Chapter

12 The Use of Botulinum Neurotoxin in Otorhinolaryngology

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Introduction

Various disorders affecting the ears, nose and throat (ENT) are suited for treatment with botulinum neurotoxin (BoNT). They can be divided into two general groups:

* disorders concerning head and neck muscles (movement disorders)
* disorders caused by a pathological secretion of glands located in the head and neck region.

Table 12.1 summarizes the diseases relevant to otolaryngology. The focus in this chapter lies on indications that are *not* reviewed in other chapters; therefore, laryngeal dystonia, hemifacial spasm, blepharospasm and synkinesis following defective healing of the facial nerve will not be covered here.

Dysphagia and Speech Problems Following Laryngectomy

Some patients are unable to achieve an adequate speech level for optimal communication after laryngectomy. One of the causes is spasms of the cricopharyngeal muscle. In this condition, BoNT can reduce the muscle activity and improve the quality of speech (Chao *et al.*, 2004). Swallowing disorders in neurological patients can result from a disturbed coordination of the relaxation of the upper esophageal sphincter and can lead to pulmonary aspiration. The cricopharyngeal muscle is a sphincter between the inferior constrictor muscle and the cervical esophagus and is primarily innervated by the vagus nerve.

The following procedure can be used as a test prior to a planned myectomy or as a single therapeutic option that has to be repeated. Botulinum neurotoxin was injection into the cricopharyngeal muscle at three injection sites under general anesthesia, using 10–20 U onabotulinumtoxinA/incobotulinumtoxinA (or 50–100 U abobotulinumtoxinA or 500–1000 U rimabotulinumtoxinB [BoNT B]) (Fig. 12.1).

In dysphagia caused by spasms or insufficient relaxation of the upper oesophageal sphincter, injection of BoNT as described can improve the patients' complaints (Fig. 12.2). Patient should be evaluated for symptoms of concomitant gastroesophageal reflux to avoid side effects such as "reflux-laryngitis." If there is gastroesophageal reflux, the etiology and treatment should be clarified prior to initiation of BoNT therapy.

Table 12.1 Diseases treated with botulinum neurotoxin type A in otorhinolaryngology

Movement disorders	Disorders of the autonomous nerve system
Facial nerve paralysis	Gustatory sweating, Frey's syndrome
Hemifacial spasm	Hypersalivation, sialorrhea
Blepharospasm, Meige's syndrome	Intrinsic rhinitis
Synkinesis following defective healing of the facial nerve	Hyperlacrimation, tearing
Oromandibular dystonia	
Laryngeal dystonia	
Palatal tremor	
Dysphagia	

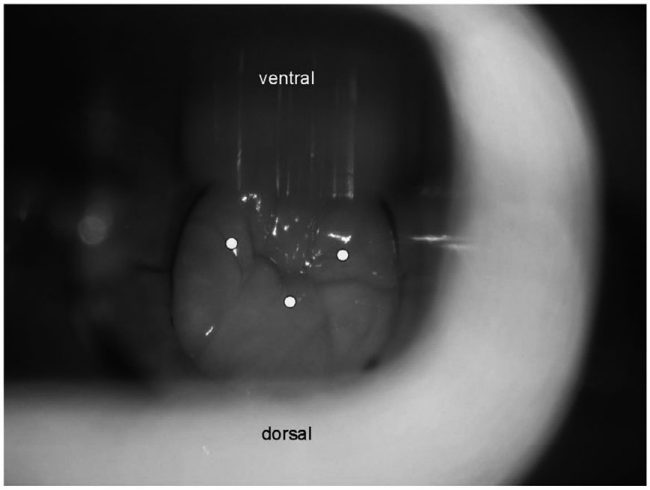

Fig. 12.1 The cricopharyngeal muscle. Intraoperative aspect prior to injection of botulinum neurotoxin into the cricopharyngeal muscle. The dots mark the injection sites (20 U onabotulinumtoxinA at each point).

