Chapter 13
Botulinum Toxin Therapy for Autonomic Dysfunction (Excessive Drooling and Excessive Sweating) and for Skin Disorders

Introduction

Salivary glands that secret saliva, and sweat glands receive their innervation from the sympathetic and parasympathetic nervous systems. Sympathetic and parasympathetic nervous systems are part of the autonomic nervous system. Autonomic nervous system is a part of nervous system that, unlike the motor system, is not under voluntary control. Saliva and sweat secret in response to peripheral stimuli independent of the individuals' wish and will. Sympathetic nervous system excites the salivary and sweat glands. Sympathetic nerves also innervate important muscles in the body such as heart and intestine. Stimulation of the sympathetic nerves increases the number of heart beats while slowing down movements of the gut. Parasympathetic nervous system is another major part of autonomic nervous system that opposes the function of the sympathetic nervous system (for example it slows heart beat or increases movements of the gut). Sympathetic and parasympathetic nerves are much thinner than motor and sensory nerves and are devoid from the fatty myelin sheet; this sheet covers motor and sensory nerves and enhances their conduction. Like motor nerves, sympathetic nerves also use a chemical agent at their endings that activates their targets (salivary or sweat glands). This chemical neurotransmitter, like that of the motor nerves, is acetylcholine.

Botulinum neurotoxins (BoNT) which are produced by a bacteria (clostridium botulinum), were purified and prepared for medical use between 1940–1970 (see Chap. 1 of this book on the history of botulinum toxins). The toxin molecule travels to the nerve endings after intramuscular or skin injection. There, through a cascade of complicated mechanisms (see Chap. 2 of this book), it blocks the release of acetylcholine from the nerve endings. This function of botulinum toxin has made it a useful commodity for treatment of a variety movement disorders, characterized by involuntary movements. Blocking acetylcholine release also decreases the muscle tone, and hence, helps spastic muscles to relax. This is another major indication of botulinum toxins that already have received approval for use in stroke, multiple

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6_13

sclerosis and cerebral palsy; intramuscular injection of BoNT can relax tense and often painful spastic muscles. Since sympathetic nerve endings also use acetylcholine as the chemical neurotransmitter to activate salivary and sweat glands, injection of BoNT into these glands can reduce secretion of saliva and sweat when excessive salivation and sweating become problematic.

Anatomy and Physiology of Salivary Glands

Three glands (parotid, submandibular, and sublingual) are the major producers of saliva (Fig. 13.1). Saliva plays an important role in lubrication, digestion, immunity and maintenance of homeostasis in the human body. The parotid gland is located under the skin in front of lower part of the ear and extends to the angle of the jaw. It is divided by the facial nerve into a superficial lobe and a deep lobe. The submandibular gland, the second largest salivary gland after the parotid, is located in the submandibular (under jaw bone) triangle. The sublingual (under the tongue) gland is the smallest of the three and lies in the anterior floor of the mouth below the tongue (Fig. 13.1).

Each gland produces high volumes of saliva relative to its mass. Since parotid gland is the largest (14–28 grams), most saliva is produced by this gland. Production of saliva is not controlled by an individual's will, but rather, controlled by autonomic nervous system, sympathetic and parasympathetic nerve fibers. In stimulated state, i.e chewing, parotids glands provide most of the saliva. In the unstimulated state, however, 70% of saliva is secreted by the submandibular (weighs 10–15 grams) and sublingual glands. The flow of saliva is five times greater in the stimulated state than in the resting state.

