31. Chang JJ, Amon E, Leet T: Is mode of delivery a risk factor for cerebral palsy? *Obstet Gynecol* 2002;99:S68–S69.
32. Mashiloane CD, Moodley J: Induction or caesarean section for preterm preeclampsia? *J Obstet Gynecol* 2002;22:353–356.
33. Nelson KB: The neurologically impaired child and alleged malpractice at birth. *Neurol Clin* 1999;17:283–293.
34. Jacobsson B, Hagberg G, Hagberg B, et al: Cerebral palsy in preterm infants: A population-based case-control study of antenatal and intrapartal risk factors. *Acta Paediatr* 2002;91:946–951.
35. Thorngren-Jerneck K, Herbst A: Low 5-minute Apgar score: A population-based register study of 1 million term births. *Obstet Gynecol* 2001;98:65–70.
36. Talvik T, Haldre S, Sööt A, et al: Creatine kinase isoenzyme BB concentrations in cerebrospinal fluid in asphyxiated preterm neonates. *Acta Paediatr* 1995;84:1183–1187.
37. Kulak W, Sobaniec W: Cerebral palsy in children in north-eastern Poland. *J Pediatr Neurol* 2004;2:79–84.
38. Vermeulen GM, Bruinse HW, de Vries LS: Perinatal risk factors for adverse neurodevelopmental outcome after spontaneous preterm birth. *Eur J Obstet Gynecol Reprod Biol* 2001;99:207–212.
39. Murphy DJ, Sellers S, MacKenzie IZ, et al: Case-control study of antenatal and intrapartum risk factors for cerebral palsy in very preterm singleton babies. *Lancet* 1995;346:1449–1454.
40. Stelmach T, Kallas E, Pisarev H, Talvik T: Antenatal risk factors associated with unfavorable neurologic status in newborns and at 2 years of age. *J Child Neurol* 2004;19:116–122.

APPENDIX: DEFINITIONS

Preeclampsia: Maternal blood pressure greater than 140/90 mm Hg in association with proteinuria (≥ 300 mg in a 24-hour urine collection) occurring after the twentieth week of pregnancy
Premature rupture of membranes: Rupture of membranes before the onset of labor
Neonatal sepsis: Positive blood culture in a symptomatic newborn
Chorioamnionitis: Maternal fever > 38°C, associated with fetal tachycardia > 160 beats/minute, maternal tachycardia > 100 beats/minute, uterine tenderness, or foul-smelling amniotic fluid
Severe cerebral palsy: Severe motor and intellectual impairment with inability to sit and walk
Moderate cerebral palsy: Moderate motor impairment, walking with aids
Mild cerebral palsy: Presence of neurologic signs without functional disability (eg, walking without aids but displaying abnormal patterns of gross and fine motor movements)

Original Article

Factors Predicting the Efficacy of Botulinum Toxin-A Treatment of the Lower Limb in Children With Cerebral Palsy

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ABSTRACT

Botulinum toxin A is widely used for spasticity management in children with cerebral palsy, although outcomes are unpredictable. The aim of this study was to identify criteria for selecting patients most likely to benefit from botulinum toxin A treatment. Fifty-five subjects, aged 2.5 to 18 years, were recruited. The assessment covered measures of spasticity (Modified Ashworth Scale), function (using the Gross Motor Function Measure and the Physician's Rating Scale), selective motor control, static range of motion at the ankle with knee extended and flexed, range of motion of the knee flexors, central and peripheral vision, and cognitive ability. Outcomes at 3 months were compared with baseline values. All of the scales showed significant differences between pre- and postinjection values. Significantly increased Gross Motor Function Measure scores were found in children aged 48 months or under and in those able to walk with support. Greater improvements in selective motor control and Physician's Rating Scale were seen in those with a less severe pattern of paralysis, lower levels of impairment, the ability to walk (with or without support), normal visual acuity, and normal or borderline cognition. We identified factors that mark out patients as most likely to achieve functional gains: young age, hemiplegia or diplegia, slight to moderate disability, walking with support, normal or borderline cognition, and normal or borderline visual acuity. (*J Child Neurol* 2005;20:661–666).

