Chapter 16
Botulinum Neurotoxin Treatment of Unusual and Rare Painful Disorders

Abstract Botulinum neurotoxins (BoNTs) can relieve painful muscle spasms through inhibition of acetylcholine release and alleviate neuropathic pain via blocking the release of pain mediators such as calcitonin gene-related peptide (CGRP), glutamate, substance P (SP), and others (detailed in Chap. 2). In addition to the common pain disorders discussed in the preceding chapters, data is now available on the possible efficacy of BoNTs in alleviating pain in uncommon and rare disorders.

In this chapter, three uncommon and rare conditions—stiff-person syndrome, painful legs–moving toes, and painful camptocormia—are discussed. The limited data from the literature about the use of BoNT in these conditions is presented. Case reports and video clips are included from the author's experience to illustrate the clinical features and the technique of BoNT injection employed to relieve pain.

Keywords Stiff-person syndrome • Painful legs–moving toes • Camptocormia • Botulinum toxin • Botulinum neurotoxin • Onabotulinum toxin • Abobotulinum toxin • Incobotulinum toxin

Introduction

Focal pain is a common complaint in some of the rare and uncommon neurological disorders. These disorders are characterized by a wide spectrum of symptoms ranging from intense increase in muscle tone to involuntary movements and unusual and abnormal postures. In most patients, conventional analgesics are only partially helpful, providing suboptimal pain control.

This chapter focuses on the effect of BoNTs on alleviation of the pain that presents as a major complaint in several rare disorders. The discussion of these rare conditions—stiff-person syndrome, painful legs–moving toes, and painful

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camptocormia—will be complimented with case reports and videotape clips from the author's experience to illustrate the patients' clinical features and the appropriate injection techniques.

Stiff-Person Syndrome (SPS)

Stiff-person syndrome is an autoimmune disorder characterized by progressive increase in muscle tone (rigidity) associated with painful, trigger-induced muscle spasms, predominantly affecting the axial and proximal limb muscles (Ciccotto et al. 2013). The exact pathophysiology of SPS is not known, but presence of antibodies against GABA decarboxylase (GAD), the rate limiting enzyme which makes GABA, suggests an inherent dysfunction of inhibitory spinal cord mechanisms (Solimena et al. 1990). Increased levels of GAD65 antibody are found in 60–80 % of the patients with SPS; however, the level of anti-GAD antibody does not correlate with the severity of the disorder (Ciccotto et al. 2013). Approximately 30 % of the patients with SPS have type1 diabetes, with autoantibodies to the same isoform of GAD65 shared by both disorders (Raju and Hampe 2008). Electromyography shows continuous muscle activity and firing of motor unit potentials which are easily triggered by photic or acoustic stimuli. This increased activity is seen in both agonist and antagonist muscles, and unlike a normal muscle, volitional activation of the agonist muscles does not reduce or stop the activity of the antagonist muscles (Rakocevic and Floeter 2012).

McKeon et al. (2012) defined SPS as a rare disorder based on their experience at the Mayo Clinic, observing an average of four new patients per year. Of their 99 patients diagnosed over 25 years, 67 were female (68 %) and 89 were Caucasian (91 %). They subdivided the clinical picture of SPS into classic SPS (65 patients), with predominantly lower trunk involvement conforming to the original description of Moersch and Woltman (1956), and a partial variant (31 patients) with involvement of one or more (usually lower) limbs. This variant is also called stiff limb syndrome (SLS) by others in the field. Included among the 99 patients, were 3 with the poorly understood disorder of progressive encephalomyelitis and rigidity (PERM). Eighteen of 99 patients (10.6 %) were seronegative for anti-GAD antibody. Seronegativity was more common among patients with the partial variant of SPS (12 out of 31 versus 6 out of 65, $P<0.05$).

SPS is occasionally a manifestation of an occult neoplasm. Paraneoplastic SPS accounts for 5 % of SPS patients and has been described in association with carcinoma of the breast, lung, colon, thymus, and lymphoma (Hadavi et al. 2011). The SPS symptoms may precede detection of the neoplasm by months or even years. Presence of antiamphiphysin antibodies in these patients correlates with adenocarcinoma of the breast or small cell carcinoma of the lung (De Camilli et al. 1993; Nguyen-Huu et al. 2006). Maurinson and Guarnacia (2008) emphasized epidemiological and clinical features of SPS with amphiphysin antibodies; these features include older age, marked predominance among women, absence of diabetes,

and cervico-brachial rigidity. Approximately 50 % of the patients complained of substantial muscle pain.

