Botulinum Neurotoxin Type A Injections Reduce Spasticity in Mild to Moderate Hereditary Spastic Paraplegia—Report of 19 Cases

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Abstract: Hereditary spastic paraplegia (HSP) is characterized by lower extremity spasticity. Symptomatic therapy generally includes physical therapy and oral antispastic agents, in selected cases intrathecal baclofen. Because of the positive results in other treatments of spasticity, the use of botulinum neurotoxin type A (BoNT-A) might also be considered for patients with HSP. We report the effect of BoNT-A injections in 19 unselected patients with HSP treated by the members of the German Spasticity Education Group. In 17 patients, the modified Ashworth scale had improved by one point. In one patient, it improved by three points. Most of the patients reported reduction of spasticity. BoNT-A injections were continued in 11 of 19 patients (57.9%). All of the patients with continued injections had a good or very good global subjective improvement. Patients with less pronounced spasticity and patients with accompanying physical therapy tended to exhibit a better effect. Only four patients reported adverse effects which were increased weakness in three patients and pain in one patient. BoNT-A injections appear to reduce spasticity effectively and safely, especially in patients with mild to moderate spasticity. The preliminary results of our case series should encourage larger studies of BoNT-A injections in HSP. © 2007 Movement Disorder Society

Key words: hereditary spastic paraplegia; HSP; botulinum toxin A; spasticity; therapy.

Hereditary spastic paraplegia (HSP) is characterized by lower extremity spasticity and muscle weakness. Sporadic forms are also known. Symptoms may evolve at various ages, from childhood to advanced age and progress slowly.1 Usually, spasticity is much more prominent than weakness.1 Spasticity is often pronounced in hip flexors and adductors and plantar flexors of the foot. Gait analysis showed significantly lower gait velocity, stride length, step height, and range of motion of the knee angle.2 Although upper extremity deep tendon reflexes are often brisk, there is usually no sign of upper extremity weakness or spasticity.1

Until now, there is no causal treatment. Symptomatic therapy to date primarily includes physical therapy and oral medication for spasticity (e.g. baclofen, tizanidine,
dantamocrine). However, oral antispastic agents often increase widespread fatigue and are only beneficial for few patients. Furthermore, intrathecal applied baclofen has also been shown to improve spasticity in selected patients.\(^3\) However, based on objective gait analysis only a small number of patients were recommended for pump implantation.\(^4\) Botulinum neurotoxin type A (BoNT-A) has been shown to reduce focal spasticity caused by various diseases and is registered for the treatment of post-stroke spasticity.\(^5\) Consequently, the use of BoNT-A should also be considered for the reduction of spasticity in patients with HSP. We report the effect of BoNT-A injections in 19 unselected patients with HSP treated by the members of the German Spasticity Education Group.

**CASE DESCRIPTIONS**

**Case 1**

A 55-year-old male patient (Patient 1 in Table 1) noticed at the age of 46 a gradually progressive gait disturbance. The clinical examination at the age of 48 showed exaggerated deep tendon reflexes in lower limbs and a slight spasticity of the legs. Family history was negative. The patient was diagnosed as having a sporadic HSP. He returned at the age of 53, reporting an increase of gait disturbance. The modified Ashworth scale of hip adduction and flexion of the feet was 2. The patient could go bicycle-riding but was unable to walk for longer distances. Physical therapy reduced the leg spasticity marginally. Oral antispastic medication did not improve the symptoms. We injected BoNT-A (1,000 MU Dysport) into the adductor muscles and the calf muscles. Physical therapy was continued. The patient reported a significant reduction of the spasticity facilitating him to go mountain hiking for up to 6 hr. The Ashworth scale improved from 2 to 1. BoNT-A injections were repeated every 12 weeks. After one treatment of 1,500 MU Dysport within a 10-week interval (due to Christmas holidays), the patient experienced a significant weakness confined to his legs persisting for 6 weeks indicating a transient local cumulative overdose. No further adverse effects have been reported. The BoNT-A therapy is continued.

