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*Pediatrics* 2001;108;1062-1071

DOI: 10.1542/peds.108.5.1062

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/108/5/1062>

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# Botulinum Toxin Type A Neuromuscular Blockade in the Treatment of Equinus Foot Deformity in Cerebral Palsy: A Multicenter, Open-Label Clinical Trial

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**ABSTRACT.** *Background.* Focal spasticity of the gastrocnemius-soleus muscles causes equinus gait in children with cerebral palsy (CP). Botulinum toxin type A (BTX-A), a neuromuscular blocking agent, reduces muscle tone/overactivity in dystonia, stroke, and CP.

*Objective.* A prospective, open-label, multicenter clinical trial evaluated the long-term safety and efficacy of repeated intramuscular injections of BTX-A on equinus gait in CP children.

*Methods.* Nine centers enrolled 207 children. BTX-A injections (4 U/Kg) were given approximately every 3 months (maximum dose 200 U per treatment). Outcome measures included a Physician Rating Scale of gait, ankle range of motion measurements, and the incidence and profile of adverse events.

*Results.* One hundred fifty-five (75%) of 207 children completed at least 1 year with a total of 302 patient years of BTX-A treatment. The mean duration of BTX-A exposure was 1.46 years per patient. Dynamic gait pattern on the Physician Rating Scale improved in 46% of patients (86/185) at first follow-up. The response was maintained in 41% to 58% of patients for 2 years. Both gait pattern and ankle position improved at every visit. The most common treatment-related adverse events included increased stumbling, leg cramps, leg weakness, and calf atrophy in 1% to 11% of patients. No treatment-related serious adverse events were reported. Only 6% (7/117) of patients with pre- and postantibody samples had both detectable antibodies and a subsequent treatment failure.

*Conclusion.* BTX-A proved both safe and effective in the chronic management of focal muscle spasticity in children with equinus gait. *Pediatrics* 2001;108:1062–1071; BTX-A, cerebral palsy, equinus foot deformity, neuromuscular blockade, pediatric patients, spasticity.

ABBREVIATIONS. CP, cerebral palsy; BTX-A, botulinum toxin type A; U, units; AE, adverse event; PRS, Physician Rating Scale.

Cerebral palsy (CP) is “characterized by aberrant control of movement or posture of a patient, appearing early in life (secondary to a central nervous system lesion, damage or dysfunction), and not the result of a recognized progressive or degenerative brain disease.”<sup>1</sup> Abnormal control of motor movement is the key defining feature of CP with muscle spasticity occurring in 88% of patients with this diagnosis.<sup>2</sup> In patients with CP, protracted muscle spasticity can lead to fixed contractures, bony torsional abnormalities in the limbs, and joint instability.<sup>3</sup> Equinus gait deformity is one of the most common motor manifestations of prolonged focal muscle spasticity in this population.<sup>4,5</sup>

Spasticity has been defined as a motor disorder characterized by an abnormal increase in the sensitivity of skeletal muscles to passive stretch.<sup>6</sup> It limits muscle movement around a joint, interferes with voluntary motor movement, and decreases longitudinal muscle growth.<sup>7</sup> Equinus gait deformity, a common problem in CP, results from dynamic overactivity or spasticity of the gastrocnemius-soleus muscle complex alone, or in combination with other muscles controlling the ankle, or from fixed muscle contractures.<sup>8</sup> Equinus gait in CP can result in knee and ankle problems, abnormal motion during gait, impaired balance and proprioception, and permanent foot deformities that may require multiple surgical interventions.<sup>3,9–13</sup>

The use of botulinum toxin type A (BTX-A) has gained widespread acceptance in the clinical management of focal muscle spasticity seen in patients with CP, stroke, and traumatic brain injury. BTX-A injections for spasticity in both children and adults have shown a dose-related decrease in muscle tone with increased joint mobility following injections into the affected limb.<sup>14,15</sup> BTX-A blocks signal transmission at the neuromuscular junction by preventing the release of acetylcholine from the presynaptic axon of the motor endplate.<sup>16</sup> The effect is a local chemodenervation with the level of muscle relaxation produced dependent on the amount of BTX-A injected. The chemical denervation is initially re-

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Preliminary results of this study were presented at the 4th European Botulinum Toxin Symposium; Vienna, Austria; February 10, 1999.

Received for publication Oct 27, 2000; accepted Apr 23, 2001.

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versed when the preterminal neurite sprouts and reinnervates the muscle.<sup>17</sup> Regression of the neurite sprouts and resumption of exocytosis from the previously BTX-A-intoxicated nerve terminals will then return the neuromuscular junction to its original state.<sup>18</sup> As a result, muscle relaxation with BTX-A is both graded and reversible.

BTX-A was first approved in 1989 for the treatment of strabismus, blepharospasm, and seventh nerve disorders.<sup>19,20</sup> Subsequently, BTX-A was used in the management of a variety of disorders involving muscle overactivity, including focal dystonias, dysphonia, spasticity, achalasia, anal fissure, and CP.<sup>21–25</sup>

A number of double-blind and open-label studies have demonstrated that injections of BTX-A can reduce spasticity and improve ambulation in children with CP.<sup>12,26–36</sup> As a result, BTX-A has been approved for the treatment of focal muscle spasticity in 34 countries. Most recently, a large, randomized, double-blind, placebo-controlled trial in children with equinus foot deformity demonstrated significant improvement in ambulation after BTX-A treatment without serious adverse effects.<sup>30</sup> This study was limited to a single treatment and a brief, 3-month study duration. As a result, a longer clinical trial was conducted as an open-label follow-up to this double-blind trial for the purpose of evaluating the safety and efficacy of repeated injections of BTX-A in children with CP.

## METHODS

### Study Population

Ambulatory patients with hemiplegia or diplegia CP between the ages of 2 and 18 years were screened for enrollment in the study. Patients who completed the previous randomized, double-blind, placebo-controlled study were invited to participate.<sup>30</sup> To be considered eligible for this study, patients had to exhibit spasticity of 1 or both lower limbs characterized by an equinus positioning of the foot during the stance phase of gait.