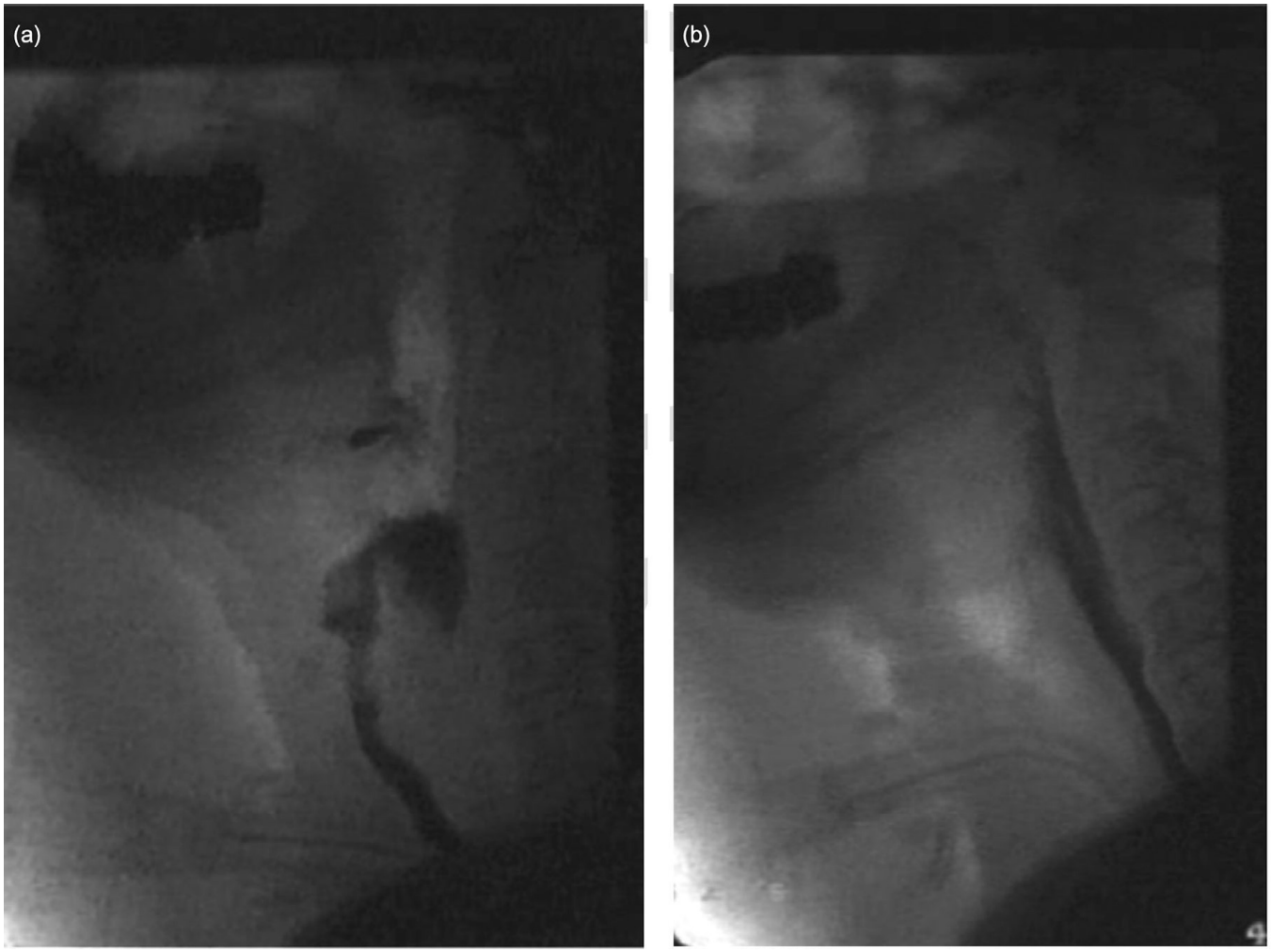

Fig. 12.2 Patient with severe swallowing disorder caused by irregular function of the upper esophageal sphincter. (a) Aspiration during swallowing. (b) Following three injections of botulinum neurotoxin (20 U onabotulinumtoxinA), the pharyngo-esophageal passage is normalized.

Palatal Tremor

Repetitive contractions of the muscles of the soft palate (palatoglossus, palatopharyngeus, salpingopharyngeus, tensor and levator veli palatini muscles) lead to a rhythmic elevation of the soft palate. This disorder has two forms, symptomatic palatal tremor and essential palatal tremor. Symptomatic palatal tremor can cause speech and also swallowing disorders through velopharyngeal insufficiency. Most patients suffering from essential palatal tremor complain of "ear clicking." This rhythmic tinnitus is caused by a repetitive opening and closure of the orifice of the eustachian tube. A particular sequel of pathological activity of soft palate muscles is the syndrome of a patulous eustachian tube. These patients suffer from "autophonia" caused by an open eustachian tube due to the increased muscle tension of the paratubal muscles (salpingopharyngeus, tensor and levator veli palatini muscles) (Olthoff *et al.*, 2007).

For the first treatment session, the injection of in total 5 U onabotulinumtoxinA/incobotulinumtoxinA (uni- or bilaterally) (25 U abobotulinumtoxinA; 250 U rimabotulinumtoxinB) into the soft palate (Figs. 12.3 and 12.4) is adequate in most patients. If necessary, this can be increased to 15 U onabotulinumtoxinA/incobotulinumtoxinA (75 U abobotulinumtoxinA; 750 U rimabotulinumtoxinB) on each side. The application is normally performed transorally (transpalatinal or via postrhinoscopy) under endoscopic control. The insertion of the tensor veli palatini muscle is used as landmark for the treatment of palatal tremor and the salpingopharyngeal fold as landmark for the treatment of a patulous eustachian tube (Figs. 12.3 and 12.4). To optimize detection of the target muscle, injection under electromyographic control is recommended.

Landmarks are given to avoid vascular injections and to indicate the most "responsible" muscle. The synergistic function of targeted soft palate and paratubal muscles (salpingopharyngeus, tensor and levator veli palatini) often interferes with clinical and therapeutical separation. To avoid side effects such as iatrogenic velopharyngeal

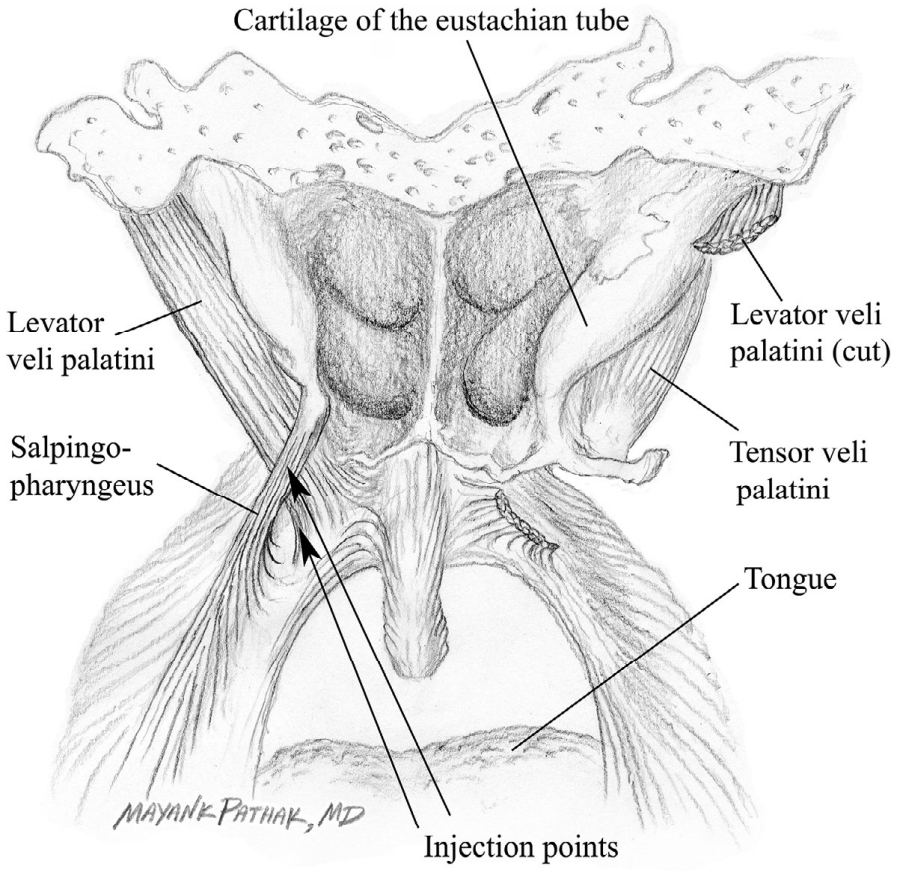

Fig. 12.3 Dorsal view of the nasopharynx and soft palate (modified after Tillmann, 2005). The arrows mark the possible sites of onabotulinumtoxinA injections. The salpingopharyngeal fold is used as a landmark.

insufficiency, treatment should be started with low doses, as described above.

Hypersalivation (Sialorrhea)

Hypersalivation can be caused by various conditions such as tumour surgery, neurological and pediatric disorders and disturbances of wound healing following ENT surgery.

Hypersalivation also is of relevance for a number of reasons in patients suffering from head and neck cancers. Some of these patients are unable to swallow their saliva because of a stenosis of the upper esophageal sphincter caused by scar formation after tumor resection. In other patients, there are disturbances of the sensory control of the "entrance" of the supraglottic tissues of the larynx, allowing saliva to pass into the larynx. In patients with Parkinson's disease, decreased swallowing also leads to hypersalivation as it interferes with saliva clearance. This may lead to continuous aspiration and aspiration pneumonia. In a third group of patients, complications of impaired wound healing after extended surgery can occur, such as fistula formation following laryngectomy. Saliva is a very aggressive agent and can inhibit the normal healing process.