Botulinum toxin type A is one of the most powerful known toxins. When injected into a muscle, it rapidly binds to the presynaptic nerve terminals and is internalized across the presynaptic membrane, from where it inhibits acetylcholine release.[1] Over the past 10 years, this toxin has been increasingly applied in the spasticity management of children with cerebral palsy, and numerous studies have confirmed its effectiveness.[2–8] In addition to reduced muscle tone,[6,8,9] a number of other benefits of botulinum toxin A have been reported: greater joint extension,[8–10] improved gait patterns,[6,11,12] and increased length of the treated muscle[13] accompanied by a reduction in the total strength of the injected muscle and activation of antagonistic muscle fibers. Koman and colleagues drew attention to improved gait and significantly increased ankle joint excursion following treatment with botulinum toxin A.[3,12]

There are currently no universally recognized guidelines or criteria for the selection of suitable candidates for botulinum toxin treatment or that establish the doses that should be administered, the optimal age at first treatment, or the time that should be allowed to elapse between injections.

Nevertheless, published recommendations do exist, supported by numerous researchers, on the use of this treatment in the management of cerebral palsy.[14] Several authors have attempted to develop guidelines on the doses required to obtain maximum benefit,[15] but very few studies have sought to identify factors predicting a favorable outcome of botulinum toxin treatment in children. Some might cite the study by Fattal-Valevski et al, in which certain parameters (an Ashworth Scale score indicating increased muscle tone, lower Gross Motor Function Measure scores, nonindependent ambulatory status) seemed to be predictors of greater effectiveness,[16] but other authors maintain that age is the crucial factor and stress the importance of early treatment.[7]

The aim of this study was to evaluate the effectiveness of botulinum toxin A treatment of lower limb spasticity in children with cerebral palsy and to attempt to identify precise clinical criteria that might help in the selection of patients most likely to benefit from the treatment.

METHODS

Fifty-five subjects (24 females and 31 males) aged between 2 years 6 months and 18 years (mean age 5 years and 4 months, ± SD 3 years), affected by pyramidal cerebral palsy, were selected according to the following criteria:

- Presence of spastic and dynamic equinus[12]
- Limited number of muscles requiring treatment (no more than two to four per patient)
- No history of orthopedic surgery, oral antispasticity medication, intrathecal baclofen treatment, or rhizotomy
- Availability of an adequate course of physiotherapy post-treatment

The patients' cerebral palsy was classified in accordance with Hagberg and colleagues' criteria[17] as diplegic (29 subjects, 53%), hemiplegic (15 subjects, 27%), or tetraplegic (11 subjects, 20%). The subjects were grouped according to an ascending scale of severity of functional impairment[18]: level 1, 14 patients (25%); level 2, 7 patients (13%); level 3, 17 patients (31%); level 4, 12 patients (22%); and level 5, 5 patients (9%).

At the first assessment, 33 of the subjects (60%) walked independently (18 diplegics and 15 hemiplegics), 10 (18%) walked with support (9 diplegics and 1 tetraplegic), and 12 (21%) did not walk (10 tetraplegics and 2 diplegics).

Each patient underwent a clinical assessment at baseline and at 1, 3, and 6 months after the treatment. However, this study focuses only on the follow-up at 3 months, which we believe to fall within the period of maximum treatment effect. Data from assessments at the other time points will be processed subsequently and do not fall within the scope of this study.

The clinical assessment involved a neurologic examination and a functional evaluation. The latter involved the use of various measures:

- Modified Ashworth Scale[19,20] for the assessment of spasticity
- Functional rating scales: the Gross Motor Function Measure and the Physician's Rating Scale (Boyd and Graham found the Physician's Rating Scale very useful when analyzing typical gait viewed on slit-screen video in slow motion. Several of its items are designed to quantify visually the relationship between the ankle and knee position during stance.)[21,22]
- Selective Motor Control test. In this test, the child sits with legs extended and is required to extend his foot dorsally; the use of various muscle groups (anterior tibialis, levators of the great toe and other toes) is observed, as is the ability to extend the foot selectively, that is, without bending the knee at the same time. The level of this selective motor control of dorsiflexion has been shown to be useful in predicting the outcome of botulinum toxin A treatment, with patients showing good selective motor control also achieving better dorsiflexion and foot clearance in swing. [22]
- Static range of motion of joints (measured by goniometry) on slow passive movement to assess musculoskeletal contractures[22–25]:
  - Ankle (gastrocnemius muscle), with knee extended
  - Ankle (gastrocnemius muscle), with knee flexed
  - Knee (flexor muscles)

To investigate the presence of the central/peripheral visual deficits to which these patients are known to be prone,[26] a neuro-ophthalmologic assessment was performed. We took visual acuity, measured using a Snellen optotype, as an index of visual impairment. All subjects with visual acuity less than five tenths were classified as visually impaired and those with visual acuity five-tenths or greater as normally sighted or borderline.