**Case 2**

A 27-year-old female patient (Patient 2 in Table 1) suffered from leg spasticity since the age of 24. Family history was positive (grandfather, father, brother). Genetically, a mutation of the SPG4 gene was found. Oral medication with baclofen and tizanidine did not reduce her symptoms. Therefore, the patient received BoNT-A injections. Initially, only the hip adductor muscles were treated (each 60 MU Botox). Two weeks later, the patient reported the ability to sit cross-legged. This position had not been possible for years. After 3 months, the treatment was repeated. In addition to the hip adductors, both posterior tibial muscles were injected (each 40 MU, total injection 200 MU Botox). The injections were repeated in 12-week intervals. The dosage was successively increased (total of 300 MU Botox, 80 MU each hip adductors, 70 MU each posterior tibial muscle). The gait improved significantly. Before the treatment, the patient needed 9 s and 14 steps to walk 10 m. After treatment, the best result was 6 s and 11 steps for the same distance. The additional trial injection of the iliopsoas muscles (50 MU Botox each) caused transient difficulties standing up and was not repeated. BoNT-A treatment is continued.

**Case 3**

A 55-year-old male patient (Patient 3 in Table 1) slowly developed a spastic gait disorder when he was 32. The family history was negative. He was diagnosed as having sporadic HSP when he was 39 years old. He was excellently trained by a physical therapist and felt that his gait disorder has become stabilized during the last years. In addition to physical therapy, he exercises by bicycling. The modified Ashworth scale was 3, especially for the adductor muscles which also showed hypertrophy. He was still able to walk but was using a walking frame. Walking velocity was reduced. Oral baclofen was poorly tolerated. After 50 \(\mu\)g of intrathecal baclofen, he experienced a bilateral foot drop. Therefore, intrathecal therapy was not continued. He was injected with BoNT-A (100 U Botox) in the adductor muscles on both sides. After 6 weeks, the modified Ashworth scale was reduced from 3 to 2 for the adductor muscles. Also the physical therapist who trained the patient three times per week after the injection observed a significant improvement of gait. Subjectively, the patient felt that gait was much more fluid. Reinjections occur every 12 weeks.