Both the parotid and submandibular glands are of interest in this context. The parotid gland is the largest of the salivary glands. It is located in the so-called parotid compartment in the pre- and subauricular region, with a large compartment lying on the masseter muscle. The gland also has contact with the sternocleidomastoid muscle (Fig. 12.5).

The submandibular gland (Figs. 12.6 and 12.7) lies between the two bellies of the digastric muscle and the inferior margin of the mandible, which form the submandibular triangle. The gland is divided into two parts – the superficial lobe and the deep lobe – by the mylohyoid muscle (Fig. 12.6c).

In the first period of our treatment series we injected according to the Ellies protocol (Ellies et al. 2014). To reduce saliva flow, we follow the SIAXI study (Jost *et al.*, 2019). We inject 30 units incobotulinumtoxinA into each parotid gland (Figs. 12.8 and 12.9) and 20 units incobotulinumtoxinA into each submandibular gland at one or two sites (Fig. 12.10). Injection of botulinum neurotoxin type A (BoNT-A) has been shown to be effective in reducing saliva flow (Fig. 12.11). Side effects such as local pain, diarrhea, luxation of the mandible and a "dry mouth" are rare.

Gustatory Sweating (Frey's Syndrome)

Gustatory sweating is a common sequel of parotid gland surgery (Laskawi and Rohrbach, 2002). The clinical picture is characterized by extensive production of sweat in the lateral region of the face. The sweating can be intense and become a

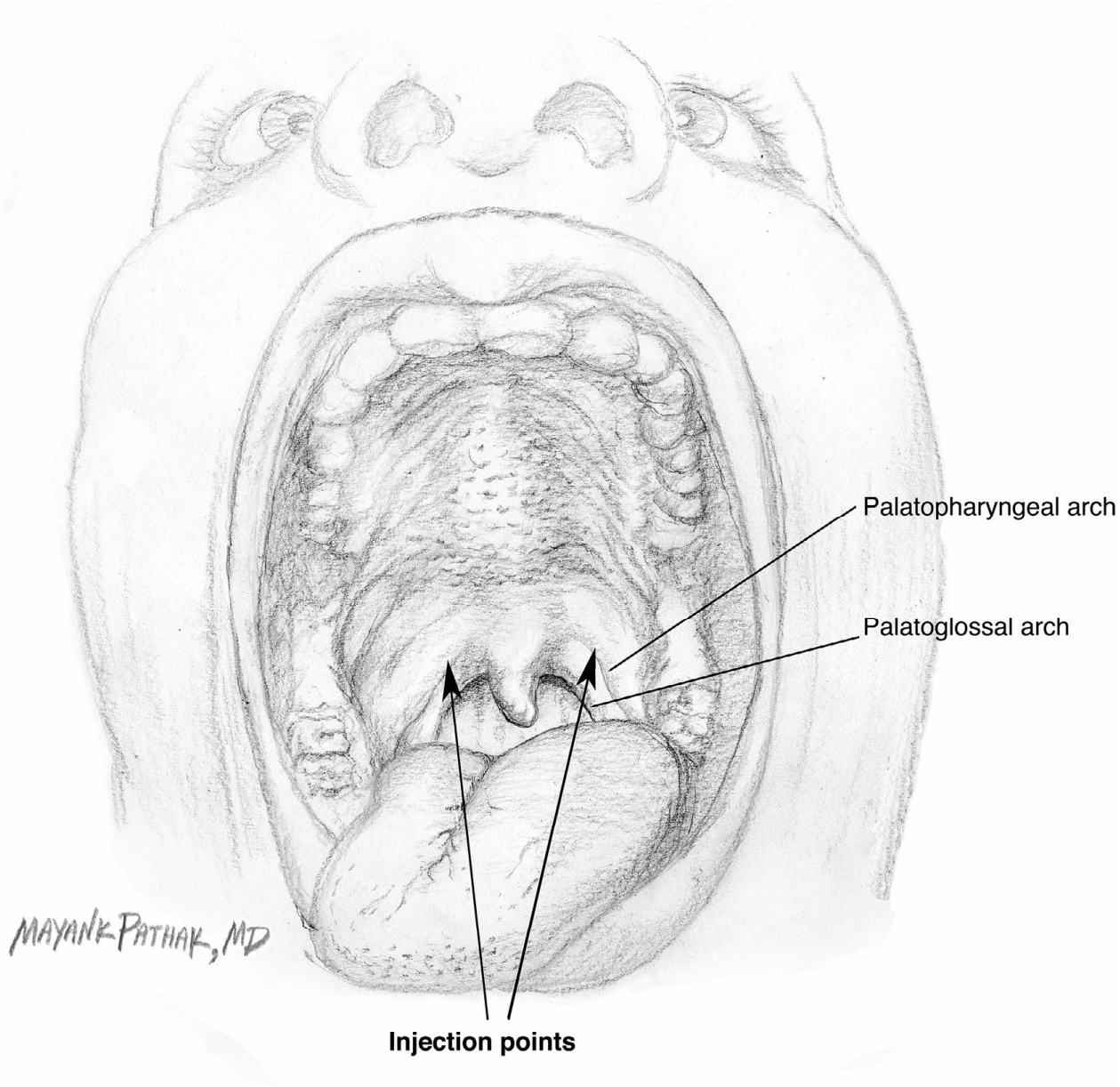

Fig. 12.4 Transoral view of injection sites in patients with palatal tremor. The insertion of the tensor veli palatini muscle is used as landmark.

cause of a serious social stigma. Injection with BoNT has become the first-line treatment (Laskawi and Rohrbach, 2002).

For an optimal outcome, the affected area should be marked with Minor's test (Fig. 12.12). First, the face is divided into regional "boxes" using a waterproof pen (Fig. 12.12b). The affected skin is covered with iodine solution before starch powder is applied. The sweat produced by masticating an apple induces a reaction between the iodine solution and the starch powder, resulting in an apparent deep blue color (Laskawi and Rohrbach, 2002).

Intracutaneous injections of BoNT (for 4 cm^2, approximately 2.5 U onabotulinumtoxinA/ incobotulinumtoxinA, 12.5 U abobotulinumtoxinA, 125 U rimabotulinumtoxinB) (Fig. 12.12c). Side effects are rare and with none of the possible sequelae, such as dryness of the skin or eczema, in some patients.

The total dose required depends on the extent of the affected area, and up to 100 U onabotulinumtoxinA/ incobotulinumtoxinA (500 U abobotulinumtoxinA, 5000 U rimabotulinumtoxinB) can be necessary. The duration of improvement persists longer than that seen in patients with movement disorders (Laskawi and Rohrbach, 2002), and some patients have a symptom-free interval of several years.