Treatment of SPS is aimed at reducing muscle tone, alleviating pain, and preventing further damage to the central nervous system (CNS). High doses of diazepam (40–100 mg daily) are commonly used for reducing muscle stiffness in SPS. Reduction of muscle tone can be achieved also by baclofen (including intrathecal route), tizanidine, or dantrolene. Levetiracetam, vigabatrin, valproic acid, clonazepam, and gabapentin are used to reduce CNS hyperexcitability. Anecdotal observations claim improvement of SPS symptoms with short courses of steroids (Blum and Jankovic 1991). Intravenous gamma globulin (IVIG) therapy is often employed to prevent further damage to the CNS. The recommended total dose is 2 g/kg, over 3–5 days, and may be repeated every 4–6 weeks. More severe cases and especially those with compromised respiratory function due to severe spasms of the thoracic muscles may require plasma exchange (PE).

A recent review of this subject (Pagano et al. 2014) found 18 publications describing the response to PE in 26 patients with SPS. Overall, 41 % of the patient had significant improvement of their symptoms after plasmapheresis, and two experienced adverse effects (one transient hypotension and one infection at the site of catheter insertion). Although a small controlled study showed no advantage for rituximab over other modes of therapy in SPS (Dalakas et al. 2009), two recent case reports claim its effectiveness against SPS symptoms (Fekete and Jankovic 2012; Sevy et al. 2012).

Pain is a common complaint in patients with stiff-person syndrome. In the classic form of SPS, rigidity of the lumbar and lower thoracic, abdominal, or paraspinal muscles is often associated with lumbar lordosis and deep pain (Bastin et al. 2002). Paroxysmal local pain in the form of muscle spasms is also common in the trunk and thigh muscles. Some patients with partial SPS and lower limb involvement manifest neuropathic pain with a significant burning quality (personal observations).

BoNT Treatment of Pain in Stiff-Person Syndrome

Davis and Jabbari (1993) first reported marked improvement of low back pain and reduction of paraspinal rigidity in SPS after injection of onabotulinumtoxinA into the paraspinal muscles of a 36-year-old African American gentleman who had developed progressive stiffness of the thighs, lower abdominal, and back muscles over an 18-month period. Initially, his problems were attributed to lumbar osteoarthritis, and he was treated with nonsteroidal anti-inflammatory agents. However, he gradually developed lumbar lordosis and severe, painful muscle spasms in the thigh, back, and abdominal muscles. These spasms were easily triggered by physical activity. His sister had non-insulin-dependent diabetes and hypothyroidism, but his past medical history was normal. On examination, pertinent physical findings were lumbar lordosis; markedly increased tone in the thigh, abdominal, and low back muscles bilaterally; inability to change position from supine to standing position unassisted; and an

awkward, hesitant, and short-stepped gait. In addition, he had diffuse hyperhidrosis. An extensive laboratory workup including muscle biopsy of the right thigh muscles and cerebrospinal fluid values was normal with the exception of electromyography (EMG) and the level of anti-GAD antibodies. On EMG, the involved muscles showed continuous motor unit firing at rest in both the agonist and antagonist muscles. Serum GAD antibody was positive at a dilution of 1/122,000, and the CSF anti-GAD level was 1/128 (normal values from Mayo Clinic were <1/120 and <1/2, respectively). Treatment with a combination of baclofen and diazepam partially improved muscle rigidity. Patient was injected with 560 units of onabotulinumtoxinA into the erector spinae and thigh muscles. Within a week, the patient reported cessation of muscle spasms and significant improvement of back and thigh rigidity. A repeat injection 6 months later produced similar effects.

In 1997, Liguori et al. described the results of the BoNT-A (aboA) injection into the affected muscles of two patients with Stiff-person syndrome. Both patients were women with the partial variant of SPS (Stiff limb syndrome). Both patients had detectable serum anti-GAD antibodies, but the exact level was not mentioned. In one patient, a total of 700 units of abobotulinumtoxinA (aboA) was injected into different muscles of one thigh. The second patient received a total of 1,000 units of aboA into the upper limb muscles (deltoid, biceps, brachioradialis). The outcome for rigidity was assessed blindly at baseline and following injections, with the Unified Parkinson Disease Rating Scale (UPDRS). The spasms were evaluated on a scale of 1–5 (5 being 30 or more spasms per day). Treatment with abobotulinumtoxinA reduced both pain and rigidity for up to 7 months, and repeat injections were also successful over a follow-up period of 2 years.