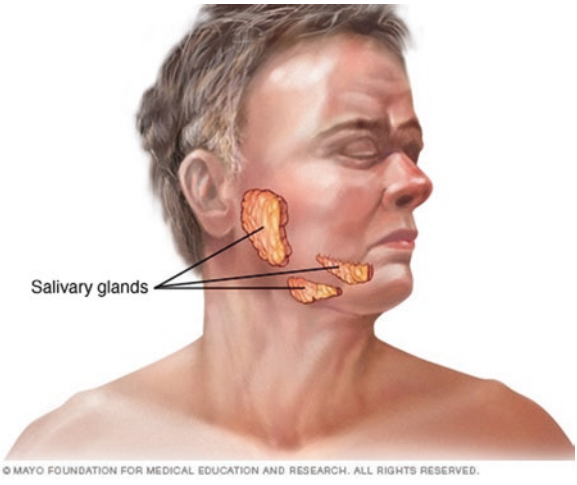

Fig. 13.1 Location of the three major salivary glands: parotid, Submandibular (*under jaw bone*) and sublingual(*under the tongue*) glands. Printed with permission from Mayo Foundation

Sialorrhea or drooling is a debilitating condition which implies presence of excess saliva in the mouth beyond the lip margin. Drooling is common in babies but subsides between the ages 15 to 36 months with establishment of salivary continence. Drooling is considered abnormal if it persists beyond 4 years of age.

Pathologic drooling can be due to increased production of saliva (usually due to certain drugs) or related to disease conditions that disrupt mechanisms that clear and remove saliva from the mouth. These diseases cause retainment of saliva in the mouth and drooling by weakening the tongue or impairing the swallowing reflexes. Drooling frequently occurs in neurological diseases such as Parkinson's disease (PD), amyotrophic lateral sclerosis (Lou Gehrig's disease -ALS) and in children with cerebral palsy (CP). In adults, PD is the most common cause [4] of drooling affecting 70%–80% the patients. In children, the most common cause of drooling is cerebral palsy with a quoted incidence of 10–38%. Drooling due to increased production of saliva is seen in 30%–80% of schizophrenic patients who are treated with clozapine. Regardless of the cause, excessive drooling can lead to social embarrassment, aspiration, skin breakout, bad odor, and sometimes local infection.

Sialorrhea is difficult to treat. Management can be conservative or invasive. Conservative treatments include changes in diet or habits of eating, oral-motor exercises, intra-oral devices such as palatal training devices, and oral medications. Behavioral modification has been advocated by some, but results have been inconsistent. Severe cases of drooling non-responsive to medications may require removal of salivary gland (s) by surgery or local radiation of the salivary glands. Surgical approach offers more permanent results, but it is an invasive process that is not without side effects. Local radiation of the glands is now hardly practiced.

The main category of drugs used for reduction of drooling is anticholinergic medications. These medications block the effect of acetylcholine that activates the glands to secret saliva. Several anticholinergic drugs are available in the market under the trade names of glycopyrrolate, benztropine, scopalamine and tropicamide. Glycopyrrolate oral solution is the first drug approved in the United States for treatment of drooling in children who have neurologic conditions. Elderly patients tolerate oral anticholinergic agents poorly due to side effects such as confusion and blurring of vision. Glycopyrrolate is a favorite of many physicians since presence of a quaternary ammonium in its molecule prevents its passage through blood-brain barrier in large amounts, ultimately decreasing the occurrence of central side effects. It is effective and safe at a dose of 1 mg, three times a day. In one high quality study (comparing the drug with placebo), application of intraoral tropicamide films (1 mg), was shown to decrease saliva volume in non-demented parkinson patients. Medications that are used for relieving heartburn and reflux have also been suggested for treatment of drooling; however, their effectiveness in managing drooling has not been shown in any high quality studies (comparing the drug with placebo).

Botulinum Neurotoxin (BoNT) Therapy for Excessive Drooling (Sialorrhea)

Two forms of botulinum toxin(types A and B) are approved for clinical practice out of 7 discovered toxin types. Three type A toxins are marketed in US under the trade names of Botox, Xeomin and Dysport. The type B toxin is called Myobloc (Neurobloc in Europe) see (Chap. 3 for description on marketed BoNTs). Due to inherent molecular differences among these toxins, the projected equivalency value of these BoNTs is only an approximation; 1 unit of Botox = 1 unit of Xeomin = 2.5–3 units of Dysport = 40–50 units of Myobloc.