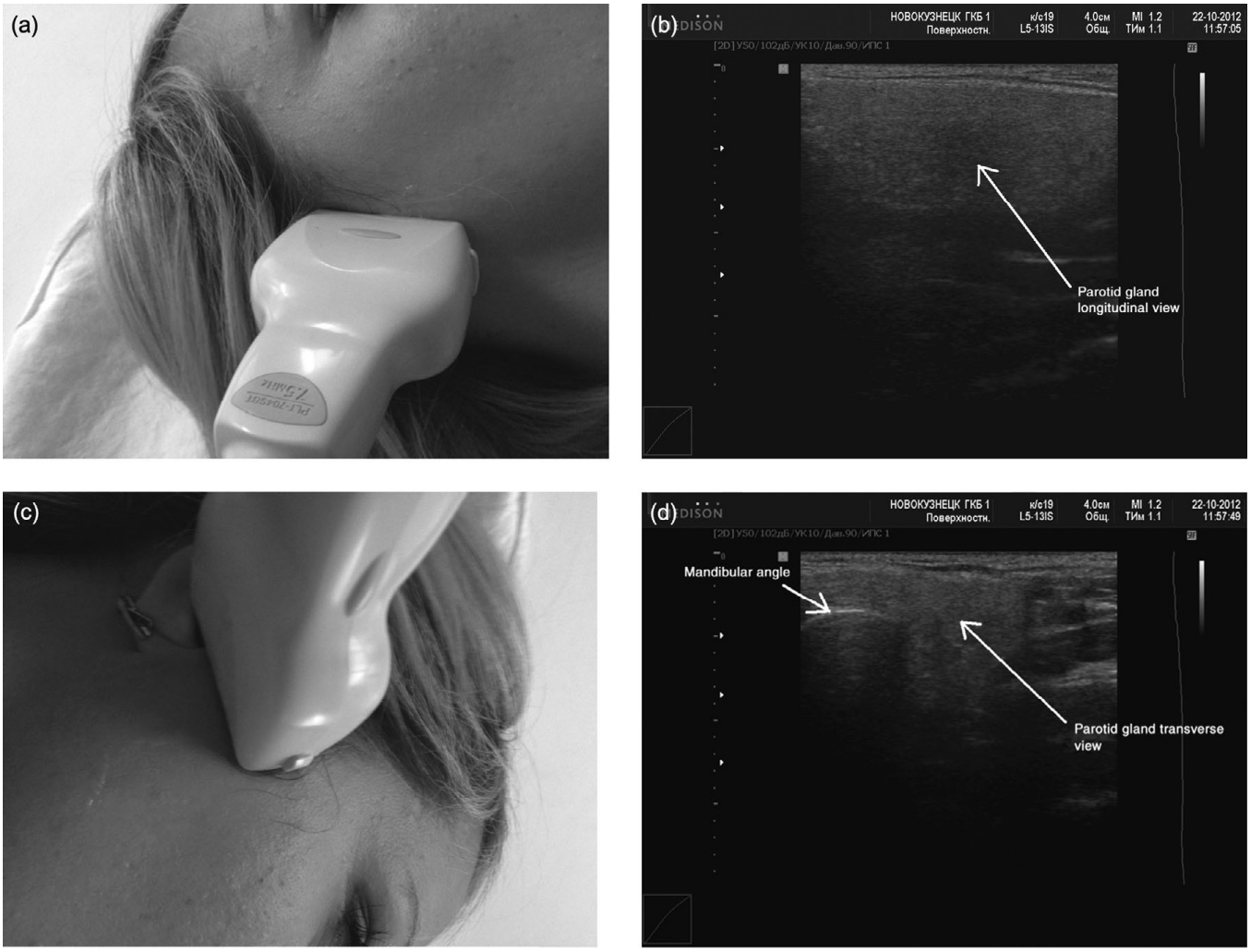

Fig. 12.5 The parotid gland under ultrasound. The presentation depends on the position of the probe. (a,b). Probe in the vertical position (a) to give a longitudinal view of the parotid (b). (c,d) Probe in the horizontal position (c) to give a transverse view of the parotid (d).

Rhinorrhea, Intrinsic Rhinitis

In the past few years, BoNT-A has been used in intrinsic or allergic rhinitis (Özcan *et al.*, 2006). The main symptom in these disorders is extensive rhinorrhea with secretions dripping from the nose.

There are two approaches for applying BoNT-A in these patients: it can either be injected into the middle and lower nasal turbinates or applied with soaked on a sponge (Fig. 12.13). For the injection approach, 10 U onabotulinumtoxinA/incobotulinumtoxinA (50 U abobotulinumtoxinA, 500 U rimabotulinumtoxinB) is injected into each middle or lower turbinate. For the sponge technique, a sponge is soaked with a solution containing 40 U onabotulinumtoxinA and a sponge is applied into each nostril.

The effect of the injections has been demonstrated in placebo-controlled studies (Özcan *et al.*, 2006). Nasal secretion is reduced for about 12 weeks (Fig. 12.14). Side effects such as epistaxis or nasal crusting are uncommon.

Hyperlacrimation

Hyperlacrimation can be caused by stenoses of the lacrimal duct, misdirected secretory fibers following a degenerative paresis of the facial nerve (crocodile tears) or mechanical irritation of the cornea (in patients with lagophthalmus).

The application of BoNT is useful in reducing pathological tearing in these patients (Whittaker *et al.*, 2003; Meyer, 2004). The lacrimal gland is located in the lacrimal fossa in the lateral part of the upper orbit and is divided into two sections (Fig. 12.15). Usually 5–7.5 U onabotulinumtoxinA/incobotulinumtoxinA (25–37.5 U abobotulinumtoxinA, 250–375 U rimabotulinumtoxinB) is injected into the pars palpebralis of the lacrimal gland, which is accessible under the lateral upper lid (Fig. 12.16). Medial injection may result in ptosis as a possible side effect. The reduction of tear production lasts about 12 weeks (Fig. 12.17) (Meyer, 2004).