Anagnustou and Zambelis (2012) reported a 40-year-old man with a history of left leg stiffness for 9 years. The patient gradually developed painful knee extension spasms. Treatment with diazepam was partially helpful. Serum anti-GAD antibody level was 500 units/ml (normal <5/ml). Injection of 900 units of abobotulinumtoxinA into the leg muscles (350 units into vastus lateralis, 350 units into vastus medialis, 200 units into rectus femoris) eliminated the painful extension spasms of the leg and reduced the muscle tone (Ashworth scale: 4, before injection; 1, 4 weeks after injection). In this patient with stiff limb syndrome, previous injections of aboA with doses smaller than 900 units had resulted in either no or only modest improvement.

Case Report 16-1

A 44-year-old man was referred to the Yale Movement Disorder Clinic for evaluation of “muscle pain and muscles stiffness.” His symptoms had begun 3 years earlier with increased daily fatigue and low motivation for engaging in physical activity. He was told by a physician to keep well hydrated and consume potassium-rich foods. Subsequently, the patient developed a chronic sensation of “tightness/stiffness” in his lower limbs and severe episodic cramping of muscles in his thighs,

calves, toes, and flanks as well as his jaw muscles. Intermittent cramping and pain in the jaw muscles made speaking difficult. The more severe episodes lasted 30 min but only occurred after physical exertion, about five times per week. The patient also reported continuous twitching of his right quadriceps and intermittent twitching of his left quadriceps and bilateral calve muscles. He had also noticed involuntary jerking of his limbs during the day and night. The patient felt his right thigh has grown larger in the last year and had noticed increased hair growth on his right upper thigh extending to the gluteus region. Diazepam, 10 mg twice daily, and Percocet, 10–325 mg two to three times daily, offered only modest relief of the symptoms.

Neurological examination demonstrated normal cognition and speech and intact cranial nerves, cerebellar, and sensory functions. There was increased muscle tone in the right thigh (Ashworth score of 3) and lower abdominal muscles. Painful muscle twitches could be provoked easily in the right thigh muscles by passive and active stretch or pressing the right foot on the floor. The rest of the neurological examination was normal. Electromyography showed continuous muscle activity at rest in the right vastus medialis and rectus femoris muscles (Video 16.1). The serum anti-GAD antibody level was 3 (normal, <0.5), significantly elevated from 0.07 obtained a year earlier. Serum glucose, total CK l, HgA1c, TSH, insulin autoantibody (<5.0), and striational and acetylcholine receptor antibodies were all normal as well as the paraneoplastic panel which included the antiamphiphysin antibody. Magnetic resonance imaging of the spine showed moderate cervical arthritic changes.

The patient was treated with intravenous immunoglobulin (IVIG), 2 g/kg given over a period of 3–5 days at 4-week intervals. This treatment improved the muscle rigidity after 3 months, but the effect on painful muscle spasms was modest. The patient then received an intramuscular injection of 400 units of botulinum toxin A (onaA) into the right thigh muscles. A total of 100 units was injected at two sites (50 units/site) into each of the following four muscles: vastus medialis, rectus femoris, vastus lateralis, and hamstring (Video 16.1). After 2 weeks, the patient reported reduction in frequency and in intensity of muscle cramps in the right vastus lateralis and rectus femoris muscles. However, the spasms of the gastrocnemius muscles responded less favorably.

Comment

Pain is a major symptom in many patients with Stiff-person syndrome. The observations listed above demonstrate that both onaA and aboA injections into rigid and painful muscles can alleviate pain in patients with SPS. In my experience with BoNT injections in a dozen patients with SPS, onabotulinumtoxinA effectively reduced pain and rigidity and improved the patients' quality of life. Due to the rarity of SPS, however, clinical trials are hard to perform. An important caveat of BoNT treatment in SPS is sufficiency of the injected dose. The involved muscles are large

muscles and, therefore, it is easy to under-dose. For bilateral low back muscles, I recommend a total dose of 400 units of onaA for a patient of average weight. This can be given at five lumbar levels into the erector spinae, 40 units/level for a total of 200 units on each side. The technique of BoNT injection into the lumbar erector spinae is shown in Video 5.1 (Chap. 5, low back pain). A comparable dose of aboA would be 500 units for each side (using 1:2.5 ratio). For the large thigh muscles, I recommend 100–200 units of onaA per muscle. It is important to remember that BoNT treatment is only for symptomatic relief and not a substitute for modulation of the immune system which is often needed for these patients.