**Case 4**

A 66-year-old female patient (Patient 14 in Table 1) noticed a progressive stiffness of her legs 14 years ago. Similar symptoms had been reported by the father, brother, and sister of the patient. The diagnosis of familial HSP was established. The patient was presented again 2 years ago with extensive spasticity of the legs. The patient was wheelchair-bound. The modified Ashworth scale was 4 for the entire legs. Oral antispastic medication had been given extensively without a significant
<table>
<thead>
<tr>
<th>Pat</th>
<th>Sex</th>
<th>Age at onset</th>
<th>Sporadic/familial</th>
<th>Ashworth before</th>
<th>Btx A dosage</th>
<th>Injected muscles</th>
<th>Ashworth after</th>
<th>Subj. effect</th>
<th>Special features</th>
<th>Physiotherapy</th>
<th>Ther. ong.</th>
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<tr>
<td>1</td>
<td>m</td>
<td>55</td>
<td>46</td>
<td>s</td>
<td>2 Total leg</td>
<td>1,000–1,500 D</td>
<td>1 Total leg</td>
<td>+++</td>
<td>After one injection with reduced injection interval reversible weakness</td>
<td>+</td>
<td>++</td>
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<tr>
<td>2</td>
<td>f</td>
<td>27</td>
<td>3</td>
<td>f (SPG4)</td>
<td>Not known</td>
<td>120–400 B</td>
<td>Not known</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
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<td>3</td>
<td>m</td>
<td>55</td>
<td>32</td>
<td>s</td>
<td>3 Hip</td>
<td>200 B</td>
<td>2 Hip</td>
<td>++</td>
<td>Knee contact reduced</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td>36</td>
<td>23</td>
<td>s</td>
<td>2 Hip 2 Knee 2 Ankle</td>
<td>200–300 B</td>
<td>1 Ankle</td>
<td>+++</td>
<td>Ability to walk continuously improved from 10 to 30 min</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>5</td>
<td>m</td>
<td>49</td>
<td>33</td>
<td>s</td>
<td>3 Hip 4 Ankle</td>
<td>200 B</td>
<td>2 Hip 3 Ankle</td>
<td>+++</td>
<td>Gait endurance and seating position improved, painful spasms reduced</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>6</td>
<td>m</td>
<td>55</td>
<td>28</td>
<td>s</td>
<td>3 Hip 3 Ankle</td>
<td>300 B</td>
<td>2 Hip 2 Ankle</td>
<td>+++</td>
<td>Gait endurance improved (15 min on treadmill 147 to 196 meter)</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>7</td>
<td>f</td>
<td>67</td>
<td>18</td>
<td>f (SPG4)</td>
<td>2 Hip 2 Knee 2 Ankle</td>
<td>200 B</td>
<td>1 Hip</td>
<td>++</td>
<td>Gait velocity not improved</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>8</td>
<td>m</td>
<td>14</td>
<td>5</td>
<td>s</td>
<td>4 Total leg</td>
<td>400 B</td>
<td>3 Total leg</td>
<td>++</td>
<td>Wheelchair bound seating position and mobility with wheelchair improved</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>m</td>
<td>25</td>
<td>16</td>
<td>s</td>
<td>3 Total leg</td>
<td>200 B</td>
<td>Not known</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>m</td>
<td>55</td>
<td>20</td>
<td>f</td>
<td>3 Total leg</td>
<td>1,000–1,500 D</td>
<td>2 Total leg</td>
<td>+++</td>
<td>Gait velocity improved (25%)</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>11</td>
<td>m</td>
<td>40</td>
<td>15</td>
<td>f</td>
<td>4 Hip 4 Knee 3 Ankle 4 Ankle</td>
<td>300 B</td>
<td>4 Hip 3 Knee 3 Ankle 3 Ankle</td>
<td>+++</td>
<td>Wheelchair bound knee contact reduced</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>12</td>
<td>f</td>
<td>41</td>
<td>10</td>
<td>f</td>
<td>4 Ankle</td>
<td>150 B</td>
<td>3 Total leg</td>
<td>(+)</td>
<td>Pes equines improved</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>m</td>
<td>14</td>
<td>7</td>
<td>f</td>
<td>4 Hip</td>
<td>400 D</td>
<td>3 Hip</td>
<td>+</td>
<td>Knee contact reduced</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>14</td>
<td>f</td>
<td>66</td>
<td>52</td>
<td>f</td>
<td>4 Total leg</td>
<td>1,000–1,500 D</td>
<td>3 Total leg</td>
<td>(+)</td>
<td>Wheelchair bound</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>15</td>
<td>f</td>
<td>70</td>
<td>65</td>
<td>s</td>
<td>3 total leg</td>
<td>1,000–1,500 D</td>
<td>2 Total leg</td>
<td>/–</td>
<td>Pain, CK elevation</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>16</td>
<td>m</td>
<td>41</td>
<td>28</td>
<td>s</td>
<td>3 Hip 2 Knee 2 Ankle</td>
<td>400 B</td>
<td>2 Hip</td>
<td>0</td>
<td>Gait velocity improved (2.9–3.1 km/h)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>17</td>
<td>m</td>
<td>23</td>
<td>8</td>
<td>f (SPG4)</td>
<td>3 Total leg</td>
<td>1,120 D</td>
<td>2 Ankle</td>
<td>0</td>
<td>Gait analysis not improved</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>18</td>
<td>m</td>
<td>12</td>
<td>5</td>
<td>f</td>
<td>4 Ankle</td>
<td>980 D</td>
<td>1 Ankle</td>
<td>0/–</td>
<td>Pes equines improved</td>
<td>+</td>
<td>–</td>
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<tr>
<td>19</td>
<td>m</td>
<td>47</td>
<td>40</td>
<td>s</td>
<td>3 Total leg</td>
<td>300 B</td>
<td>Not known</td>
<td>0</td>
<td>Subjective weakness</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

Pat, patient number; m, male; f, female; s, sporadic; f, familial; Ashworth before, modified Ashworth score before botulinum toxin A treatment; Btx dosage, injected amount of mouse units (MU) botulinum toxin A and preparation; B, Botox®; D, Dysport®; IP, M. iliopeus; RF, M. rectus femoris; AD, hip adductor muscles; GC, M. gastrocnemius; TP, M. tibialis posterior; IC, ischiocrural muscles; Ashworth after, modified Ashworth score after botulinum toxin A treatment; subj. effect, global subjective effect (scale steps ++++, ++, +, 0, –); ther. ong., therapy ongoing (“–” = not continued, “+” = 1–5 repetitions, “+++” = more than 5 repetitions).
improvement. The patient was injected with BoNT-A (1500 MU Dysport) in the hip adductor and calf muscles. The patient did not receive physical therapy after the injection. Spasticity of the hip adductors was slightly reduced from 4 to 3. Subjectively, the patient perceived a slight reduction of the muscle tone. However, this reduction was not helpful in her activities of daily life and she refused further injections.