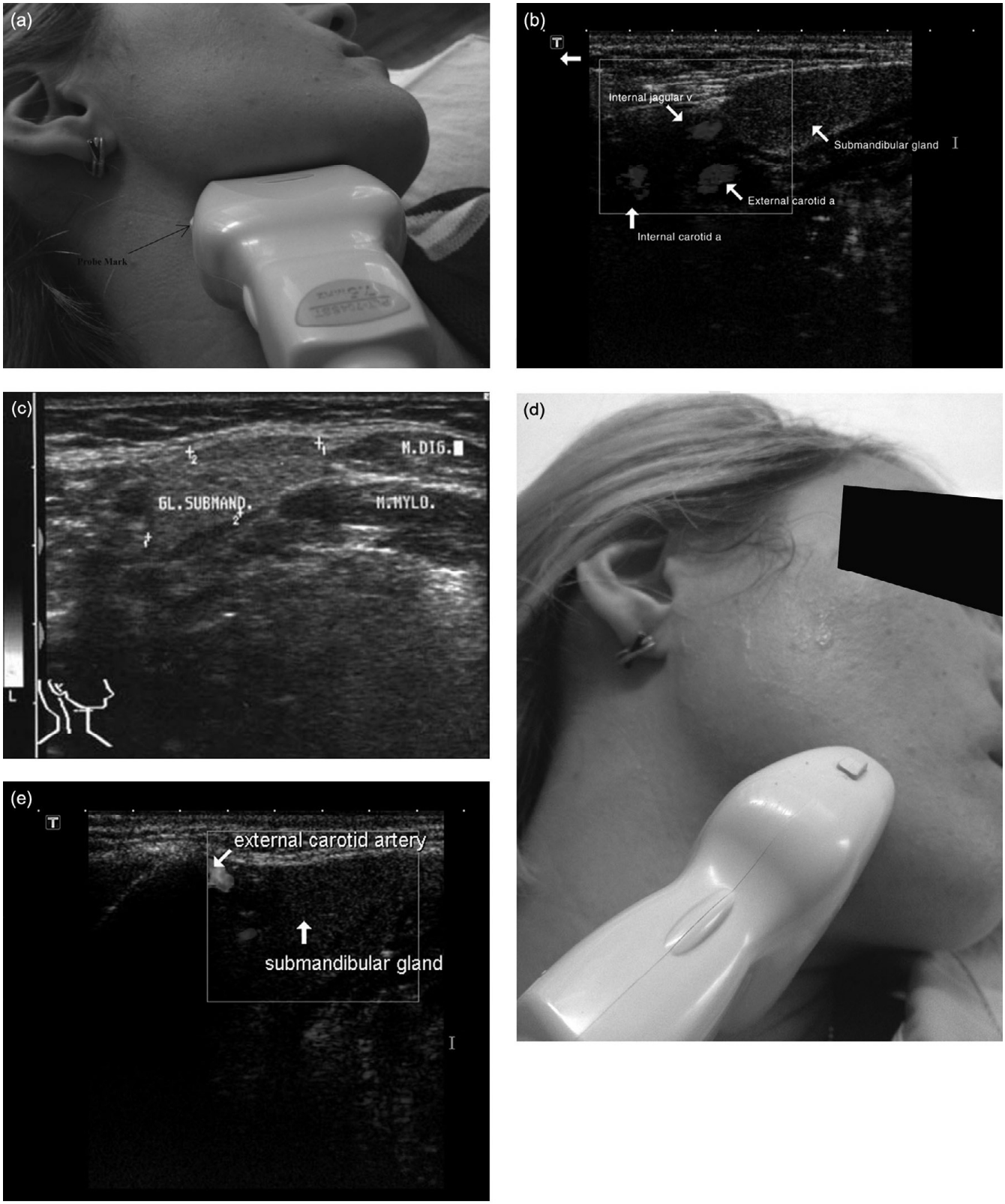

Fig. 12.6 Submandibular gland. (a) Probe in longitudinal position. (b) Longitudinal ultrasound showing the submandibular gland and other structures. Note the localization of the internal and external carotid artery and the external jugular vein. (c) The submandibular gland (GL.SUBMAND.; borders of the gland clearly marked by the four crosses) and the surrounding structures (mylohyoid muscle [M.MYLO.] and digastric muscle [M.DIG]. (d) Probe in transverse position. (e) Transverse ultrasound probe showing the submandibular gland and other structures. Note the localization of the internal and external carotid artery and the external jugular vein position.

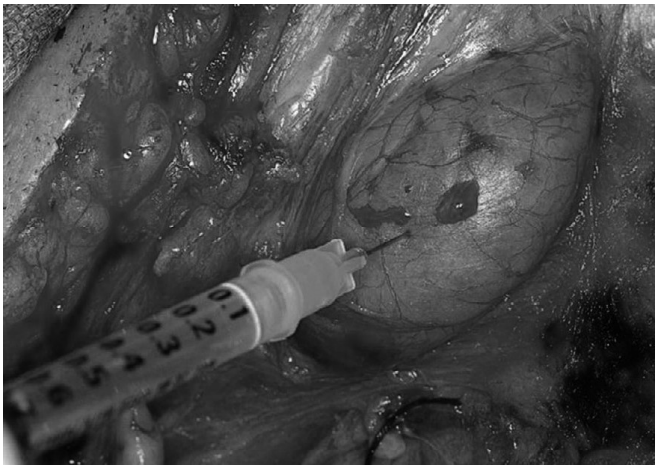

Fig. 12.7 Intraoperative injection of 15 U onabotulinumtoxinA into the submandibular gland during laryngectomy showing the anatomical position of the gland in the submandibular fossa.

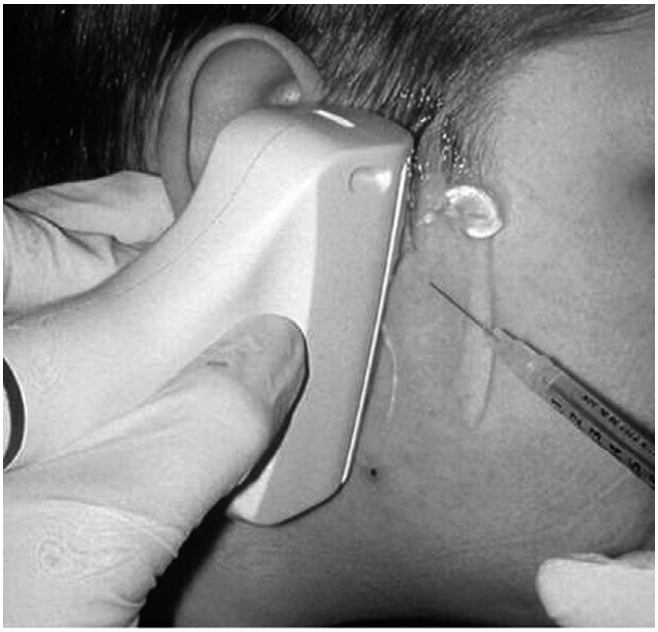

Fig. 12.8 Injection of botulinum neurotoxin type A into the parotid and submandibular glands (same technique used for both). We prefer to inject both glands, with 7.5 U onabotulinumtoxinA into each of the three points of each parotid gland and with 15 U onabotulinumtoxinA into each submandibular gland. Ultrasound-guided injection is recommended.

