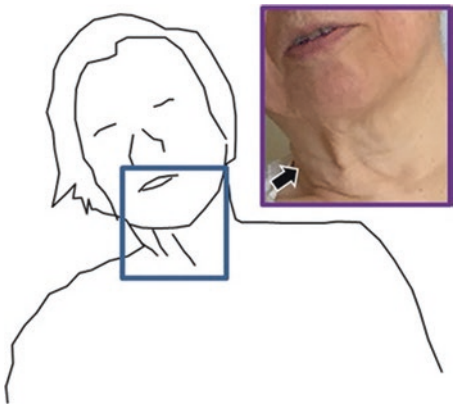

Fig. 6.6 Dystonia after stroke. From Ogawa et al. in journal of medical case reports 2018 – printed with permission from publisher – Biomed Central

right, slight neck rotation to the right flexion dystonia and pulled down right shoulder. Although in this patient dystonic posture improved gradually and spontaneously, if persistent botulinum therapy can be of significant assistance (see Chap. 11 – botulinum toxin treatment of dystonias and cervical dystonia).

Conclusion

Introduction of botulinum toxin therapy to clinical medicine has revolutionized the management of stroke related spasticity. Treatment of spastic muscles after stroke with botulinum toxins is effective and has improved the patients' quality of life. Recent data indicates safety of this treatment even with relatively high doses (up to 800 units for Botox or Xeomin). Botulinum toxin therapy also relieves the pain associated with spasticity or chronic joint pain in the paralyzed limb as well as reducing drooling and improving limb dystonia after stroke.

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