The first study (open label, no placebo used for comparison) indicating efficacy of BoNTs in reducing excessive saliva in 9 patients with Parkinson's disease was published in the year 2000. All patients demonstrated reduction of saliva after injection of Botox into the parotid gland. None reported any side effects. Since then, the efficacy and safety of BoNTs in management of sialorrhea was assessed by 9 high quality studies (comparing toxin injection with placebo) both in adults and in children. Six of these studies were conducted with the type B toxin. These studies have found objective evidence (measured by reduction in the saliva volume) after BoNT injection into the glands. This was associated, in most patients, with expression of satisfaction and improvement of their quality of life. In adults, side effects were infrequent and minor consisting of slight local pain at the time of injection, minor local bleeding and subtle-transient swallowing difficulty. Patients with drooling in Parkinson's disease responded better than other patients. The effect lasted 3–6 months. It has been shown that the composition of the saliva does not change after BoNT injections. One study compared the effect of type A and type B toxins in sialorrhea and found earlier onset with type B toxin, but equal efficacy. Another study found equal efficacy between two type A toxins (Botox and Xeomin). In children with cerebral palsy the results were equally impressive and side effects were infrequent and subtle: however, one study reported development of swallowing difficulties (transient) in several children.

Technique of Injection

A small narrow syringe (1 cc) with 10 divisions of 0.1 cc and a short, thin needle (½ to ¾ inch, gauge 30) is used for injection of the toxin into the glands. Although many physicians inject parotid gland only, injection of both parotid and submaxillary glands is advisable for achieving best results. Many physicians, perform injections merely based on the anatomical knowledge of the parotid and sumaxillary gland locations without the use of ancillary techniques. (Fig. 13.2).

The number of injection per gland varies among different physicians. Most physicians recommend injecting into more than one site for the parotid gland.

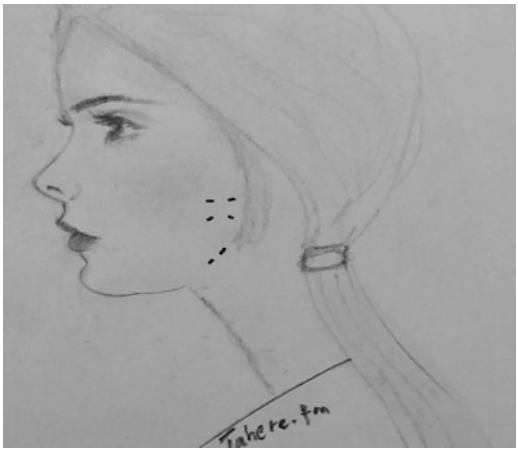

Fig. 13.2 Author's injection technique using 4 injection sites for the parotid gland and 2 injection sites for the submaxillary gland (located below the jaw bone close to angle of the jaw). Drawing courtesy of Dr.Tahereh Mousavi

A more precise way to perform parotid and submaxillary injections for drooling is via the use of ultrasound. Under ultrasound guidance, it is possible to visualize the gland, see the tip of the needle as it is approaching and entering into the gland as well as visualization of the injected material into the gland. In adults, usually, no local anaesthesia is necessary before injections. The glands are under the skin and easily accessible. In children, local application of a numbing cream such as Emla cream and/or application of a numbing skin spray seconds before each injection is helpful.

Excessive Sweating (Hyperhidrosis)

Hyperhidrosis (excessive sweating) is a debilitating condition that can lead to emotional and social embarrassment. In severe cases, it can cause occupational, physical and psychological disability. One epidemiologic survey in 2004 estimated that as many as 0.5% of the US population may be suffering from the debilitating effects of hyperhidrosis with major interference in daily activities.

Hyperhidrosis can be classified into primary and secondary hyperhidrosis. Primary hyperhidrosis has an incidence of 06–1% in general population [3]. Many cases of childhood hyperhidrosis are hereditary with more than one member of the family being affected. A genetically dominant form of excessive sweating with the onset in childhood is now recognized with a defined abnormality of chromosome 14.

The diagnostic criteria for primary hyperhidrosis include excessive sweating for at least 6 months, no obvious cause and least two of the following features: sweating occurring at least once per week, sweating impairing daily activities, a bilateral and relatively symmetric pattern of sweating, an age of onset younger than 25, positive family history and cessation of focal sweating during sleep.