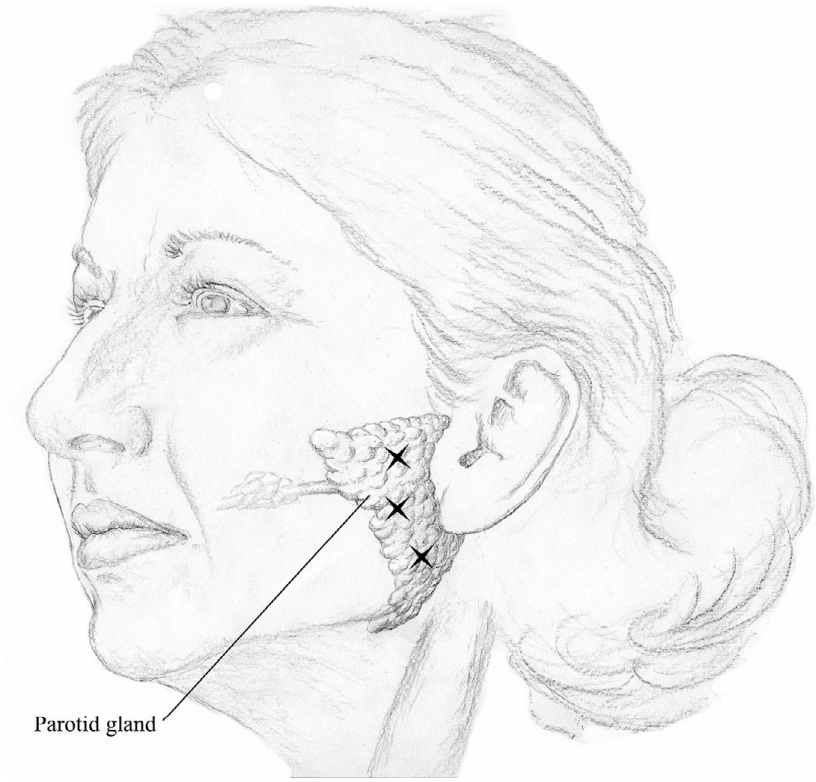

Fig. 12.9 Frontolateral view of the left parotid gland with typical injections sites for botulinum neurotoxin.

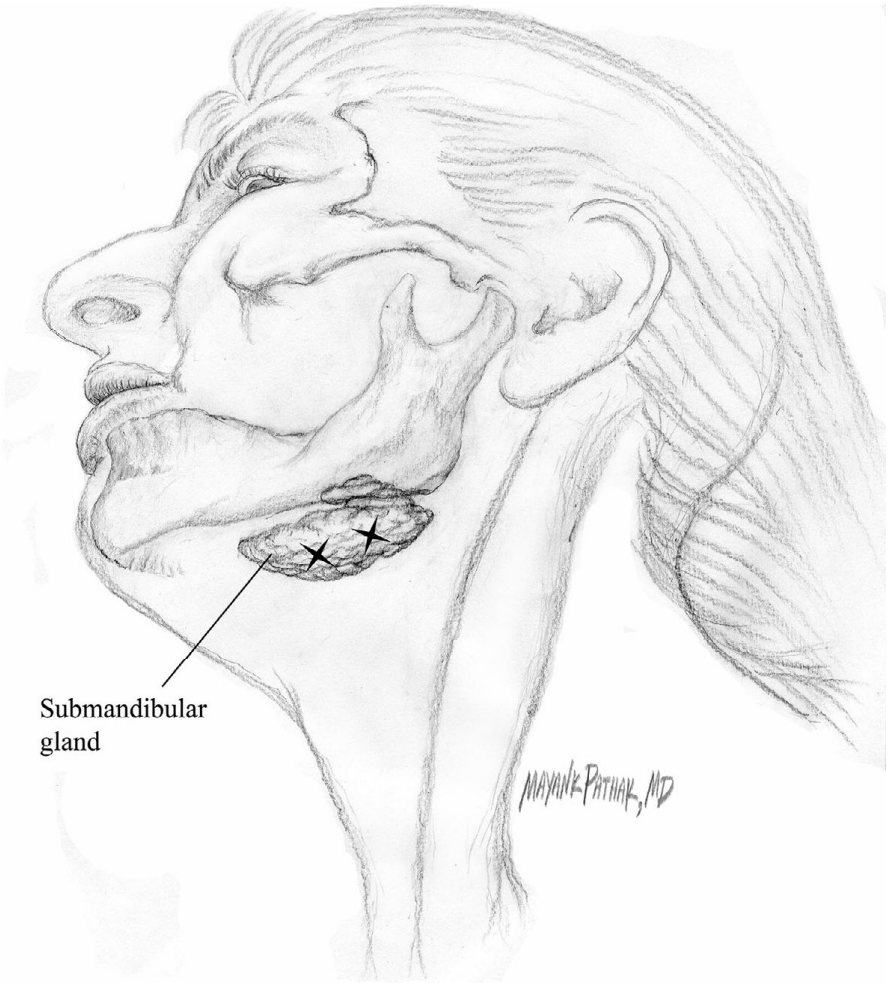

Fig. 12.10 Laterocaudal view of the left submandibular gland with typical injections sites for botulinum neurotoxin.

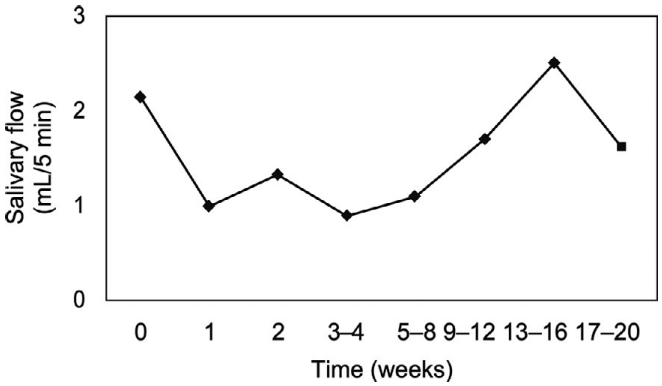

Fig. 12.11 The effect of botulinum neurotoxin injection on saliva flow in patients with hypersalivation. Pretreatment status returns after 12 weeks (Ellies *et al.*, 2004).

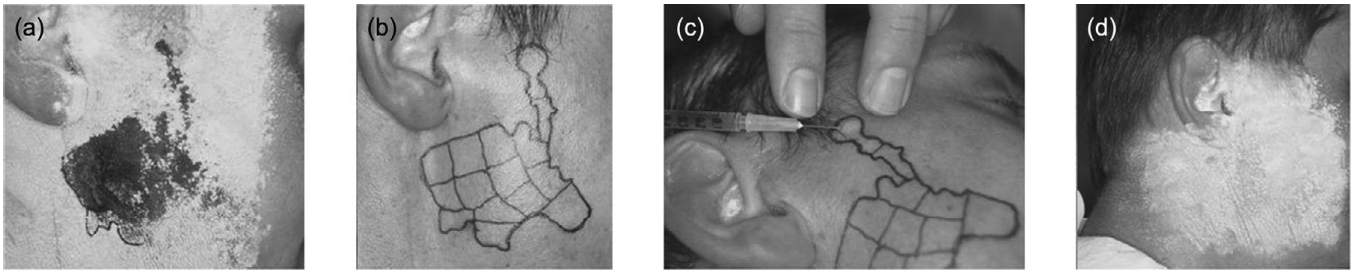

Fig. 12.12 Treatment of gustatory sweating (Frey's syndrome) with botulinum neurotoxin. (a) Patient with extensive gustatory sweating following total parotidectomy. The affected area is marked by Minor's test, showing a deep blue color. (b) The affected area is marked with a waterproof pen and divided into "boxes" to guarantee that the whole plane is treated. (c) Intracutaneous injections of onabotulinumtoxinA are performed. The white color of the skin can be seen during the intracutaneous application of onabotulinumtoxinA. (d) Patient eating an apple 2 weeks after treatment. The marked area that was sweating prior to treatment is now completely dry.