A cognitive assessment was also performed. In subjects under 5 years of age, the Griffiths Scale of Mental Development (developmental quotient) was used, and for those over 5 years of age, the Wechsler Intelligence Scale for Children-Revised (IQ) was used.[27,28]

All subjects were treated with botulinum toxin (Dysport® 12 to 17 U/kg per muscle in the treated leg or Botox® 4 to 6 U/kg per muscle in the treated leg) using a 27-gauge needle. The patients were given a local anesthetic prior to injection. This was either lidocaine and prilocaine (EMLA) cream applied at the site of injection 30 to 60 minutes prior to the procedure or ethyl chloride applied immediately beforehand.

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The patients were selected from those referred to the Department of Child Neurology and Psychiatry of the C. Mondino Foundation, University of Pavia, between 1997 and 2003.

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Dysport® (500 U) was reconstituted with 2.5 mL of sodium chloride (0.9%) so that 0.5 mL of the solution obtained contained 100 U of Dysport®. Instead, Botox® (100 U) was reconstituted with 1 ml of sodium chloride (0.9%).

In all, 147 striated skeletal muscles were injected (84 gastrocnemius, 4 soleus, 45 hamstring, 12 adductor, and 2 posterior tibialis muscles). Of the 55 patients, 36 (65.5%) underwent a single treatment, 11 (20%) had 2 treatments, and 8 (14.5%) had 3 treatments, taking the total number of treatments administered to 82. A period of 4 to 28 months (mean 14 months) was allowed to elapse between consecutive treatments. In all subjects undergoing more than one treatment (34.5% of the sample), each treatment administered was considered singly. No patient received any additional spasticity therapy between treatments. Each patient was then prescribed a personalized rehabilitation program and the application of braces.

Data Analysis

The outcome of the treatment was primarily assessed at 3 months, which we believe to fall within the period of maximum effect. Each of the measures was compared with the values recorded at baseline.

We also investigated whether a favorable therapeutic outcome was significantly influenced by any of the following clinical parameters:

- Sex
- Age at the time of injection (≤ 48 months: 23 patients, 42%; > 48 months: 32 patients, 58%)
- Type of paralysis (hemiplegic, diplegic, tetraplegic)
- Degree of functional impairment[18]: more severe (level 4 or 5: 17 cases, 31%) versus less severe (levels 1–3: 38 cases, 69%).
- Ambulatory status (able to walk independently, able to walk with support, unable to walk).
- Cognitive level (Developmental Quotient or IQ < 70: 22 patients, 40%; ≥ 70: 33 patients, 60%)
- Visual acuity (< five tenths: 16 patients, 30%; ≥ five tenths: 38 patients, 70%).

Statistical Analyses

The differences between pre- and post-treatment scores were analyzed using a parametric (paired *t*-test) or nonparametric (Wilcoxon signed ranks) test, depending on the type of data being analyzed. Furthermore, each clinical parameter (sex, age, type of paralysis, degree of severity, ambulatory status, cognitive level, visual acuity) was submitted to univariate (*t*-test/analysis of variance or Wilcoxon/Kruskal-Wallis, as appropriate) and then to multivariate (multiple regression) analysis to detect factors possibly predictive of treatment response.

RESULTS

The treatment was well tolerated: the patients who cried when injected (50%) stopped crying within 1 to 2 minutes. Of the remainder (made up of the older, more collaborative patients), 30% reported a burning sensation at the injection site, whereas 20% did not show any reaction to the treatment.

Score changes on the various assessment scales were taken as indicators of treatment efficacy. In all of the scales, significant differences (paired tests) emerged between pre- and postinjection values (Table 1).

When changes in the mean scores from the various scales were analyzed in relation to several clinical parameters (Table 2), a number of these parameters appeared to be associated with the observed changes. Univariate and multivariate statistical analysis of these data showed the significance of these associations (Table 3).