Patient exclusion criteria included the following: 1) evidence of fixed contracture; 2) severe athetoid movements in the target leg(s); 3) a significant difference (>5 cm) between the length of the right and left legs; 4) obvious atrophy of the calf muscles of leg(s) to be treated in the study; 5) current need for surgery; 6) previous surgery of the foot, leg, and/or ankle; or 7) previous injections of alcohol into the muscles to be injected in the study.

The study complied with the Declaration of Helsinki recommendations regarding biomedical research involving human patients. Previous study approval was obtained from the governing institutional review board at each site. Written, informed consent was obtained from the parent or legal guardian and the patient as appropriate.

### Study Injection and Dosage

Each vial contained 100 units (U) of Clostridium botulinum toxin type A with human serum albumin and sodium chloride in a sterile, vacuum-dried form without preservatives (Botox Purified Neurotoxin Complex, Formulation 8051X, Allergan, Inc, Irvine, CA). All injections were prepared by reconstituting a 100-U vial of BTX-A with 1 mL of sterile preservative-free saline to achieve a concentration of 10 U/0.1 mL in the BTX vials.

Patients received a total dose of 4 U/kg body weight of BTX-A, up to a maximum of 200 U, at each treatment visit. The appropriate amount of BTX-A based on the dose calculation of 4 U/kg body weight was diluted to a 4-mL volume for hemiplegic patients and an 8-mL volume for diplegic patients so that the total volume injected was held constant. Based on the previous work by Koman,<sup>29,30</sup> an injection of 2 mL of BTX-A per muscle site (2 mL in the medial and 2 mL in the lateral gastrocnemius of each involved

leg) was selected as the appropriate volume to cover the large end-plate region of this muscle. Local anesthetic was not required to administer the injection but was permitted. Injections were performed under sterile conditions, by using 23- to 26-gauge needles and appropriately sized syringes. The muscle was palpated while being stretched passively and the needle was inserted into the proximal one third of the muscle (approximate region of the motor end plates) using sterile technique. Clinical experience demonstrated that the target muscle location could be easily pinpointed without electromyography guidance.<sup>29,30</sup>

Patients not part of the previous double-blind, controlled trial received their first injection of BTX-A at study entry. Patients participating in the preceding double-blind, controlled trial<sup>30</sup> may have already received both a first (4 U/kg) and possibly a second treatment (4 U/kg) of BTX-A in the previous trial. Thus, approximately half of the original cohort received their second or third treatment with BTX-A on enrollment in the current open-label trial, but their first treatment for this study. Patients injected with placebo in the previous controlled trial received their first injection of BTX-A at study entry.

### Study Visits and Procedures

Patients were evaluated at baseline to determine if they were qualified to participate in the study. After obtaining written informed consent, qualified patients were enrolled with baseline assessments completed by both the physician investigator and the physical therapist. Patients received their initial study injection at that visit. For the duration of the study, additional study treatments with BTX-A were administered as medically indicated, but no sooner than 3 months from the previous treatment for the duration of the study. Treatment outcome measures were performed at follow-up visits scheduled every 6 weeks for the first year and every 12 weeks for the following 2 to 4 years of this study.

Demographic data, medical history, and physical and neurologic examinations were obtained at the baseline visit. Interval medical histories, including the use of concomitant medications, vital signs, and a focused physical examination, as well as documentation of any adverse events (AEs), were performed at follow-up visits.

At the time of the baseline visit and at each 6 week follow-up visit, the following outcome measures were performed: The Physician Rating Scale (PRS) of dynamic gait pattern and the physician's and physical therapist's assessment of active and passive ankle range of motion.

### PRS of Dynamic Gait Pattern

The primary efficacy measure was the PRS of dynamic gait pattern during active walking (Table 1). This scale was originally developed by Koman et al<sup>29</sup> with interrater reliability demonstrated for the gait pattern component by Corry.<sup>7</sup> The PRS was created because of the unavailability of any other scales with appropriate specificity and intraobserver and interobserver reliability.<sup>29</sup> Sutherland subsequently demonstrated that the PRS correlated with 3-dimensional gait analysis in a subset of CP patients treated with BTX-A.<sup>12</sup> On this scale, the physician evaluated 6 functional components of the human gait cycle while patients walked barefoot over a distance of at least 15 feet. This scale graded each functional component as follows: gait pattern (0–2 scale); ankle position during gait (0–2 scale); hindfoot position during foot strike (0–3 scale); knee position during gait (0–3 scale); degree of crouch (0–3 scale); and speed of gait (0–1 scale). In patients with bilateral disease, the investigator graded each leg separately and the scores for the 2 legs were averaged. The PRS composite score was the sum of the 6 component scores for that patient (0–14 scale, where 0 = “worst” score and 14 = “best” score).

The responder rate was defined as the percentage of patients in each treatment group that exhibited an improvement from baseline in the composite PRS score of  $\geq 2$  points. The responder rate for each component of dynamic gait pattern in each treatment group was defined as the percentage of patients that exhibited any improvement from baseline in that particular component of the rating scale.

**TABLE 1.** PRS: Dynamic Gait Patterns

Gait Component	Observation	Score
Gait pattern	Toe-toe	0
	Occasional heel-toe*	1
	Heel-toe	2
Hindfoot (ankle) position: maximum foot/floor contact during stance	Equinus	0
	Calcaneus	1
	Neutral	2
Hindfoot position during foot strike	Valgus	0
	Varus	1
	Occasionally neutral	2
	Neutral	3
Knee position during gait (stance phase)	Recurvatum >15°	0
	Recurvatum 6–15°	1
	Recurvatum 1–5°	2
	Neutral or flexed	3
Degree of crouch (hip-knee- ankle)	Severe (>20°)	0
	Moderate (5–20°)	1
	Mild (<5°)	2
	None	3
Speed of gait	Only slow†	0
	Variable (slow-fast)	1

\* Flat-foot and toe-heel gait patterns were assigned the same score as occasional heel-toe.