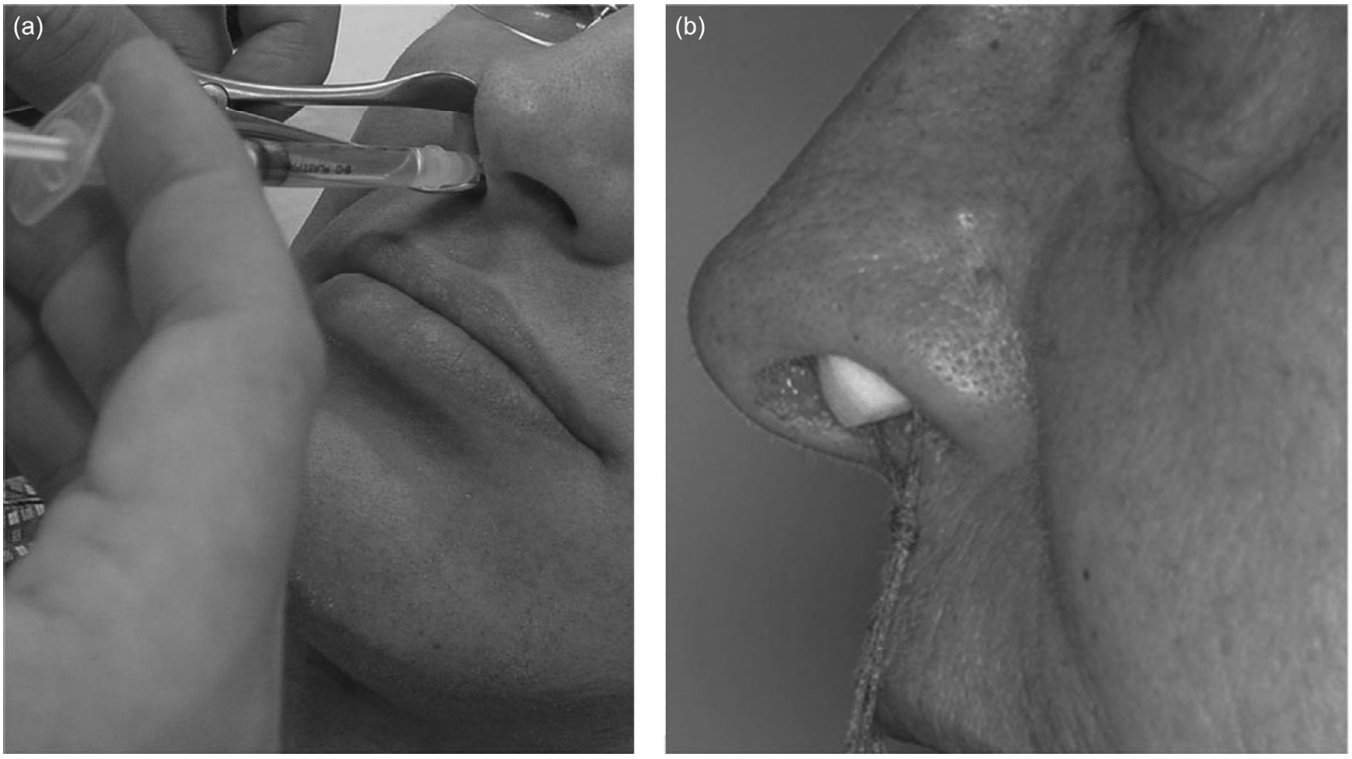

Fig. 12.13 Botulinum neurotoxin is injected into the middle and lower turbinates to treat rhinorrhea or applied with a sponge soaked with a solution of botulinum neurotoxin.

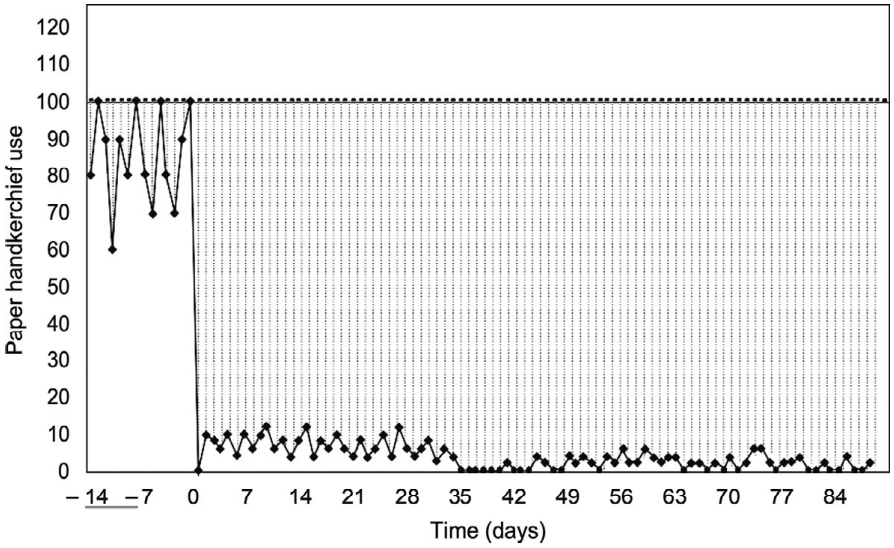

Fig. 12.14 Example of a patient with extensive intrinsic rhinitis. Botulinum neurotoxin type A has been applied with sponges. The consumption of paper handkerchiefs (number shown on vertical axis) is reduced dramatically for a long period after the application (horizontal axis).