Age at injection was significantly correlated with improvement in Gross Motor Function Measure score. The post-treatment increases were found to be significantly greater in the children aged 48 months or under than in those older than 48 months, $P < .01$ (univariate) and $P = .008$ (multivariate). There was no correlation between age at injection and any of the other measures recorded.

Changes in both Selective Motor Control test and the Physician's Rating Scale were associated with the type of paralysis. A greater improvement was seen in those with less severe paralysis (hemiplegia > diplegia > tetraplegia) ($P < .001$ to $< .05$). Changes in these measures (ie, in Selective Motor Control and Physician's Rating Scale scores) were also associated with the level of functional impairment.[18] Greater changes were observed in patients with lower levels of impairment (1–3) compared with those with greater impairment (level 4 or 5) ($< .0001$ to $< .01$).

The walking ability of the children at baseline was associated with the observed changes in Gross Motor Function Measure, Selective Motor Control, and Physician's Rating Scale scores. Those able to walk with support showed a significantly greater increase in the Gross Motor Function Measure score than nonwalkers ($P < .05$), but no significant differences emerged when the children able to walk independently were compared with those able to walk with support and with the nonwalkers. Significant differences also emerged between the increases in Selective Motor Control and Physician's Rating Scale scores, in walkers compared with nonwalkers ($P < .05$), and in those able to walk with support compared with nonwalkers ($P < .05$).

Patients with normal visual acuity (≥ five tenths) gained significantly more points on the Physician's Rating Scale ($P < .01$) and

Table 1. Comparison of Pre- and Post-Treatment Mean ± (SD) Values in the Various Scales

Scale	*Mean ± (SD) Pretreatment*	*Range*	*Mean ± (SD) Post-Treatment*	*Range*	*Change from Baseline Mean (± SD)*	*Statistical Significance* P
AS	2.60 (0.65)	1.00–4.00	1.66 (0.76)	0–4.00	0.94 (0.54)	< .0001
GMFM	69.56 (28.65)	0–99.40	71.67 (28.88)	0–99.40	2.10 (4.15)	< .0001
SMC	1.99 (1.38)	0–4.00	2.31 (1.46)	0–4.00	0.33 (0.59)	< .0001
PRS	2.73 (1.94)	0–8.00	4.45 (2.68)	0–10.00	1.69 (1.68)	< .0001
ROMKE	−0.92 (14.30)	−45.00–80.00	7.85 (10.82)	−10.00–70.00	9.30 (7.15)	< .0001
ROMKF	3.57 (10.35)	−42.00–30.00	11.36 (10.53)	−30.00–35.00	8.01 (4.81)	< .0001
ROMH	68.46 (20.41)	4.00–90.00	56.23 (18.24)	16.0–85.0	13.7 (10.0)	< .0001

AS = Ashworth Scale; GMFM = Gross Motor Function Measure; PRS = Physician's Rating Scale; ROMH = range of motion of hamstring muscles; ROMKE = range of motion of the ankle with the knee extended; ROMKF = range of motion of the ankle with the knee flexed; SMC = Selective Motor Control test.

Table 2. Mean (SD) Change in Score in the Various Assessment Scales in Relation to the Parameters Sex, Type of Paralysis, Degree of Functional Impairment, Ambulatory Status, Cognitive Level, and Visual Acuity