Painful Legs–Moving Toes

This syndrome was originally described in six patients who presented with involuntary toe or foot movements associated with pain in the toes, feet, or leg (Spillane et al. 1971). The pain often precedes the movements and has been described variably as aching, burning, jabbing, throbbing, and so forth. Movements are often slow and writhing with a flexion–extension pattern (Videos 16.2 and 16.3). Subsequently, a number of variants of this syndrome were described and designated as painful hand moving fingers and painless moving toes/painless moving fingers. The movements can start in one limb and gradually progress to the other limb or move from the lower limb to the upper limb (Ebersbach et al. 1998; Jabbari et al. 2000). The syndrome is rare with only 14 cases observed among 4,780 patients referred to the Mayo Clinic for evaluation of movement disorders over a 10-year period (Alvarez et al. 2008).

Nathan (1978) and Schott (1981) proposed that the condition results from injury to the peripheral nervous system (nerves, plexus, roots), citing several examples of this association. Support for this view has emerged from cases of cervical and lumbar spine disease that have improved after surgical intervention. Miyakawa et al. (2010) reported a patient with painful arm–moving fingers with cervical spondylosis at the C5–C6 level in whom foraminectomy stopped both the finger movements and the arm pain. Their second patient had developed leg pain and toe movements (PLMT) 2 weeks after L5–S1 discectomy. The pain and movements disappeared after lumbar nerve blocks. Others have also reported various levels of pain relief following lumbar epidural block or spinal cord stimulation (Okuda et al. 1998; Takahashi et al. 2002).

In the largest series of patients reported to date with this syndrome, Dressler et al. (1994) noted a variable age of onset in adults (youngest, 28 years of age) and a predominance among women (14 out of 20). Also, a majority of their patients had peripheral nervous system injury. Due to bilateral symptom distribution in some patients, the authors proposed existence of a central generator for the movements which presumably develops by a cascade of events after the peripheral injury. Presence of a “central oscillator” above the spinal cord level has been strongly suggested from transcortical magnetic simulation of the left motor cortex which has

demonstrated failure of cortical facilitation in a patient with bilateral finger movements and painful hands. A detailed electrophysiological assessment of this case showed no abnormality of the spinal inhibitory mechanisms (Jabbari et al. 2000). In another patient with bilateral finger movements, presence of out-of-phase discharges in the involved hand muscles suggested existence of two independent central generators (Ebersbach et al. 1998).

In the series reported from Mayo Clinic, 11 of 14 patients also had electrophysiological evidence of peripheral nervous system dysfunction and were affected by a variety of neuropathies caused by diabetes, vitamin deficiencies, lupus, and Sjogren's syndrome (Alvarez et al. 2008). In most affected patients, electromyography (EMG) demonstrated rhythmic 1–3 HZ discharges with duration of each discharge ranging from 0.5 to 2 s. In several patients, the pattern of EMG discharge resembled that of myokymia.

Treatment of pain in PLMT is challenging and was called "notoriously difficult" by Dressler et al. (1994). In the Mayo Clinic series (Alvarez et al. 2008) which was published 12 years after Dressler's series, most patients were treated with gabapentin and pregabalin (GABAergic and calcium channel blocker) which provided the patients with partial pain relief. Others have used opioids in patients with persistent pain. A more extensive description of clinical features and therapeutic measures in PLMTs has been published by Reich (2011) in a recent review.

BoNT Treatment of Painful Legs–Moving Toes

Three open-label observations have reported on the effect of local BoNT injection in PLMT syndrome. In collaboration with Dr. Carlos Singer's group in the University of Miami, we described significant reduction of pain and movements in two patients with PLMT syndrome after injection of onaA into the affected muscles (Eisa et al. 2006). One of the patients, a 62-year-old man, complained of low back pain for a year followed by development of pain in both calves and feet associated with involuntary flexion–extension of the toes bilaterally. OnabotulinumtoxinA was injected into the following muscles bilaterally: gastrocnemius (50 units, each side), flexor digitorum brevis (45 units, each side), and lower lumbar paraspinal muscles (60 units on each side). The second patient, a 72-year-old female, also had bilateral PLMTs with irregular toe movements and pain in the feet. Injection of 25 units of onaA into the flexor digitorum brevis of each foot relieved pain and slowed down the movements.