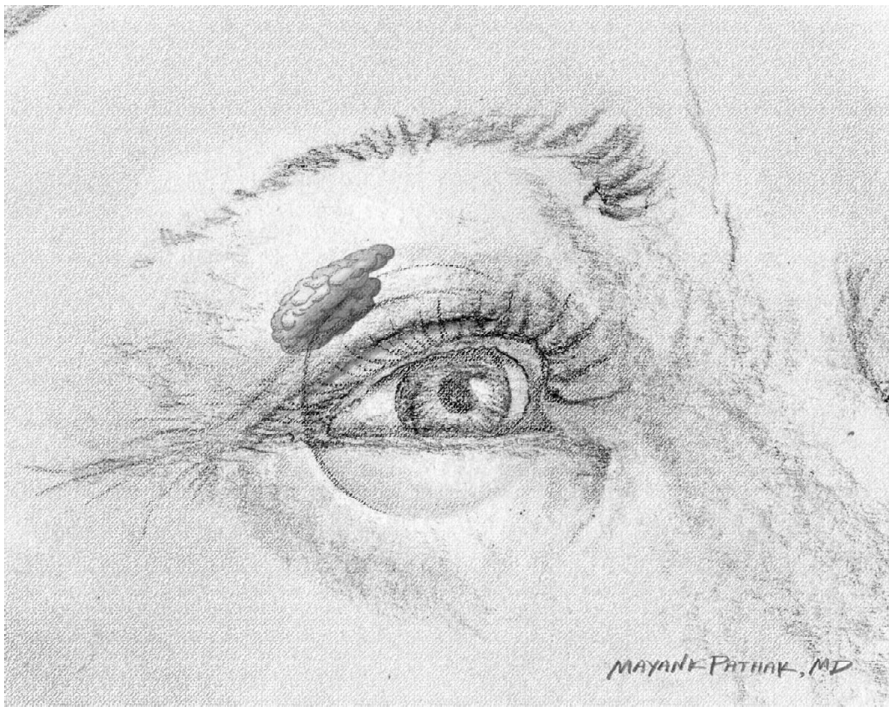

Fig. 12.15 The localization of the lacrimal gland and the upper lid/orbit.

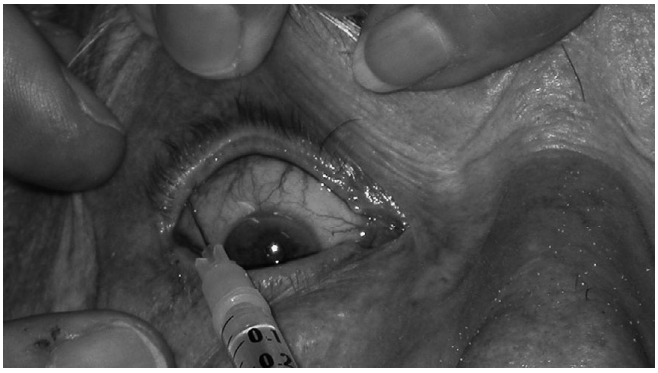

Fig. 12.16 Injection into the pars palpebralis of the lacrimal gland. With the patient looking strongly in the medial direction; the upper lid is lifted, and a little "lacrimal prominence" becomes evident.
Entering here in a lateral direction, the gland tissue can be approached easily.

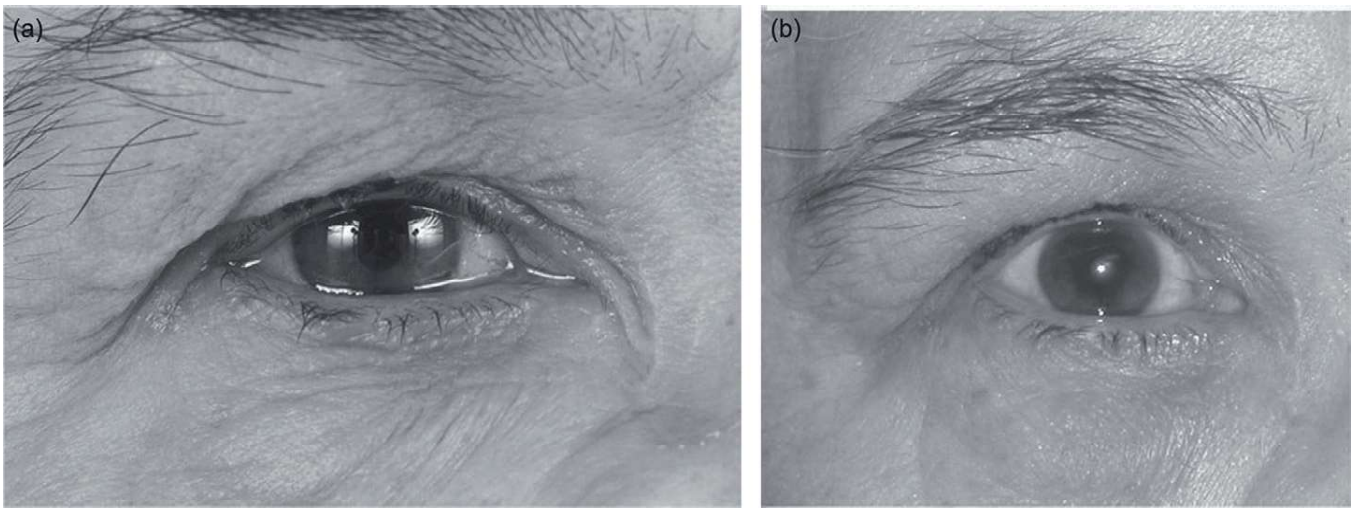

Fig. 12.17 Patient with extensive tearing caused by a stenosis of the lacrimal duct after resection of a malignant tumor of the right maxilla. (a) Pretreatment; (b) post-treatment.

References

Chao SS, Graham SM, Hoffman HT (2004). Management of pharyngoesophageal spasm with Botox. *Otolaryngol Clin North Am*, **37**, 559–66.

Ellies M, Gottstein U, Rohrbach-Volland S, Arglebe C, Laskawi R (2004). Reduction of salivary flow with botulinum toxin: extended report on 33 patients with drooling, salivary fistulas, and sialadenitis. *Laryngoscope*, **114**, 1856–60.

Jost WH, Friedman A, Michel O, *et al.* (2019). SIAXI: placebo-controlled, randomized, double-blind study of incobotulinumtoxA for sialorrhea. *Neurology*, **92**, e1982–e91.

Laskawi R, Rohrbach S (2002). Frey's syndrome: treatment with botulinum toxin. In Kreyden OP, Böni R, Burg G (eds.) *Hyperhidrosis and Botulinum Toxin in Dermatology*. Basel: Karger, pp. 170–7.

Meyer M (2004). Störungen der Tränendrüsen. In Laskawi R, Roggenkämper P (eds.) *Botulinumtoxintherapie im Kopf-Hals-Bereich*. Munich: Urban & Vogel.

Özcan C, Vayisoglu Y, Dogu O, Gorur K (2006). The effect of intranasal injection of botulinum toxin A on the symptoms of vasomotor rhinitis. *Am J Otolaryngol*, **27**, 314–18.

Olthoff A, Laskawi R, Kruse E (2007). Successful treatment of autophonia with botulinum toxin: case report. *Ann Otol Rhinol Laryngol*, **116**, 594–8.

Tillmann B (2005). *Atlas der Anatomie des Menschen*. Berlin: Springer-Verlag, p. 180.

Whittaker KW, Matthews BN, Fitt AW, Sandramouli S (2003). The use of botulinum toxin A in the treatment of functional epiphora. *Orbit*, **22**, 193–8.