† Patients requiring a walker were scored as “slow”; the PRS dynamic gait pattern composite score was the sum of the scores from these 6 components (0–14 scale, where 0 = “worst” score and 14 = “best” score). The data represent average values for patients with both legs in the study.

### Measurement of Active and Passive Ankle Range of Motion

Passive ankle range of motion after dorsiflexion of the foot was measured as the final angle subtended by the foot and the ankle in the neutral position.<sup>67</sup> For this measurement, patients were seated with the knee flexed at 90° and in full/neutral extension with the subtalar joint stabilized. If the patient’s foot could not be pushed into dorsiflexion, the degree of plantarflexion was measured. Degrees of dorsiflexion from the neutral position were indicated by a positive (+) measurement, whereas degrees of plantarflexion from the neutral position were indicated by a negative (–) measurement.

Active ankle range of motion was measured while the patient voluntarily attempted to move his/her foot into dorsiflexion (past neutral) while in a sitting position. This measurement was the final angle subtended by the foot and ankle in the neutral position (0°). If the patient could not actively move his/her foot into dorsiflexion, the least degree of plantarflexion was measured. Degrees of dorsiflexion were indicated with a positive (+) measurement, whereas degrees of plantarflexion were indicated with a negative (–) measurement.

### Safety Measures

AEs were analyzed for type, incidence, and causality. AE data were calculated at each study visit and all AEs were recorded and evaluated for severity. AEs were further classified as either not related to study medication or as probably, possibly, or remotely related to the study medication. In addition, the investigator who administered the study medication evaluated the child’s level of discomfort/pain associated with each injection visit on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe).

### Blood-Serum Antibodies

Whenever possible blood-serum samples were collected from the children for antibody determination at baseline and for at least 1 follow-up visit. Samples were stored frozen until they could be analyzed for the presence of antibodies to BTX-A. Samples were sent to a central facility (Northview Pacific Laboratories, Berkeley, CA) to be tested for neutralizing antibodies to BTX-A using the mouse protection bioassay.<sup>37</sup> Two milliliters of each serum sample

were incubated with 0.5 mL of stock BTX-A solution (50.0 U/ml). After a 1-hour period of incubation at room temperature, 0.5 mL of the test serum/BTX-A mixture was injected intraperitoneally into each of 4 mice. Survival of 3 or more mice 72 hours from the injection was consistent with the presence of protective antibodies (positive result).

### Statistical Analysis

For this study, eligible patients included all nondisqualified enrolled patients. Patients were only disqualified from the study if they never received study medication or did not meet study entry criteria. Two statistical analyses were performed: a modified intent-to-treat analysis and a safety analysis. The modified intent-to-treat analysis included all data from all eligible patients who were evaluable. Evaluable patients for each treatment cycle were those who received the study injection and had at least 1 postinjection visit. The safety analysis included all data from the previous double-blind study, as well as all data from the open-label study. This incorporated 8 patients exposed to BTX-A in the previous study who did not continue into the current study, 131 patients who participated in both trials, and 76 patients only enrolled in the current open-label study.

All group comparisons were done in the form of a mean change from baseline analysis. The change from baseline at each study time point was analyzed using the paired *t* test for both the PRS of dynamic gait pattern composite scores and component scores, as well as the hindfoot (ankle) active and passive range of motion assessments.<sup>38</sup>

The primary endpoint for the study was the PRS for dynamic gait pattern, which resulted in both an overall composite score and individual component scores. The PRS composite data score was analyzed by mean change from baseline and success rate, where “success” or “response” was defined as a 2-U or more increase from baseline in the composite score. A Clopper-Pearson 95% confidence interval<sup>39</sup> was calculated for each time point. Individual PRS component scores were analyzed by the percentage of patients who experienced any improvement from baseline in a given component at each time point. A Clopper-Pearson 95% confidence interval was provided for each component at each time point. For both active and passive range of motion measures, change from baseline was statistically evaluated using the paired *t* test.<sup>38</sup>

AE incidence (the percentage of patients who reported an AE) was calculated from the total number of patients at risk (the number of patients exposed to the treatment). The effect of between-group differences such as cumulative dose, number of injections, and length of exposure, on the incidence of AEs was evaluated using a Fisher exact test. The incidence of AEs was also analyzed by causality (treatment-related or treatment-unrelated).

Antibody test results were tabulated by result: either positive, negative, or no-follow-up and by cumulative dose, number of injections, and exposure time, and were then tested for differences between antibody groups with a 1-way analysis of variance.

All statistical tests were 2-sided and *P* values were reported unadjusted for multiplicity. Two-sided 95% confidence intervals were calculated for selected variables. A *P* value of ≤.05 was considered statistically significant.

## RESULTS

### Study Population

Nine investigators enrolled 207 patients, combining 131 patients from the preceding randomized, double-blind trial<sup>30</sup> with an additional 76 new patients. There were 122 boys (59%) and 85 girls (41%) with an average age of 5.6 ± 2.76 years. Sixty-three percent (130/207) of the patients were diagnosed as diplegic and the remaining 37% (77/207) were hemiplegic. Patient characteristics are further described in Table 2.

Of the 207 patients enrolled, only 4 were not evaluable for any treatment cycle because either they did not meet study entry criteria, or they never received study medication. Of the 203 evaluable patients, 47

**TABLE 2.** Patient Demographics

Age (y) at first exposure			
Mean (range) SD 5.6 (2–14.3) ± 2.8			
Gender			
Male	122 (59%)		
Female	85 (41%)		
Race			
White	169 (82%)		
Asian	5 (2%)		
Hispanic	13 (6%)		
Black	17 (8%)		
Other*	3 (1%)		
Diagnosis		Injection Site	
	Right Only	Left Only	Both
Diplegia	11† (8%)	11 (8%)	108 (83%)
Hemiplegia	38 (49%)	38 (49%)	1 (1%)

\* One patient was Palestinian, 1 was Asian-Hispanic, and 1 was Chinese-Indian.

† Counts include 2 patients with quadriplegia.