Schoffer (2010) described a 17-year-old boy who developed burning sensation and cramps in the calf and writhing involuntary movements of the fourth and fifth toes a year after a hamstring injury. Injection of 20 units of onabotulinumtoxinA into the adductor digiti minimi and 10 units into the flexor digiti minimi eliminated the movements and the calf pain.

Rodriguez and Fernandez (2013) reported a 43-year-old man who developed adduction–abduction movements of the right big toe and, to a lesser extent, other

toes with significant foot and lower leg pain. Injection of onabotulinumtoxinA (onaA) under electromyographic guidance into the foot muscles stopped the movements and significantly reduced the pain intensity. The dose was as follows: 25 units in the flexor hallucis brevis, 25 units in the adductor hallucis, and 50 units in the flexor digitorum brevis. A long-term follow-up of 3 years showed continued efficacy of treatment with onaA injections every 3 months.

Comment

Painful legs–moving toes is a rare disorder but can be a cause of significant pain and discomfort to the patients. The observations cited above suggest efficacy of local BoNT injection in the management of pain and movements in patients with this syndrome. The mechanism of pain relief is probably multifactorial, partly related to suppression of muscle spasms via inhibition of acetylcholine release from the neuromuscular junction and partly related to other analgesic effects of the BoNTs (Chap. 2). The technique of injection needs to be individualized according to the patient's symptomatology. In the case of PLMT, injections of BoNT-A into the gastrocnemius and flexor digitorum brevis as well as flexor or adductor pollicis when the big toe is involved have been helpful. With experience, refinement of injection techniques can lead to better results.

Camptocormia

Camptocormia is an abnormality of posture characterized by marked thoracolumbar flexion which manifests during standing and walking and abates in the position of repose (Video 16.5). The term camptocormia was coined by two French neurologists Souques and Rosanoff-Saloff describing the posture in shell-shocked soldiers who fought in trenches during World War I (Souques and Rosanoff-Saloff 1914). The authors suspected a psychogenic cause for this form of camptocormia. However, almost a century earlier, another neurologist had used the term "bent spine" describing the posture of a Spanish painter (Brodie 1818). It is now clear that most cases of camptocormia are not psychogenic and camptocormia can be caused by a large number of pathologic conditions (Finsterer and Strober 2010). Typical camptocormia is usually seen in neurodegenerative disorders, especially Parkinson's disease (PD) and multiple system atrophy (MSA) (Azhar and Jankovic 2005; Melamed and Djaldetti 2006; Jankovic 2009), and in myopathies of posterior trunk muscles. Other common causes include drug-induced camptocormia, spine and disc disease, and even certain neuropathies. Most recently, acute camptocormia has been described as a manifestation of tetanus (Kaji et al. 2014). Camptocormia of PD or MSA seems to be related to basal ganglia dysfunction, a view which is supported by significant improvement of camptocormia in some of

such patients after bilateral pallidal or bilateral subthalamic deep brain stimulation (Reese et al. 2014; Lyons et al. 2012). Margraf et al. (2010), however, hold the view that camptocormia in PD is a myopathy of the paraspinal muscles. In a study of 15 such patients, both electromyography and muscle biopsy have demonstrated a pattern of myopathy. Also a case of inclusion body myositis (proved by biopsy) has been reported as the cause of an isolated camptocormia (MA et al. 2013). Treatment of camptocormia is difficult. Pharmacological treatment is not usually effective. Anecdotal reports indicate that some patients may respond to dopaminergic drugs (Bloch and Houeto 2006; Ho et al. 2007; Oravivattanakul et al. 2014). Improvement of camptocormia has been reported after transcranial magnetic stimulation, but the effect is transient (Arii et al. 2014).

BoNT Treatment of Camptocormia

In recent years, several medical groups have reported on the effects of BoNT injections into abdominal and iliopsoas muscles of patients with camptocormia. The Baylor group (Azher and Jankovic 2005) noted moderate to marked improvement of camptocormia in four of nine patients with neurodegenerative disorders. OnabotulinumtoxinA, 300–600 units, was injected into the rectus abdominis muscles bilaterally. Presence of pain or the effect of injections on pain was not mentioned. No side effects were reported.

In contrast, Van Coellen et al. (2008) reported no improvement of camptocormia after BoNT injection in four patients with PD and MSA. AbobotulinumtoxinA was injected, 500 units per side, into the deep iliopsoas muscle under ultrasound guidance. Injections were repeated every 4–6 months with escalating doses of 1,000 and 1,500 units per side. Patient's posture was monitored at baseline and every 4–6 months; there was no mention of problems with pain in these four patients.