Secondary hyperhidrosis can be caused by certain drugs (for example sertraline), induced by toxins (acrylamide)], caused by a systemic illness (endocrine and metabolic disorders, tumors, spinal cord lesions). Certain congenital disorders that involve the autonomic nervous system such as familial dysautonomia (Riley-Day syndrome) are also often associated with excessive sweating. . Among the other causes of secondary hyperhidrosis is compensatory hyperhidrosis. In this condition, there is increased sweating in parts of the body below the level of a surgery called sympathectomy. Gustatory hyperhidrosis is a familial disorder in which, the face sweats during eating. Gustatory hyperhidrosis is sometimes the results of trauma to the face or neck.

The glands that secret sweat are called eccrine glands. Eccrine glands have the highest concentration in the region of armpit (axilla), palms and sole of the feet; hence these are the primary areas involved in excessive sweating. Excessive sweating of the face and scalp is less common. Sympathetic nervous system, a division of autonomic nervous system, stimulates sweat glands. As mentioned earlier this chapter, the nerves of autonomic nervous system (sympathetic or parasympathetic) are very thin fibers with slow conduction (compared to motor nerves) and function independent of individual's will. Sympathetic nerves use acetylcholine at their end as the chemical transmitter that excites the sweat glands.

Anatomy and Physiology of Sweating

The pathway for control of sweating (sudomotor pathway) starts in the cortex, the 3–4 mm superficial layer of the brain that contains millions of nerve cells**.** From cortex, the fibers travel down to lower centers of the nervous system which exert autonomic control such as hypothalamus and medulla (elongated lower part of the brain before spinal cord). The sweat fibers cross in medulla and travel on the other side of the spinal cord. Emerging from the lateral part of the spinal cord, sympathetic nerves involved in secretion of sweat enter sympathetic ganglia. Sympathetic ganglia are, a group of sympathetic nerve cells send fibers to the sweat glands. These fibers are thin sympathetic fibers with acetylcholine at their end as chemical activator of the sweat gland. A lesion anywhere in this pathway, can interrupt the secretion of sweat.

Sweat glands in the palms and soles are mostly activated by emotional stimuli. Primary hyperhidrosis which is usually familial and absent during sleep, most likely results from abnormal function of the areas of the brain responsible for emotional sweating such as hypothalamus. Sweating also happens during exposure to external heat. It is believed this form sweating which has a more diffuse distribution (including face and scalp) has a different anatomic pathway in the brain.

Treatment of Excessive Sweating (Hyperhidrosis)

Treatment strategies to control excessive sweating include application of topical agents on the skin, administration of oral medications, a procedure called iontophoresis and local injection of botulinum toxins into the sweated areas:

Aluminum salts are the main topical agents used for treatment of hyperhidrosis. Their mechanism of action is not clear but, is attributed to either an interaction between aluminum chloride and keratin in the sweat ducts leading to sweat duct closure or to a direct action on the excretory eccrine gland epithelium (lining cells of the sweat gland). Aluminum salts are only effective for mild cases of hyperhidrosis; their duration of effect is often limited to 48 hours. Skin irritation, probably related to high salt concentration is the main side effect of aluminum salt treatment.

Glycopyrrolate 1–2 mg twice a day, oxybutynin 5–7.5 mg twice a day [20], and methantheline bromide 50 mg twice a day are commonly used anticholinergic agents for pharmacological management of hyperhidrosis. Side effects, especially in elderly, can be disabling to include dry mouth, blurring of vision, urinary hesitancy, dizziness, tachycardia, and confusion. Clonidine, given as 0.1 mg twice a day, is also partially effective by inhibiting the sympathetic output. Side effects include dry mouth, dizziness, constipation, sedation and a fall in blood pressure.