Percentages may not add to 100% because of rounding.

patients (23%) left for reasons unrelated to the study treatment. Thirty-nine patients (19%) were discontinued from the trial because of lack of efficacy. Lack of efficacy was defined as either 1) presence of a fixed contracture after the first injection (20 patients); 2) need for heel cord surgery in the target limbs after any injection (18 patients); or 3) no benefit (1 patient). One hundred eight patients (53%) were discontinued prematurely when the sponsor terminated the study. Eight patients completed the study as planned before study termination. A single patient left the study for an AE of self-limiting, generalized weakness, probably related to study medication.

One hundred fifty-five (75%) of 207 enrolled patients completed at least 1 year of treatment. Forty-two patients completed 2 years or more and 7 patients completed 3 years or more. The mean duration of BTX-A exposure was 1.46 years per patient for a total of 302 patient-years.

The first 8 treatment cycles had adequate patient enrollment (range: 31–207 patients) to permit analysis of efficacy. A total of 215 patients were analyzed for long-term safety. In addition to the 207 enrolled patients, 8 patients treated with BTX-A in the previous study<sup>30</sup> but not continuing participation in the current study, were evaluated for both AEs and serum antibody production.

### Injection and Dose

The average dose of BTX-A was 84.8 U per injection visit. One hundred fifty patients received 4 treatments, and 31 patients received 8 treatments. The mean cumulative dose by number of injections is displayed in Table 3. For all patients receiving a second injection, the mean interval from the first to the second injection was 2.4 months, but this group included patients from the previous study whose second BTX-A injection was always 1 month after the first injection. Subsequent injection intervals ranged from 3.3 to 4.6 months for the first 2 years of treatment. The average time interval between all injections is shown in Table 4.<sup>4</sup>

### PRS of Dynamic Gait Pattern

Treatment with BTX-A significantly improved ambulation in children with CP and equinus gait disorder

**TABLE 3.** Cumulative Dose (U) of BTX-A

Injection Number	N	Mean	SD	Minimum	Maximum
1	207	78.2	34.3	25.0	200.0
2	200	157.7	69.0	70.0	420.0
3	175	239.4	103.0	134.0	600.0
4	150	319.3	134.4	180.0	800.0
5	124	408.2	173.2	228.0	1000.0
6	83	506.5	220.5	283.4	1200.0
7	53	632.7	285.2	339.4	1400.0
8	31	728.9	319.8	397.6	1600.0
9	19	906.7	429.2	451.6	1800.0
10	12	983.2	510.8	503.6	2000.0
11	6	1280.7	730.9	557.6	2200.0
12	1	791.6	–	791.6	791.6
13	1	873.6	–	873.6	873.6

SD indicates standard deviation.

**TABLE 4.** Interval Between BTX-A Injections (Months)

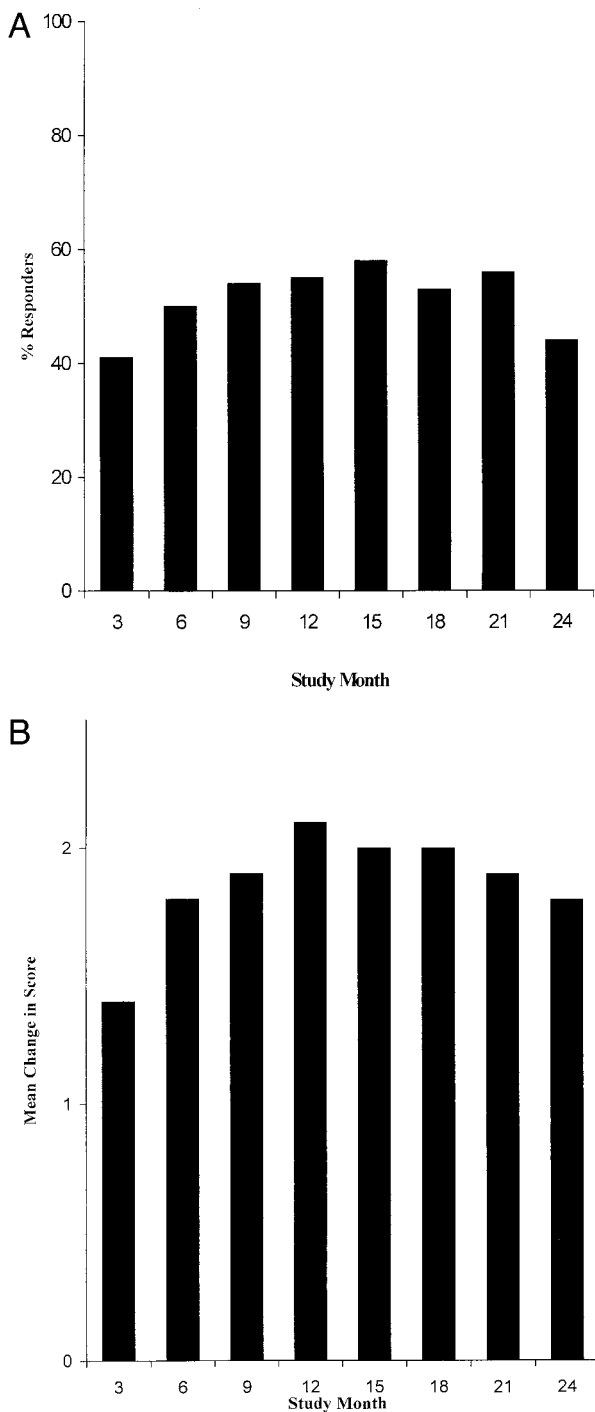
Injection Number	N	Mean	SD	Minimum	Maximum
1	207	–	–	–	–
2	200	2.4	1.2	0.5	7.8
3	175	3.3	1.6	0.7	11.4
4	150	3.7	1.7	1.4	9.6
5	124	3.9	1.9	1.4	16.8
6	83	3.9	1.6	1.6	10.7
7	53	4.1	2.1	1.5	14.0
8	31	4.6	2.3	1.8	10.5
9	19	4.4	2.0	2.6	8.6
10	12	4.2	1.4	2.6	6.3
11	6	2.7	0.8	1.2	3.4
12	1	3.0	–	3.0	3.0
13	1	3.0	–	3.0	3.0

as measured by the PRS over a 2-year follow-up period. (Fig 1A) A total of 46% of patients (86/185) were treatment responders at the first follow-up visit having improved at least 2 Us on their composite PRS scores compared with baseline. The mean baseline PRS composite score was 6.9 (0–14 scale) and the improvement on the mean PRS composite score was 1.6 U at the first follow-up visit.