Parameter	*AS*	*GMFM*	*PRS*	*SMC*	*ROMKE*	*ROMKF*	*ROMH*
Sex							
F	0.96 (0.53)	3.11 (5.92)	1.71 (1.52)	0.37 (0.65)	10.13 (6.16)	8.62 (5.82)	12.8 (6.9)
M	0.93 (0.56)	1.40 (2.05)	1.68 (1.80)	0.29 (0.54)	8.89 (7.60)	7.71 (4.25)	14.3 (11.8)
Age							
≤ 48 mo	0.93 (0.50)	3.92 (6.50)	1.73 (1.77)	0.41 (0.66)	7.73 (4.64)	8.57 (5.76)	12.5 (6.2)
> 48 mo	0.95 (0.57)	1.29 (2.10)	1.68 (1.65)	0.29 (0.55)	9.96 (7.91)	7.77 (4.39)	14.1 (11.1)
Type of paralysis							
Hemiplegic	0.94 (0.53)	1.32 (1.33)	3.38 (2.25)	0.88 (0.83)	7.16 (5.29)	7.16 (4.43)	
Diplegic	0.93 (0.54)	2.71 (5.03)	1.63 (1.38)	0.27 (0.52)	10.1 (7.93)	8.42 (4.96)	15.0 (10.2)
Tetraplegic	0.96 (0.57)	0.87 (2.16)	0.52 (1.123)	0.08 (0.28)	8.72 (4.54)	7.18 (4.72)	9.8 (8.3)
Degree of functional impairment							
Levels 1–3	0.94 (0.52)	2.26 (4.65)	2.11 (1.72)	0.45 (0.66)	9.56 (7.81)	8.23 (5.09)	11.2 (5.0)
Levels 4–5	0.94 (0.58)	1.73 (2.77)	0.82 (1.22)	0.09 (0.29)	8.47 (4.47)	7.28 (3.83)	15.1 (11.8)
Ambulatory status							
W	1.00 (0.56)	1.70 (2.12)	2.34 (1.80)	0.46 (0.71)	9.30 (8.06)	7.75 (5.06)	13.5 (7.1)
WS	0.90 (0.53)	4.07 (7.07)	1.72 (1.26)	0.36 (0.48)	10.04 (6.26)	9.13 (4.54)	13.4 (9.1)
NW	0.89 (0.55)	0.61 (2.03)	0.07 (0.27)	0 (0)	8.00 (4.45)	7.07 (4.19)	14.1 (13.0)
Cognitive level							
< 70	0.87 (0.54)	1.44 (2.31)	1.09 (1.40)	0.21 (0.45)	8.39 (6.31)	6.78 (4.45)	12.6 (10.4)
≥ 70	1.00 (0.55)	2.53 (4.98)	2.12 (1.75)	0.41 (0.65)	9.85 (7.61)	8.74 (4.91)	15.0 (9.4)
Visual acuity							
I	0.97 (0.56)	1.32 (2.58)	1.12 (1.49)	0.11 (0.40)	10.00 (6.86)	7.05 (4.41)	11.2 (6.1)
N-B	0.93 (0.55)	2.41 (4.59)	1.94 (1.70)	0.42 (0.63)	9.11 (7.26)	8.27 (4.91)	16.2 (11.0)

AS = Ashworth Scale; GMFM = Gross Motor Function Measure; I = visually impaired; N-B = normal-borderline visual acuity; NW = not able to walk; PRS = Physician's Rating Scale; ROMH = range of motion of hamstring muscles; ROMKE = range of motion of the ankle with the knee extended; ROMKF = range of motion of the ankle with the knee flexed; SMC = Selective Motor Control test; W = able to walk independently; WS = able to walk with support.

on the Selective Motor Control test ($P < .01$) than those whose visual acuity was impaired or borderline (< five tenths).

The cognitively normal and borderline subjects gained more points on the Physician's Rating Scale than the cognitively impaired group ($P < .001$).

No significant differences were found between male and female subjects across any of the measures recorded, nor did any of the clinical parameters investigated show any influence on Modified Ashworth Scale scores, range of motion with knee extended, range of motion with knee flexed, or range of motion of the knee flexor muscles.

DISCUSSION

The results of this study confirm the effectiveness of botulinum toxin treatment of lower limb spasticity in children with cerebral palsy. In accordance with published data, we observed a reduction in the spasticity of the treated muscle[6,8,9] and an increase in passive joint excursion (static range of motion).[8–10] We also observed significantly improved scores on scales and tests designed to assess function. These improvements were reflected in the gait pattern (Physician's Rating Scale scores),[6,11,12] in selective motor control of foot dorsiflexion, and in the acquisition of new motor items (on the Gross Motor Function Measure).

Few studies have sought to identify parameters that might help the clinician select patients most likely to benefit (in terms of improved functional outcome) from the treatment. Fattal-Valevski and colleagues identified low baseline Gross Motor Function Measure score, initially severe spasticity, and walking with support as factors predictive of a favorable response. Factors such as age, sex, type of paralysis, total injected dose, and range of motion were not found to predict outcome. In this study, these authors evaluated treatment outcome on the basis of a questionnaire aimed at the parents and divided their subjects into two groups: good responders and poor responders.

