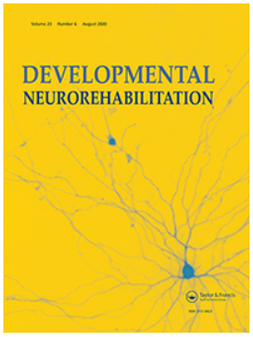

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Upper-extremity Spasticity-reducing Treatment in Adjunct to Movement Training and Orthoses in Children with Cerebral Palsy at Gross Motor Function- and Manual Ability Classification System Levels IV-V: A Descriptive Study

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ABSTRACT

Covering a 20-year period of work with children with severe cerebral palsy (CP) within a Swedish habilitation service, changes in passive wrist extension with fingers extended (PWE-FE) and current hand function are described and compared between children receiving systematic upper-extremity treatment with botulinum neurotoxin type A and intervention programs from before 7 years of age (Group 1, n = 7), those whom for various reasons did not undergo this treatment (Group 2, n = 10), and those not having the option to receive treatment until later during childhood/adolescence (Group 3, n = 8). Group 3 showed more critical and less normal PWE-FE values for both wrists, and poorer hand function scores, particularly compared with Group 1. Findings cautiously suggest that repeated upper-extremity spasticity-reducing treatment and movement training/orthoses from an early age may help prevent critical loss of passive range of motion of the wrist joint flexion/extension and promote hand function development in children with severe CP.

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Severe cerebral palsy; botulinum toxin; upper-extremity interventions; passive wrist extension; hand function; development

Introduction

Cerebral palsy (CP) is a unifying concept for a range of developmental deficiencies in motor, sensory and cognitive functioning as a consequence of early brain damage.[1] Typically, CP leads to critical problems with voluntary control of the extremities, with different levels of disability.[2] In Sweden, about 31% of children born with CP are classified as severe CP (Gross Motor Function Classification System, GMFCS, levels IV and V).[3] Children with severe CP are characterized by a combination of many critical disabilities, although heterogeneous with regard to presentation, causes, and symptoms. Spastic muscle overactivity has a negative impact on muscles and joints, adversely affecting joint motion and causing joint contractures and bone deformation which is particularly problematic in growing children. Apart from a motor impairment, intellectual disability and one or more of a range of additional functional, behavioral and/or medical complications are commonly displayed.[4] Further, due to the severity of the conditions, there is an increased risk for death during childhood.[5] Consequently, children with severe CP and multiple disabilities are in a great and enduring need for care.

If the treatment of children with severe CP is reduced to mainly basic support and care, it typically leads to loss of passive movement which causes contractures and may require multiple invasive surgical procedures during development. During the last two decades, however, the treatment of children with severe CP has gone through important changes and, today, treatment methods include orthotics, passive stretching, movement stimulation and training, often combined with spasticity-reducing medication (e.g. baclofen and botulinum neurotoxin type A, BoNT-A) and/or surgery.

Since the turn of the century, an increased focus has also been put on treatment of the upper-extremity in children with CP. Several studies have correspondingly been performed to investigate the effects of BoNT-A and other treatment methods regarding the upper-extremity in children with spastic CP. An influential Cochrane review concluded that there was an evident effect of treatment with BoNT-A in the upper-extremity if injections were combined with orthoses and/or training paradigms.[6] A similar result was obtained in a more recent systematic review of interventions for the upper-limb in children with CP,[7] showing evidence for combinations of BoNT-A and bimanual training, constraint-induced movement therapy, context-focused therapy, goal-directed functional training, home-based activities, and occupational therapy. Unfortunately, few studies have included children with severe CP in this research effort, likely due to the challenges involved in studying this vulnerable population. A systematic review of studies including children with GMFCS levels IV and V showed inconclusive results regarding the effects of BoNT-A on pain reduction, improved care, and motor functions.[8] More specifically regarding the upper-extremity, one study observed improved upper limb function following BoNT-A treatment in children and adolescents with severe CP and multiple disabilities.[9] Another study compared BoNT-A and sham treatment, combined with physio- and occupational therapy, in children and adolescents with severe CP.[10] Significant differences were found in improved satisfaction of

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fulfilled occupational performance goals in favor of BoNT-A treatment (16 weeks after treatment), although performance measures did not differ between groups. One additional study reported a similar result regarding positive short- and long-term (12 months) effects of BoNT-A combined with training on occupational performance and arm/hand function in school-aged children with bilateral spastic CP (BSCP).[11]

While these results generally indicate positive effects of treatment with BoNT-A combined with training paradigms for upper-limb function in children with severe CP, there is clearly a need for additional studies to expand on existing knowledge. Given the life-long need for treatment in children with severe CP and multiple disabilities, it is of particular importance to learn more about the effects of repeated treatments over a long-standing time period. For example, children with severe CP typically have critical problems with using the hands due to spasticity, dystonia and/or paresis, causing loss of passive range of motion (ROM) of the wrist flexion or extension and pain and affecting daily care and living activities.[12] Thus, it is clinically significant to learn whether early and repeated treatment with BoNT-A in adjunct to movement training and orthoses durably prevents loss of passive ROM of the wrist flexion or extension and aids in avoiding an excess of multiple and repeated surgical procedures during childhood and adolescence.