Fifty-five percent of patients (63/115) were treatment responders at 1 year, and 44% of patients (20/45) were treatment responders at 2 years, as measured by the PRS composite score. The improvement in the mean PRS composite score remained consistent ranging from 1.4 to 2.1 Us for 2 years, and was statistically significant throughout this period ( $P < .001$ ; Fig 1B). The proportion of treatment responders also remained constant ranging from 41% to 58% of patients evaluated at every time point for 2 years.

Treatment response for any individual component of the PRS scale was previously defined as a 1 U or more increase from baseline. The 2 components of gait most closely related to spasticity of the gastrocnemius muscle, specifically gait pattern and hindfoot (ankle) position, were significantly improved at every visit for the first 2 years ( $P < .001$ ). A total of 41% of patients (78/192) were treatment responders on the gait pattern component of the PRS scale at the first follow-up visit (Fig 2A).

Gait pattern improvement was demonstrated in 61% of patients (72/119) at 1 year and in 58% of



**Fig 1.** Composite score from the PRS. A) Percentage of BTX-A-injected patients (responders) that improved from baseline by  $\geq 2$  grades in the PRS composite score (range: 0–14) charted at 3-month intervals. B) Mean change from baseline in the PRS composite score at 3-month intervals. The improvement was statistically significant at all time points ( $P < .05$ ). Baseline was 6.9.

patients (26/45) at 2 years. The response rate for the gait pattern component of the PRS ranged from 39% to 64% at each 3-month interval for 2 years ( $P < .001$ ; Fig 2A). The improvement in mean change from baseline on the gait pattern component ranged from 0.4 to 0.6 Us from a mean baseline score of 0.2 (0–2 scale;  $P < .001$ ; Fig 2B).

Forty percent of patients (76/191) were treatment

responders on the hindfoot (ankle) position component of the PRS scale at the first follow-up visit. The mean baseline score was 0.4 (0–2 scale) and the mean change was 0.6 Us at the first follow-up visit. The improvement in the mean hindfoot (ankle) position component score ranged from 0.6 to 0.9 U at each time point for 2 years ( $P < .001$ ; Fig 2B). A total of 55% of patients (65/119) were treatment responders for the hindfoot (ankle) position component of the PRS Scale at 1 year, and 44% of patients (20/45) were responders at 2 years. The proportion of patients with improvement in ankle position ranged from 38% to 55% for the first 2 years of follow-up (Fig 2A).

Three additional components of dynamic gait pattern, including knee position during gait, hindfoot position during foot strike, and degree of crouch, were improved but the proportion of patients showing statistically significant improvement on these components was less robust.

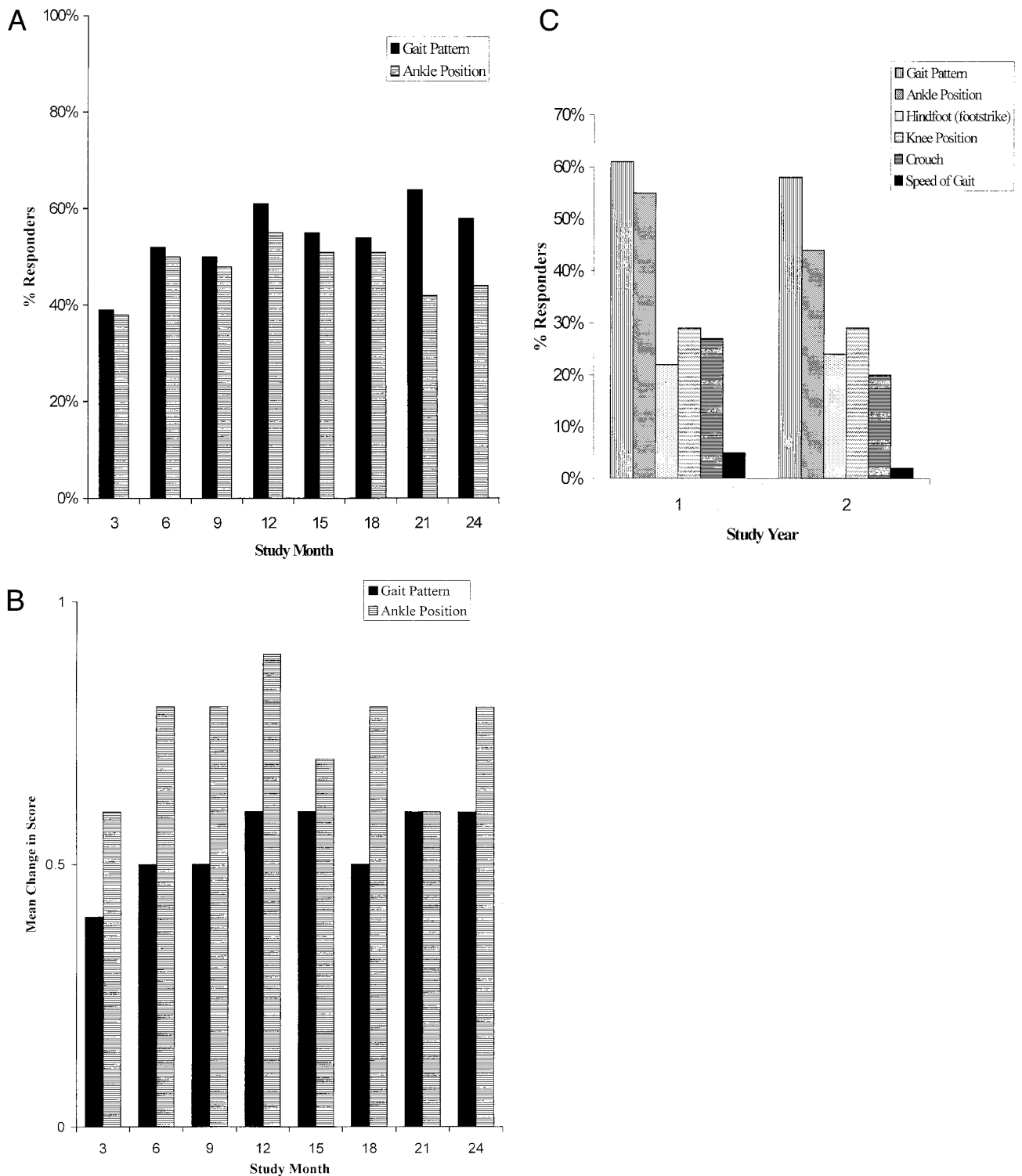
For the knee position during gait, 21% of patients (41/192) were defined as treatment responders at the first follow-up and 29% of patients were treatment responders at 1 year (35/119) and again at 2 years (13/45). For the hindfoot position during foot strike component, 21% of patients (43/192) were treatment responders at the first follow-up visit. By year 1, 22% of patients (26/119) demonstrated a treatment response for hindfoot position during foot strike with 24% of patients (11/45) responding at 2 years. For the degree of crouch component, 27% of patients (50/186) were treatment responders at the first follow-up. At 1 year, 27% of patients (31/116) were treatment responders but by 2 years, the improvement in degree of crouch was no longer statistically significant. The sixth component of dynamic gait pattern, speed of gait, was unchanged throughout the study period.