In our investigation of the effectiveness of botulinum toxin treatment, quantitative variables, such as significant differences between pre- and post-treatment scores on functional scales, were taken into account and the following parameters emerged as significant predictors of a favorable treatment outcome: age, type of paralysis, severity of functional impairment, ambulatory status, cognitive level, and visual acuity. It is worth underlining that these parameters were found to correlate not so much with the strictly quantitative measures (Modified Ashworth Scale, ranges of motion) that measure spasticity and joint excursion as with significant improvements in functional measures, which indicate improved motor performances (Gross Motor Function Measure, Selective Motor Control test, and Physician's Rating Scale).

Age (in accordance with the findings of other authors[7]) emerged as a factor predictive of outcome, and the younger the subject is when treated, the more effective the treatment will be. Children treated by 48 months of age recorded significantly greater Gross Motor Function Measure score increases than older children. This finding would seem to support the view that the motor pattern of very young children, still being plastic and modifiable, offers more scope for development and functional recovery (a younger child has greater motor potential than an older child owing to the increased plasticity of the central nervous system).

The children with hemiplegia were found to benefit the most from the treatment (recording significant improvements on the Selective Motor Control test and Physician's Rating Scale). It can be remarked that the type of paralysis influences not so much motor acquisitions as a whole (Gross Motor Function Measure scores) as gait pattern (Physician's Rating Scale scores) and selective motor control. These observations are confirmed by a previous gait analysis study of children treated with botulinum toxin[29]:

Table 3. Results of Univariate and Multivariate Statistical Analysis (Multiple Regression Analysis)

	Delta GMFM		*Delta SMC*		*Delta PRS*	
	Univariate Analysis P *Value*	*Multivariate Analysis* P *Value*	*Univariate Analysis* P *Value*	*Multivariate Analysis* P *Value*	*Univariate Analysis* P *Value*	*Multivariate Analysis* P *Value*
Sex						
M vs F	NS	—	NS	—	NS	—
Age group						
≤ 48 mo vs > 48 mo	< .01	.008	NS	—	NS	—
Type of paralysis	NS	—	< .001	.001	< .001	.01
Hemiplegia vs diplegia			< .05		< .05	
Hemiplegia vs tetraplegia			< .05		< .05	
Diplegia vs tetraplegia			NS		< .05	
Degree of functional impairment						
Levels 1–3 vs levels 4–5	NS	—	< .01	—	< .0001	—
Ambulatory status	< .05	—	< .01	—	< .01	.0009
W vs WS	NS		NS		NS	
W vs NW	NS		< .05		< .05	
WS vs NW	< .05		< .05		< .05	
Cognitive level < 70 vs ≥ 70	NS	—	NS	—	< .001	—
Visual acuity						
I vs N-B	NS	—	< .01	—	< .01	—

	Delta AS		*Delta ROMKE*		*Delta ROMKF*		*Delta ROMH*	
	Univariate Analysis P *Value*	*Multivariate Analysis* P *Value*	*Univariate Analysis* P *Value*	*Multivariate Analysis* P *Value*	*Univariate Analysis* P *Value*	*Multivariate Analysis* P *Value*	*Univariate Analysis* P *Value*	*Multivariate Analysis*† P *Value*
Sex	NS	—	NS	—	NS	—	NS	—
Age group	NS	—	NS	—	NS	—	NS	—
Type of paralysis	NS	—	NS	—	NS	—	NS	—
Degree of functional impairment (2 groups)	NS	—	NS	—	NS	—	NS	—
Ambulatory status	NS	—	NS	—	NS	—	NS	—
Cognitive level	NS	—	NS	—	NS	—	NS	—
Visual acuity	NS	—	NS	—	NS	—	NS	—

AS = Ashworth Scale; Delta = mean of the differences between the pre- and post-treatment values; GMFM = Gross Motor Function Measure; I = visually impaired; N-B = normal-borderline visual acuity; NS = not significant; NW = not able to walk; PRS = Physicians' Rating Scale; ROMH = range of motion of hamstring muscles; ROMKE = range of motion of the ankle with the knee extended; ROMKF = range of motion of the ankle with the knee flexed; SMC = Selective Motor Control test; W = able to walk independently; WS = able to walk with support.