Case 5

A 41-year-old male patient (Patient 16 in Table 1) suffered from a progressive spastic gait disorder for 13 years. The family history was negative. Sporadic HSP was diagnosed after exclusion of other causes. The disorder forced him to eventually wear peroneal splints and knee-braces 5 years earlier. Oral baclofen had only a minimal positive effect on the gait disorder. The neurological examination revealed no pathological deficiency in the upper extremity but marked increased muscle tone for hip movements (modified Ashworth 3), knee movements (modified Ashworth 2), and ankle movements (modified Ashworth 2). The gait was clearly spastic with circumduction of both feet during the swing phase, but the main problem was an excessive hip flexion during the entire gait cycle. Initially, a test higher dosage of oral baclofen was prescribed with severe side effects as a result. The next approach was to give intrathecally applied baclofen. However, 25 μg intrathecal baclofen was ineffective and 50 μg produced a bilateral foot-drop. Therefore, the patient received BoNT-A to improve hip flexion and influencing positively his gait pattern. Both iliopsoas muscles were injected CT-guided with 100 U Botox. A further dose of 100 U Botox was injected in the both rectus femoris muscles. Resulting in a total dose of 400 U Botox. Before and after injection, a complete 3D gait analysis was completed in a gait lab. After 6 weeks, the modified Ashworth scale at the hip joint improved from 3 to 2. The range of motion of the hip during gait increased from 33° to 39° (Fig. 1). The velocity also increased from 2.9 to 3.1 km/hr. Although these results demonstrated a clear improvement, the patient experienced no benefit during daily activities. Therefore, after one reinjection the patient refused further BoNT-A injections. During the treatment, the patient had no accompanying physical therapy.

Case 6

This 23-year-old male patient (Patient 17 in Table 1) was diagnosed to have familial HSP with a SPG4 type mutation at the age of eight. First symptoms manifested at age six. His spastic gait became evident when he shuffled his feet and a lacking heel strike was observed. He was not treated with oral medication. Physical therapy was highly frequent in his youth but ended 6 months before presentation. The neurological examination showed a slight paresis (MRC 4) for the hip abductors and ankle extensors. The modified Ashworth scale was 3 for the complete lower extremities. The muscle reflexes were increased and pyramidal signs were positive in both legs. The equinovarus feet were prominent while the heel never touched the floor. The gait velocity was not reduced compared to normals. The patient asked for BoNT-A therapy and was injected with 320 MU Dysport in the gastrocnemius muscles on each side and 240 MU in the tibialis posterior muscle on each side (total dose 1,120 MU Dysport). The patient did not have physical
therapy, but walked extensively. After 6 weeks, the gait pattern had not improved in the patient’s opinion. The modified Ashworth scale at the ankle was reduced from 3 to 2. The quantitative gait analysis failed to show an improvement of gait. The patient refused further injections.

All 19 injected patients (14 men and 5 women) are summarized in Table 1. Mean age at the time of treatment was 41.6 ± 18.6 years. Mean disease duration was 18.5 ± 10.9 years (range 5–49 years). The modified Ashworth scale of the injected muscles was 2 in three patients, 3 in nine patients, and 4 in six patients (in one patient the modified Ashworth scale was not completed).

Botulinum toxin injections were continued in 11 of 19 patients (57.9%). Divided according to the modified Ashworth scale before the BoNT-A treatment, all three patients (3/3) with an Ashworth scale of 2 and five of nine patients (5/9) with an modified Ashworth score of 3 continued BoNT-A treatment. In the patient group with the most severe symptoms (modified Ashworth scale of 4), only two of six (2/6) patients received further BoNT-A injections. In all patients, the modified Ashworth scale improved by one point and it changed in one patient by three points. A majority of the patients perceived noticeable reduction of spasticity. However, only patients with a relevant global subjective improvement (+ + or + + +; scale steps + + +, + +, +, 0, −) decided to continue the treatment. Only one of four patients (1/4) not receiving physical therapy continued the BoNT-A injections. Ten of fifteen patients with physical therapy (10/15) continued botulinum toxin treatment.

Adverse effects were rare. Side effects were reported in only four patients. Three of them showed a reversible increase in muscle weakness. The fourth patient experienced pain during walking for several weeks and had a CK-elevation unknown at that time. Because of this finding, a muscle biopsy was performed and exposed an additional peripheral neuropathy with slight secondary myopathy.