#### Active and Passive Ankle Range of Motion

The physician's measurement of active ankle dorsiflexion range of motion with the knee flexed was obtained in only one fourth of patients at baseline and only 14 patients at 1 year because patient cooperation made it difficult to obtain the measure. Despite this admittedly small sample, an increase in active range of motion was observed. The mean maximal active ankle dorsiflexion was  $-3.0$  degrees at baseline and improved to a range of  $+4.7$  to  $+12.5$  degrees, reaching the level of statistical significance at all visits for the first year ( $P \leq .016$ ). The physical therapist's measurement of active ankle dorsiflexion with the knee in extension resulted in a mean baseline score of  $-15.3$  degrees that improved post BTX-A to  $+5.8$  to  $-0.2$  degrees in the first 2 years of follow-up with statistical significance demonstrated at months 7.5 and 9 ( $P \leq .044$ ). No statistically significant changes on either physician or therapist measurements of passive range of motion were noted.

#### Efficacy Measures in Patients Followed for 2 to 4 Years

BTX-A treatment maintained the improvement in PRS scores in 40 patients followed longer than 2 years (range: 24–44.8 months). Although the num-



**Fig 2.** Component scores from the PRS. A) Percentage of BTX-A-injected patients showing any change in the component scores (range: 0–2) of gait pattern or ankle position charted at 3-month intervals. B) Mean change from baseline in the PRS gait pattern and ankle position component scores at 3-month intervals. This change was statistically significant for gait pattern and ankle position throughout the 2-year period ( $P < .05$ ). Baselines were 0.2 and 0.4, respectively. C) Percentage of BTX-A-injected patients showing any change in the component scores (range: 0–2) charted at 12-month (1-year) intervals.

bers are too small to permit formal statistical analysis, the PRS responder rate ranged from 47% (9/19) to 67% (4/6) between years 2 and 4 and the mean change in composite score remained robust ranging from 1.7 to 2.7 U. The PRS component scores for gait

and ankle position remained at levels similar to those seen during the first 2 years of the study. For the gait component, responders ranged from 58% (11/19) to 80% (4/5) from years 2 to 4 with a mean change in the component scores ranging from 0.6 to 0.7. For

ankle position, responders ranged from 42% (5/12) to 60% (3/5) with a mean change in component score ranging from 0.6 to 1.0 between years 2 to 4.

## RELATED EVENTS

### AEs

AEs were reported in 183 (85%) of 215 treated patients. There were 19 serious AEs, but none were related to study medication. One serious AE resulted in a death attributable to herpes simplex encephalopathy. The remaining AEs were mild to moderate in severity. The most frequently reported events judged not related to treatment were ear infections (32%, 68/215), common colds (27%, 58/215), flu symptoms (16%, 34/215), upper respiratory infections (15%, 33/215), fever (12%, 26/215), cough (10%, 21/215), and chicken pox (9%, 19/215). The most frequently reported events thought to be related to treatment were falling (9%, 20/215), leg pain (2%, 5/215), leg weakness (2%, 5/215), generalized weakness (2%, 4/215), and leg cramps (1%, 3/215). In addition, calf atrophy was noted on physical examination in 11% percent of patients (22/207). The mean discomfort or pain associated with the study injections was mild with a pain score ranging from 0.8 to 1.1 (scale 0–3).

### Blood-Serum Antibodies

One hundred seventeen of 215 treated patients had both a baseline and 1 or more postinjection blood serum samples analyzed for the presence of antibodies to BTX-A as determined by the mouse protection bioassay. No antibodies were detected in any of the baseline serum samples. In the postinjection serum samples, 72% of patients (84/117) had no detectable antibodies while 28% of patients (33/117) had detectable antibodies.

Antibody detection did not seem to correspond with treatment response. Response rates in the antibody negative patients ranged from 43% to 58% over the first 2 years. By comparison, response rates in the antibody positive patients ranged from 48% to 68% over the same time period.

Of the 33 patients who had detectable levels of antibodies at follow-up, 31 were responders (increase of  $\geq 2.0$  U in the PRS composite score) and 2 were nonresponders before developing antibodies. After a positive antibody test, 5 of the 31 patients lacked PRS composite score data for additional analysis. Of the remaining 26 antibody positive patients, 7 (27%) patients became nonresponders compared with 19 (73%) patients who maintained their response.