**t*-test/Anova or Wilcoxon/Kruskal Wallis

†Multiple Regression Analysis

these authors, too, found hemiplegic subjects to be the group deriving most benefit, in terms of gait improvement, from the treatment.

Severity of functional impairment also emerged as a significant factor: in the subjects showing (according to Palisano et al's classification[18]) less severe impairment of neuromotor functions, gait and motor function (reflected, respectively in increased Physician's Rating Scale scores and better selective motor control) were found to improve.

The children able to walk supported were the ones who recorded the greatest functional improvements (Gross Motor Function Measure). Their gait (Physician's Rating Scale) and selective motor control also improved. On the other hand, the independent walkers, despite showing improvements on the Selective Motor Control test and Physician's Rating Scale, failed to record significantly increased scores on the Gross Motor Function Measure.

It can thus be hypothesized that the Gross Motor Function Measure is a scale that evaluates motor function in quantitative terms but is not sensitive enough to detect motor function changes. In other words, a qualitative change (such as increased stability, fluidity, or rapidity of movement) observable in the independent walker cannot be highlighted using this scale, which instead records, for example, the achievement of independent walking in children previously unable to walk without support.

Another interesting point is the influence of cognitive level and visual status. The role of cognitive and sensory development in the acquisition of motor skills is well known, and it appears crucial to consider these factors in the context of botulinum toxin treatment too. Cognitive level seems to be an element that should be taken into consideration in the assessment of treatment efficacy: in this study, the best responders to the treatment, in terms of gait improvement (number of points gained on the Physician's Rating Scale), were the patients with normal or borderline cognition.

Similarly, normal or borderline visual acuity was associated with significantly improved gait (Physician's Rating Scale) and selective motor control. This is a new aspect not considered in previous studies.

In conclusion, this study has highlighted several factors—some of which can also be recognized intuitively—that mark out

patients as especially suitable candidates for botulinum toxin treatment. These are preschool age (in particular, age under 4 years), hemiplegia or diplegia, slight to moderate disability, walking with support, normal or borderline cognition, and normal or borderline visual acuity. This is not to say that more severely affected, nonwalking, tetraplegic patients will not benefit from the treatment: indeed, in terms of spasticity and range of motion, no differences in treatment responses emerged between any of the subgroups considered in this study. What it does mean is that severely affected patients receive only some of the benefits of the toxin, that is, only those strictly linked to its antispastic action, whereas a patient with a less severe picture (higher cognitive level, milder functional disability, higher visual acuity) is able not only to exploit the antispastic effect of the toxin but also to derive greater functional benefits from the treatment (in terms of an improved gait pattern, the acquisition of new motor functions, better distal motor control) and to acquire, even long term, motor skills that are beyond the scope of the strictly pharmacologic effect of the toxin.

It would certainly be interesting to investigate the duration, over time, of the beneficial effects of botulinum toxin in an attempt to confirm our clinical impression, which is that whereas the pharmacologic antispastic effect recedes (over a period ranging from 3 to 6 months), some functional benefits (evaluated using the Physician's Rating Scale, Selective Motor Control test, and Gross Motor Function Measure) can be long lasting.