**DISCUSSION**

BoNT-A injections reduced spasticity in our patients with HSP. In all patients, the Botulinum toxin injections reduced the modified Ashworth scale of the injected muscle-joint system. However, not all patients perceived an improvement of activities of daily life. In this situation, they discontinued the BoNT-A treatment. Correlating to the positive subjective effect, injections were continued in the majority of patients (57.9%).

Some of our patients reported a reduction of falls. Accidental falls are common in patients with spasticity and often lead to secondary complications, e.g. bone fractures. The prevention of falls might therefore be of significant importance. Recently, it has been suggested that botulinum toxin therapy might reduce falls in post-stroke patients. A similar effect seems feasible in spasticity due to HSP.

An interesting question is whether predictors for a relevant positive effect can be identified. In our case series, the likelihood of a relevant subjective improvement and a subsequent treatment continuation seemed to be related to the degree of spasticity. The higher the modified Ashworth scale before the treatment the less likely was the continuation of the treatment. Therefore, we assume that a lower degree of spasticity (Ashworth scale 2 or 3) could be a positive predictor for a functional gain and BoNT-A treatment continuation. Several reasons might support this finding: In severe spasticity, the reduction of spasticity by botulinum toxin treatment might fail to reduce the muscle tone sufficiently to effectively improve functional movement. Also, more severely affected patients also are more inclined to suffer from mechanical consequences of prolonged spasticity such as contractures or shortening of tendons. Patients in a more advanced stage might also suffer in a higher ratio from relevant muscle weakness in addition to spasticity. Reduction of spasticity by botulinum toxin treatment might unmask the underlying weakness. As a consequence, the total effectiveness of the treatment might be reduced.

In addition, we observed in our case series that an accompanying physical therapy was often correlated to a positive effect of the botulinum toxin treatment. Physical treatments increase the effectiveness of botulinum toxin theoretically by facilitating the endocytosis of botulinum toxin. Support for a positive effect of nerve and muscle activation is also given by studies reporting an increase of BoNT-A action by muscle or nerve stimulation. Generally, physical therapy reduces muscle overactivity and improves the strength of the muscles. Furthermore, it could be conceivable that physical therapy could attain a further functional gain after muscle tone reduction due to BoNT-A treatment. In the European consensus statement for the use of botulinum toxin type A in the management of spasticity, a program of exercise, muscle stretching, and/or splinting is strongly recommended. The importance of an accompanying physical therapy is commonly acknowledged by botulinum toxin injectors, but has not yet been empirically demonstrated. The experience in our patients might support the hypothesis of an additional positive effect of physical therapy when combined with botulinum toxin therapy. However, the benefit of this combination with botulinum toxin treatment will need to be investigated in a systematic randomized study.
In our case series, the botulinum toxin treatment of the hip adductors and the calf muscles was especially important in HSP patients. Most of the patients received injections in these two muscle groups. The botulinum toxin treatment of hip adductors is also useful in spasticity due to other causes. For example, botulinum toxin reduced the degree of hip adductor spasticity associated with multiple sclerosis.10,11 The effectiveness of calf muscle botulinum toxin treatment has also been shown in patients with spasticity of another origin, e.g. after stroke.12,13 Treatment of further muscles, the iliopsoas muscle or rectus femoris muscle, appears to be beneficial in selected patients only.

Adverse effects were seldom and reversible. In all indications, botulinum toxin therapy contains the possibility of an overdose resulting in weakness of the injected or adjacent muscle groups. Especially in advanced cases of HSP, the disease by itself results in weakness in addition to spasticity. These patients might have a pronounced risk to obtain an increased weakness during BoNT-A treatment. However, weakness due to BoNT-A treatment is temporary and can be avoided in further injection sessions through dose reduction. CK elevation has not been reported as a side effect of botulinum toxin treatment to date. The CK elevation in one of our patients was observed after the patient reported about pain in the calf muscle. Despite specific instructions, the patient continued to be physically very active. Muscle biopsy 9 months after BoNT-A treatment revealed an additional peripheral neuropathy and secondary myopathy independently of botulinum toxin treatment. In summary, botulinum toxin treatment in HSP patients seemed to be safe in our case series.

In conclusion, further treatment options for the symptomatic treatment of spasticity in HSP are needed. The experience of our case series indicates that for selected patients, especially patients with mild to moderate spasticity, BoNT-A injections seem to be an effective and save additional treatment. The preliminary results of our case series should encourage larger studies of BoNT-A injections to verify the hypothesis that BoNT-A is an effective treatment of spasticity in HSP patients.

REFERENCES