It should be noted that patients with positive antibody results were treated with more BTX-A ( $543.3 \pm 267.1$  U vs  $330.2 \pm 234.2$  U respectively;  $P \leq .001$ ) and more injections (mean  $6.7 \pm 1.6$  vs  $3.9 \pm 2.1$ ;  $P \leq .001$ ) than patients with negative results. Patients with positive antibodies also had a longer exposure time (mean  $18.9 \pm 6.2$  months vs  $9.2 \pm 8.4$  months;  $P \leq .001$ ) compared with patients with negative antibody results. Overall, patients with detectable antibodies who showed no response on the PRS composite score after subsequent BTX-A treatment(s)

composed 6% (7/117) of the population of patients with antibody data.

## DISCUSSION

This prospective study demonstrated the safety and efficacy of repeated intramuscular injections of BTX-A in the treatment of children with CP and equinus gait. Both gait pattern and ankle position, the 2 components of gait most closely related with spasticity of the gastrocnemius-soleus muscle complex, were significantly improved with BTX-A treatment. The improvement in gait pattern from baseline in patients followed for 2 years was statistically significant and was maintained in a smaller cohort of patients for up to 4 years. This study confirms and extends the results of the previous double-blind trial demonstrating improved ambulation in the BTX-A treated patients compared with placebo.<sup>30</sup>

Besides improvement in overall gait pattern and ankle position, BTX-A treatment had an effect on improving knee position resulting in less knee recurvatum during gait for the first 2 years of the trial. Although muscles in the upper leg are more critical to knee position during gait,<sup>9,40</sup> spasticity of the gastrocnemius muscle can contribute to knee recurvatum. In fact, a normal foot contact in the presence of persistent ankle equinus can be accomplished by knee recurvatum. It can therefore be postulated that by decreasing the equinus foot position, knee recurvatum would become less evident over time. The observed change in knee position was most likely attributable to the improved foot position seen during prolonged BTX-A treatment and would only be observable in a study with an extensive follow-up period.

A small but significant improvement in hindfoot position during foot strike was also described in this report. Improvement in the foot position is a potentially important finding as it suggests that the muscles controlling the foot and ankle may become better balanced over time with repetitive neuromuscular blockade with BTX-A. Physiologic explanations for this phenomenon could include weakening of the gastrocnemius-soleus muscle complex, increase in the length of the gastrocnemius muscle-tendon unit, shortening of the antagonist muscles, or a combination of these events. Any of these effects could be a direct result of BTX-A chemodenervation and are unlikely to occur spontaneously.

The observation that the small BTX-A doses used in this study produced a response is especially important considering that patients with bilateral disease received only 2 U/kg per leg and that a significant number of patients had concomitant hamstring, quadriceps, adductor, and iliopsoas spasticity which was not addressed.

The effects of a single BTX-A injection on ambulation lasted an average of 3 to 5 months, which was consistent with the 3- to 6-month average interval between injections reported in other studies of pediatric CP,<sup>28,34,36</sup> as well as in adult studies of focal dystonia.<sup>42,43,44</sup> Although there is some variation in the literature regarding the duration of the effect of BTX-A, it is a generally accepted view that BTX-A

injections are efficacious for at least 3 months.<sup>45</sup> Injection intervals of 6 months to 1 year have also been reported in several studies of children with CP.<sup>3,28,34</sup> Boyd and Graham<sup>3</sup> even reported a subset of 2- to 4-year-old CP patients who gained significant functional improvement which lasted up to 1.5 years after BTX-A injections. Clearly BTX-A treatment must be adjusted to individual patient needs as duration of effect depends on the following: ability to deliver toxin to the target muscle(s); preinjection muscle physiology including power, endurance and spasticity; connective tissue extensibility; and joint range of motion.

This study focused on improving gait in a pediatric population with CP who were already independent ambulators at the start of the study. Other published reports have evaluated the use of BTX-A at the other end of the clinical spectrum.<sup>27,36</sup> Both Wong and Cosgrove and Wong<sup>27,36</sup> reported that BTX-A treatment allowed nonambulatory CP patients to learn to walk with assistance or become independent.<sup>27</sup>

Untreated, long-term muscle spasticity may result in a fixed contracture in children with CP often requiring corrective surgery.<sup>45</sup> Predicting the long-term success of surgical intervention to improve ambulation is particularly difficult in children because of maturational changes of the musculature and developmental changes in gait patterns. Recurrence of equinus deformity after corrective surgery in children is common after surgery performed in early childhood.<sup>9,46</sup> Decreasing muscle spasticity with serial injections of BTX-A may delay the necessity for surgery allowing time for muscles and gait patterns to mature.<sup>47</sup> When and if surgery is required, the likelihood of recurrence of equinus deformity may be decreased. Long-term benefit seemed to be secondary to repeated injections with appropriate continued physical therapy. Richardson<sup>41</sup> has hypothesized that the effect of BTX-A over time provides a window of opportunity to make changes in muscle length, function, and pattern of movement as well as in antagonist motor control.

Longitudinal muscle growth in children requires active and passive stretch, which is facilitated with BTX-A. The availability of longer muscle fibers increases the arc of effective motor power. Muscle fiber growth in the hereditary spastic mouse model after BTX-A demonstrated improved muscle growth and contracture reduction.<sup>48</sup> Although little work has been done on muscle growth in children with CP, one clinical report by Eames et al<sup>49</sup> demonstrated increased gastrocnemius muscle length after BTX-A. Decreasing focal muscle spasticity with BTX-A may also provide an opportunity for children to learn to use and strengthen opposing muscles through physical and occupational therapy. The result would be a better balance of mechanical forces around the ankle over time, better long-term function, and prolongation of treatment effect. Improved orthotic footwear becomes possible with better biomechanical alignment.