References

1. Dolly JO, Black J, Williams RS, Melling J: Acceptors for botulinum toxin reside on the motor nerve terminal and mediate its internalisation. *Nature* 1984;307:457–460.
2. Koman LA, Mooney JF III, Goodman A: Management of valgus hindfoot deformity in pediatric cerebral palsy patients by medial displacement osteotomy. *J Pediatr Orthop* 1993;13:180–183.
3. Koman LA, Mooney JF III, Smith BP, et al: Management of cerebral palsy with botulinum-A toxin: Preliminary investigation. *J Pediatr Orthop* 1993;13:489–495.
4. Koman LA, Mooney JF III, Smith BP, et al: Management of spasticity in cerebral palsy with botulinum-A toxin: Report of a preliminary, randomized, double-blind trial. *J Pediatr Orthop* 1994;14:299–303.
5. Denislic M, Meh D: Botulinum toxin in the treatment of cerebral palsy. *Neuropediatrics* 1995;26:249–252.
6. Cosgrove AP, Corry IS, Graham HK: Botulinum toxin in the management of the lower limb in cerebral palsy. *Dev Med Child Neurol* 1994;36:386–396.
7. Boyd RN, Graham HK: Botulinum toxin A in the management of children with cerebral palsy: Indications and outcome. *Eur J Neurol* 1997;4(Suppl 2):15–22.
8. Corry IS, Cosgrove AP, Walsh EG, et al: Botulinum toxin A in the hemiplegic upper limb: A double blind trial. *Dev Med Child Neurol* 1997;39:185–193.
9. Calderon-Gonzalez R, Calderon-Sepulveda R, Rincon-Reyes M, et al: Botulinum toxin A in management of cerebral palsy. *Pediatr Neurol* 1994;10:284–288.
10. Zelnik N, Giladi N, Goikhman I, et al: The role of botulinum toxin in the treatment of lower limb spasticity in children with cerebral palsy—A pilot study. *Isr J Med Sci* 1997;33:129–133.
11. Sutherland DH, Kaufman KR, Wyatt MP, et al: Double-blind study of botulinum A toxin injections into the gastrocnemius muscle in patients with cerebral palsy. *Gait Posture* 1999;10:1–9.
12. Koman LA, Mooney JF III, Smith BP, et al: Botulinum toxin type A neuromuscular blockade in the treatment of lower extremity spasticity in cerebral palsy: A randomized, double-blind, placebo-controlled trial. Botox Study Group. *J Pediatr Orthop* 2000;20: 108–115.
13. Eames NW, Baker R, Hill N, et al: The effect of botulinum toxin A on gastrocnemius length: Magnitude and duration of response. *Dev Med Child Neurol* 1999;41:226–232.
14. Graham HK, Aoki KR, Autti-Ramo I, et al: Recommendations for the use of botulinum toxin type A in the management of cerebral palsy. *Gait Posture* 2000;11:67–79.
15. Bakheit AM, Severa S, Cosgrove A, et al: Safety profile and efficacy of botulinum toxin A (Dysport®) in children with muscle spasticity. *Dev Med Child Neurol* 2001;43:234–238.
16. Fattal-Valevski A, Giladi N, Domanievitz D, et al: Parameters for predicting favorable responses to botulinum toxin in children with cerebral palsy. *J Child Neurol* 2002;17:272–277.
17. Hagberg B, Hagberg G, Olow I: The changing panorama of cerebral palsy in Sweden 1954-1970. I. Analysis of the general changes. *Acta Paediatr Scand* 1975;64:187–192.
18. Palisano RJ, Rosenbaum PL, Walter SD, et al: Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214–223.
19. Ashworth B: Preliminary trial of carisoprodal in multiple sclerosis. *Practitioner* 1964;192:540–542.
20. Bohannon RW, Smith MB: Inter-rater reliability of a modified Ashworth Scale of muscle spasticity. *Phys Ther* 1987;67:206–207.
21. Russell DJ, Rosenbaum PL, Cadman DT, et al: The Gross Motor Function Measure: A means to evaluate the effects of physical therapy. *Dev Med Child Neurol* 1989;31:341–352.
22. Boyd RN, Graham HK: Objective measurement of clinical findings in the use of botulinum toxin type A for the management of children with cerebral palsy. *Eur J Neurol* 1999;6(Suppl 4):23–25.
23. Tardieu G, Stentoub S, Delarue R: [Research on a technique for measurement of spasticity]. *Rev Neurol (Paris)* 1954;91:143–144.
24. McDowell BC, Hewitt V, Nurse A, et al: The variability of goniometric measurements in ambulatory children with spastic cerebral palsy. *Gait Posture* 2000;12:114–121.
25. Allington NJ, Leroy N, Doneux C: Ankle joint range of motion measurements in spastic cerebral palsy children: Intraobserver and interobserver reliability and reproducibility of goniometry and visual estimation. *J Pediatr Orthop B* 2002;11:236–239.
26. Lanzi G, Fazzi E, Uggetti C, et al: Cerebral visual impairment in periventricular leukomalacia. Neuropediatrics 1998;29:145–150.
27. Griffiths R: *The Abilities of Babies*. London, The Test Agency, 1986.
28. *Wechsler Intelligence Scale for Children-Revised*. New York, The Psychological Corporation, 1974.
29. Galli M, Crivellini M, Santambrogio GC, et al: Short-term effects of "botulinum toxin A" as treatment for children with cerebral palsy: Kinematic and kinetic aspects at the ankle joint. *Funct Neurol* 2001;16:317–323.