Fietzek et al. (2009) also injected BoNT-A (incoA), 100–300 units, either into the rectus abdominis or iliopsoas muscles of ten patients with camptocormia. Patients were asked to choose an outcome goal for the study. Six patients chose improvement of posture while three chose alleviation of pain as a desired outcome. None of the patients showed any improvements when assessed at 3 weeks postinjection. Two other patients were also reported in whom ultrasound-guided injection of onabotulinumtoxinA, 100 units per each iliopsoas, failed to improve camptocormia (Colosimo and Salvatori 2009).

Comment

Some patients with camptocormia have significant pain (Fietzke et al. 2009; Dupeyron et al. 2010, and personal observations). The literature on the effect of botulinum toxins on pain of camptocormia is very limited. Of the two techniques

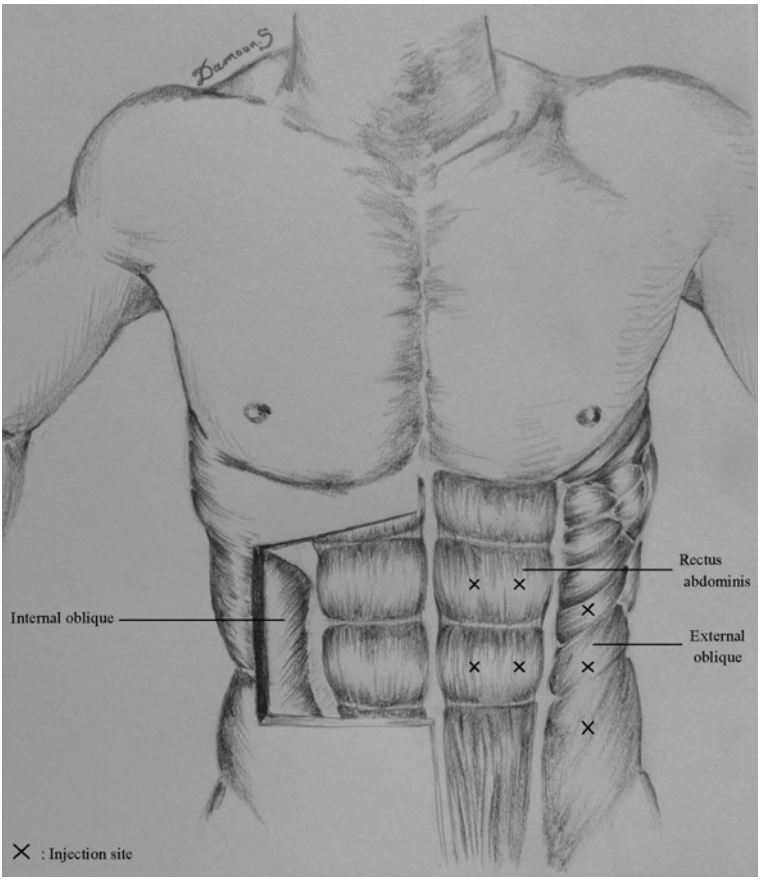

Fig. 16.1 Position of the rectus and oblique abdominal muscles and points of injections for camptocormia (created by Damoun sufarpouz, published with permission from © Bahman Jabbari 2014. All rights reserved

employed for treatment of camptocormia, negative results on pain have been reported with the iliopsoas injection method. This method seems to be ineffective also in improving the camptocormic posture itself.

Botulinum toxin treatment of camptocormia requires significant familiarity with anatomy of the abdominal muscles and a solid background in electromyography. In my experience with onabotulinumtoxinA in six patients with camptocormia, three have demonstrated notable improvement with a technique which combines injection of the rectus abdominis and oblique abdominal muscles (Fig. 16.1, Video 16.6). In one of these three patients who had painful camptocormia, onaA injections also significantly alleviated the pain (pain level of VAS 7 was lowered to VAS 2). I have used a total of 200 units for the rectus abdominis and 150 units for the abdominal oblique muscles on each side, a total of 700 units per session. The injections were

done under electromyographic guidance. No side effects were noted. (Video 16.7) Treatment of camptocormia is difficult due to the heterogeneity of the causative factors. Larger and preferably blinded studies are needed for assessing the efficacy of BoNT treatment of painful or painless camptocormia. These studies should focus on the techniques which have produced positive results as cited in the aforementioned open observations.

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