Iontophoresis is a procedure that introduces an ionized substance through application of a direct electrical current on intact skin. Tap water and anticholinergic agents (glycopyrrolate) are usually used for iontophoresis. Tap water iontophoresis must be performed initially every two-three days until therapeutic effect is achieved. Once therapeutic effect is achieved for two weeks, treatment can be done once every two to three weeks. Duration of the effect for both tap water and anticholinergic iontophoresis is only a few days which makes iontophoresis an undesirable mode of treatment of hyperhidrosis.

Botulinum Toxin Treatment of Hyperhidrosis

Injection of botulinum toxin into the skin is now an established mode of treatment for excessive sweating. Its advantage over other modes of treatment include less frequent side effects and long duration of action after a single injection (3–9 months) eliminating the need for taking daily oral medications or daily application of topical creams.

Over the past 15 years, several high quality studies (comparing toxin injections with placebo injections) have demonstrated that injections of BoNTs into or under the skin, reduces the volume of the local sweating way out of proportion to placebo injections. Although the injection are painful (despite topical application of numbing cream before injections), 90% of the adults tolerate the injections and prefer 15–20 min of discomfort for every 3–9 months to the debilitating excessive

sweating. At the present time only Botox is FDA approved for management of hyperhidrosis; the medical literature however indicates the other two type A toxins (Xeomin and Dysport) and the type B toxin (Myobloc) are equally effective for this indication. Long term follow ups exceeding 10 years are now available and have shown continued efficacy of BoNT injections in hyperhidrosis with no reduction of efficacy after prolonged use.

Technique of Injections

Injections are performed with a thin (guage 30) and short needle (½ inch) into the skin, using a grid like scheme (Figs. 13.3 and 13.4). Since the skin is sensitive, it is advisable to numb the skin before injections. Emla cream can be applied to the intended areas (axilla, palm, sole of the foot) an hour before the injections. The author, also uses a numbing spray intermittently during the injection that provides additional numbing of the skin for a few seconds. The injected dose of toxin per site should be very small in order to avoid weakening of the muscles underneath the skin. This is particularly important in the palm area to avoid weakness of the fingers. For Botox and Xeomin, the advocated dose per injection site is 2–2.5 units. For Dysport (another type A toxin) and Myobloc (type B toxin) the units are 2.5 to 3 times and 40–50 times larger than Botox units, respectively. Most authors inject at 20 sites in each armpit and inject more sites for the palm and foot injections. Usually fingers and toes are also covered in the plan of injections (Fig. 13.3). Excessive sweating in bilateral, hence injections should cover both sides. In experienced hands Botox (or other toxins) injections can be performed quickly over 10–15 min for

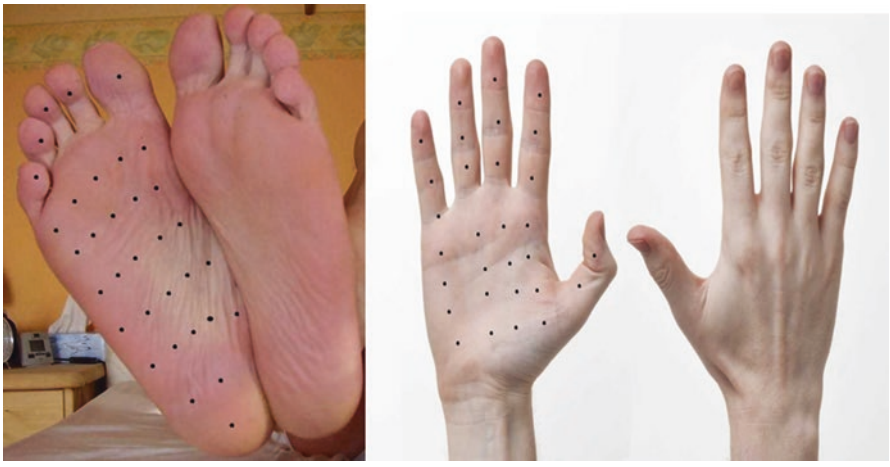

Fig. 13.3 The sites of Botox injections for excessive sweating of the sole of the foot and plam tuition. The images slightly modified from wikemedia under creative common attribution