In terms of overall function, decreasing the level of focal muscle spasticity with BTX-A may allow chil-

dren with CP to learn more normal patterns of locomotion,<sup>36</sup> improve balance, increase gait velocity, and augment stride length with ambulation.<sup>11</sup> A previous study with BTX-A has been shown to significantly improve the subject's walking velocity from 87.5 cm/s to 101 cm/s, stride length, electromyography results of the tibialis anterior during the swing phase, and the ankle dorsiflexion during stance and swing phases.<sup>12</sup>

Overall, the safety profile of BTX-A in this trial was excellent. Repeated injections proved to be a safe and effective therapy in children with CP with a total of 302 patient years of BTX-A exposure. Long-term treatment with BTX-A in this population resulted in relatively few AEs, and only 1 event of self-limiting, generalized weakness, that was considered serious. The number of patients with AEs related to treatment was greatest the first year and decreased thereafter. The most commonly reported treatment-related event was stumbling or falling, probably related to decreased muscle tone after BTX-A treatment. As patients adjusted to the decreased muscle tone, the reported episodes of falling decreased, similar to the pattern of the occurrence of other AEs.

The results of this prospective trial are supported by 2 previous retrospective chart reviews by Gormley and Delgado,<sup>50,51</sup> which describe an excellent safety profile for BTX-A when used to treat children with CP. Gormley's review found that only 22% of 158 CP patients had minor AEs, and none of these patients had serious AEs related to BTX-A injections.<sup>50</sup> The events commonly reported were constipation, low grade fever, and extremity weakness.<sup>50</sup> Two patients with a previous history of seizure had a seizure within 3 months of BTX-A injections. Both patients were subsequently reinjected without additional AEs. It is interesting to note that no weakness or AEs of any kind were reported in this study after the third injection. Delgado also reported a low incidence of AEs with 14 AEs occurring after 257 injections in 104 patients.<sup>51</sup> None of the events related to BTX-A were serious.<sup>51</sup>

One concern with long-term BTX-A treatment is the possibility of antibody development leading to resistance to additional BTX-A treatment. In this study, only 6% of patients were concordant for both detectable antibodies and subsequent BTX-A nonresponse. These results are in agreement with several longitudinal studies in adult dystonia patients, who remained responsive to continued BTX-A treatment for 4 years or more.<sup>21,52,53</sup> The successful use of repeated BTX-A treatment for limb spasticity in adult patients who were treated for up to 8 years has also been reported.<sup>54</sup> To date, the incidence of patients with neutralizing antibodies (approximately 5%) who become nonresponders remains quite low.<sup>21,52,53</sup>

Antibody development has been linked to the total amount of protein exposure from the neurotoxin protein over time.<sup>44,52</sup> In fact, there was a direct correlation between the cumulative amount of BTX-A patients received during this trial and the subsequent development of neutralizing antibodies. As a result, physicians initially recommended that treatment be tailored to minimize patients exposure to the neuro-

toxin protein.<sup>52,55</sup> Concern about antibody development has now lessened with the formulation of a new bulk toxin with a significantly lower protein load. The original BTX-A formulation used in this study had 25 ng protein/100 U whereas the current bulk toxin source used in the production of BTX-A formulation (approved by the Food and Drug Administration in 1997) has approximately 5 ng of protein/100 U.<sup>55</sup> The availability of a toxin source with decreased antigenic potential is an important development.<sup>37,55</sup>

In this trial, serial treatment with BTX-A resulted in improved gait in children with equinus deformity which was maintained over a 2-year period of follow-up. BTX-A proved to be both safe and effective in this population. The outcome of our trial supports the developing consensus that reduction of excessive foot and ankle tone with BTX-A may improve gait and be a reasonable first therapeutic option in the treatment of equinus foot deformity<sup>12–36</sup>.

The addition of BTX-A to the management of focal muscle spasticity in children with CP decreases muscle overactivity, and may, in the long run, normalize ambulation, improve muscle growth, and enhance quality of life.

#### ACKNOWLEDGMENTS

Research supported by a grant from Allergan, Inc. The research at Bowman Gray School of Medicine of Wake Forest University was also supported by the General Clinical Research Center of the Bowman Gray School of Medicine, Grant Number M01RR07122.

We thank Julie Mordaunt, MS, Chia-Ho Lee, MS, LouAnn McGeever, and Elizabeth Sandoval for their assistance with this study.

Patricia T. Molloy, MD, Catherine Turkel, PharmD, and Jennifer M. Walcott, MS, are co-authors of the paper and are currently employed by the company (Allergan, Inc) that provided the study support and study medication, botulinum toxin type A (trade name Botox). Botox is referred to in the manuscript as BTX-A or botulinum toxin type A and not by the trade name, except for once in the "Methods" section as appropriate.

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## THE FIRST TO CONNECT MOBILE PHONES TO THE INTERNET

“The Finns were successful because they were especially good at guessing what others would want from their mobile phones. One big reason for this—or so the people at Nokia believed—was that they spent a lot of time studying children. The kids came to each new technology fresh, without preconceptions, and they picked it up more quickly. They dreamed up uses for their phones that, for reasons no one fully understood, never occurred to grown-ups. The instant text message, for instance. The instant message is fast becoming a staple of European corporate communication. To create an instant message, you punched it by hand into your telephone, using the keypad as a typewriter. On the face of it this is not an obvious use of a telephone keypad. The difference between the number of letters in the alphabet and the number of keys on the pad meant you wound up having to type a kind of Morse code. The technique had been invented by Finnish schoolboys who were nervous about asking girls out on dates to their face, and Finnish schoolgirls who wanted to tell each other what had happened on those dates as soon as it happened. They’d proved that if the need to communicate indirectly is sufficiently urgent, words could be typed into a telephone keypad with amazing speed. Five and a half million Finns had sent each other more than a billion instant messages in the year 2000. The technique had spread from Finnish children to businessmen because the kids had taught their parents how to use their phones. Nokia employed anthropologists to tell them this.”

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Submitted by Student

## Botulinum Toxin Type A Neuromuscular Blockade in the Treatment of Equinus Foot Deformity in Cerebral Palsy: A Multicenter, Open-Label Clinical Trial

L. Andrew Koman, Allison Brashear, Samuel Rosenfeld, Henry Chambers, Barry Russman, Mercer Rang, Leon Root, Eugenio Ferrari, J. Garcia de Yebenes Prous, Beth P. Smith, Catherine Turkel, Jennifer M. Walcott and Patricia T. Molloy

*Pediatrics* 2001;108;1062-1071

DOI: 10.1542/peds.108.5.1062

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