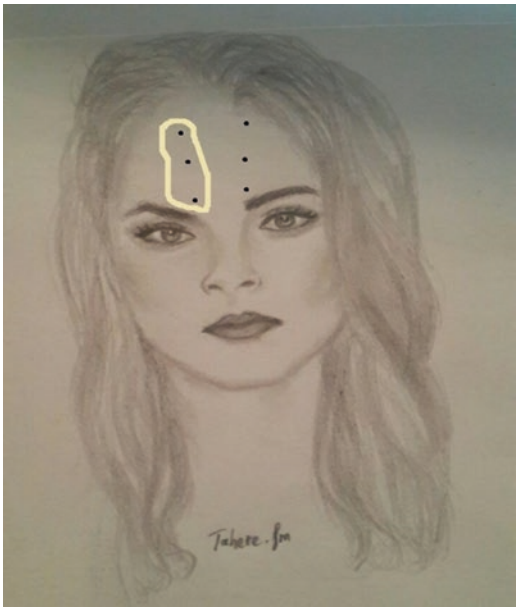

Fig. 13.4 Botox injection for recalcitrant itch of the right forehead (area of itch is painted in yellow). Injection dose is 5 units of Botox per site- Dawing courtesy of Dr.Tahere Mousavi

each side. Side effects are uncommon and usually limited to local pain and minor bleeding. As other indications of BoNT therapy, a mild, transient flu like reaction may occur in 5–10% of the patients.

Case Report

A 42 year- old women was referred to Yale Botulinum Toxin Clinic for excessive seating of the sole of the feet since childhood. Her mother and younger brother had the same problem since early teens. She had no other health problems. She has tried different anticholinergic medications for management of her foot hyperhidrosis but the effect was modest and oral drugs caused disturbing dry mouth and blurring of vision. After numbing the sole of the feet with Emla cream she was injected with Botox on both feet (Fig. 13.3). The total dose per feet was close to 100 units; 2.5 units was injected per each site. She tolerated the procedure and had no side effects. Over the next 6 years of follow up, patient visited the clinic every 4–6 months and received similar injections. She continued to do well; each time expressing satisfaction with treatment.

Current strategies for treatment of drooling (sialorrhea) and excessive sweating (hyperhidrosis) are discussed in detail in several recent publications [1–8].

Potential Indications of BoNT Therapy in some Skin Disorders: Intractable Itch and Psoriasis

Recalcitrant Ich

Itch is an irritating sensation involving a part of skin often provoking a scratch response to relieve it. In many cases, acute itch is part of a body defense mechanism against an external noxious stimulus. Chronic itch can be seen in a variety of medical diseases such as skin disorders (i.e. psoriasis), systemic disorders (kidney or liver dysfunction), infectious conditions and nerve damage from an external cause. It is believed that itching sensation is conveyed to the brain by very thin nerve fibers similar to those that carry pain sensation.

Treatment of persistent itch includes non-pharmacological approaches, pharmacological approaches an neurostimulation. Non-pharmacological approaches include wearing protective garments, avoiding warm temperature and ultravioletB exposure. Pharmacological therapy includes application of capsaicin, lidocaine 5%, cortisone creams and tacrolimus. Anecdotal reports suggest efficacy of antiepileptic drugs pregabalin, carbamazepine and lamotrigine in management of chronic itch disorder. Transient stimulation of peripheral nerves (neural stimulation) has been reported to provide temporary relief from recalcitrant itch in a limited number of patients.

After injection into the muscle or skin, botulinum toxins block the release and action of several specific proteins which are important in transmission of pain sensation to the brain. Some of these proteins such as histamine and substance P are believed to be important in the pathophysiology of itch as well. In 2008, the author's group at Yale University were first to report the utility of botulinum toxin injection into the skin in a patient with recalcitrant facial itch [9]. Four years later, another group of doctors published a similar result with botulinum toxin therapy in chronic itch disorder.

Case Report

A 55 year- old women presented to Yale Botulinum toxin clinic for evaluation of intense right facial itch for the past 6 years. The affected area extended from the medial part of the right eye brow up across the forehead ending at the hair line. She had had a right frontal sinus injury 14 years ago. The skin at the region of forehead surgery had a tingling sensation for several years before the intense itch developed in the same area. Patient complained of poor quality of life due to her debilitating facial itch. Treatment with oral medications and local novocaine injections provided minimal relief. Botox was injected into the forehead at the area of intense itch (5 units at three sites –Fig. 13.4). Similar areas were injected on the left side of the forehead in order to maintain forehead symmetry.

After a week, the patient reported marked reduction of the itch intensity which lasted for months. The patient moved out of the area and lost to follow up for

6 months. She returned to the clinic a year later for a second injection. The injection again relieved her itch. In her words "Botox injection was the only thing that helped her itch problem ".

Psoriasis

Psoriasis is a common skin lesion characterized by proliferation of skin cells causing raised and discolored skin areas. The affected skin areas often itch and cause local pain and are cosmetically unpleasant. In plaque psoriasis lesions can affect any part of the body whereas in inverse psoriasis, psoriatic lesions involve the area of skin folds (arm pit, groin, etc). Psoriasis is considered an autoimmune disease in that the immune system of the patient mistakenly attacks the patient's own tissue, skin in case of psoriasis.

In 1998, Dr. Zanchi and his colleagues published results of their study on 15 patients with inverse psoriasis who were given Botox injections into the psoriatic skin lesions [10]. Lesions were in the armpit, groin and in several women below the breast in the inframammary fold. Injections were performed in a grid-like pattern, 2.8 centimeters apart with each site receiving 2.4 units of Botox. Patients were followed for 2, 4 and 12 days. All patients reported improvement of itch and local pain. Photographs of the lesions demonstrated notable improvement of redness and healing of the lesions in 13 of 15 patients. In the following years, other investigators have published case reports demonstrating clearing of skin lesions in both plaque and inverse psoriasis after botulinum toxin injections Fig. 13.5.

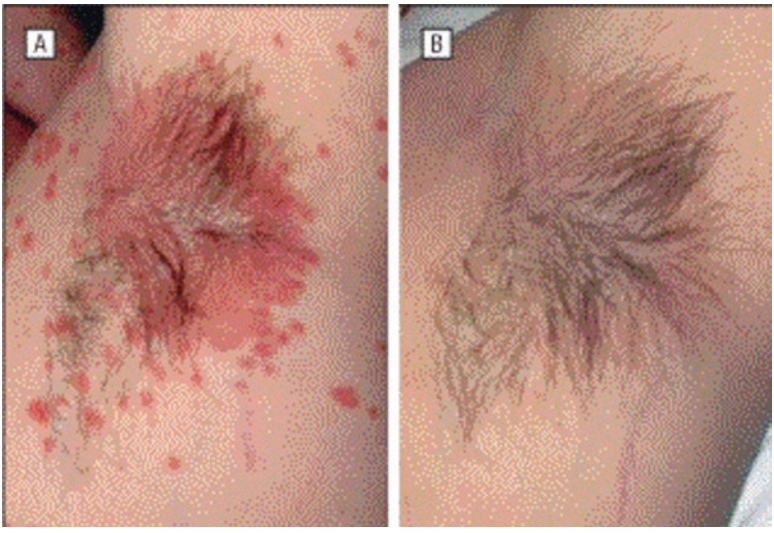

Fig. 13.5 Psoriasis of armpit: a- before and b- after treatment with Botox injections (100 units). From Saber and Co-workers Archieves of Dermatology 2011. Printed with permission from Publisher American Medical Association

Conclusion

Local injections of botulinum toxins (A or B) have been shown to be effective in reducing saliva and sweat in patients affected by drooling or excessive sweating. This mode of treatment is already practiced by many clinicians to alleviate many patients' symptoms. Botulinum toxin treatment of drooling and excessive sweating is safe; with only infrequent and minor side effects. Limited data from uncontrolled studies (no comparison with placebo) suggest that injection of Botox into the skin can alleviate local pain and itch in patients affected by psoriasis and heal their skin lesions. Case reports suggest that recalcitrant itch due to other causes may also respond to injection of Botox into the affected area.

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