Maintained range of wrist and finger motion, as measured by passive wrist extension with fingers extended (PWE-FE), is one highly important factor in order to develop hand use capacity, together with additional benefits such as reduced pain and improved hand hygiene. The present study aims to describe and compare changes in PWE-FE values over a 20-year period (1997–2017) and current hand function/activity in children with severe CP and multiple disabilities whom either received no systematic treatment until adolescence/young adulthood (i.e. born before implementation of BoNT-A treatment within the habilitation service) or had the possibility to receive treatment with BoNT-A and upper-extremity interventions from young childhood (i.e. born after such implementation).

Materials and Methods

Habilitation Setting

The habilitation service in Sweden is a public health service specialized in functional disability and include interdisciplinary teams working with developing children up to approximately 20 years old. Within the habilitation service in Västerbotten county, a specialized multidisciplinary team (hand surgeon, physiotherapist, occupational therapist) has utilized intramuscular BoNT-A injections together with orthotics and training paradigms as a treatment of upper-extremity in children with CP since 2001. The BoNT-A treatment regime has principally been the same over the time course of this study. The multidisciplinary team has consistently performed evaluations of treatment indication from an as early age as possible (≥1 ½ years old), and intramuscular injections have been individually tailored and carried out by the team hand surgeon (IB and two additional hand surgeons between the years 2001–2006). Before each BoNT-A treatment, baseline measures including PWE-FE and capacity for manual activity have been performed. Observations of increased muscle tone in the wrist/finger flexors and/or forearm pronators have resulted in scheduling of BoNT-A injections of these muscles. If needed, other upper-limb muscles were also treated. Within 2–3 weeks after treatment, the child has been invited back to the team for establishment of an individualized home training program promoting passive range of motion (including stretching of all treated muscles) and manual activities (e.g. pressing or pushing a contact/object), and, if applicable, manufacturing of individually adjusted wrist/finger resting (6 h) orthoses. Orthoses have been recommended to be used overnight to maximize stretching duration.[13] The majority of participants adhered to this recommendation (56%). A remaining 20% used orthoses during day time (due to affecting sleep when used at night), 12% did not use orthoses (due to frequent changes in muscle tone), and 12% used an alternative thumb orthosis and/or wrist support. None used orthoses both night and day. When the treatment effect wore off, a new evaluation of whether the treatment should be repeated and/or whether any changes in the home training program and/or adjustment of orthoses are needed has been made, and the above procedures replicated. Importantly, the whole process has further relied on a collaboration with caregivers and assistive personnel, and a flow of information to the child's general habilitation service team.

Participants

The present study is a retrospective medical record review including children born 1986–2007 receiving habilitation service in Västerbotten county with a diagnosis of BSCP (tetraparesis or tetraplegia), dyskinetic CP (dystonia or choreoathetosis) or mixed CP (bilateral spastic and dyskinetic CP), GMFCS level IV-V, and major impairment in both hands (Manual Ability Classification System, MACS, levels IV and V). A total of 30 children/families were identified, of which 26 gave consent to participate. An additional six children who were deceased at the time of this study were also included. All children had been assessed by a hand surgeon at the habilitation service center due to hypertonia and disability in the upper-extremity. Seven of the children had BSCP with one functional hand and consequently were excluded. The final sample thus consisted of 25 children with severe CP (GMFSC IV-V, MACS IV-V), multiple disabilities, and no or very limited functional hand use capacity (initial House classification 0–1, see 2.3 below). Of these, 7 were born 1999–2006 and had received upper-extremity treatment with BoNT-A in the wrist/finger flexors and/or forearm pronators and interventions from <7 years of age (Group 1). Ten children were born 1995–2007 but had not received early upper-extremity treatment with BoNT-A and interventions due to passing away while being on waiting list for treatment (n = 3), no indication (n = 1), family declining treatment (n = 1), or receiving treatment with BoNT-A in the wrist/finger flexors and/or forearm pronators at >7 years of age (n = 4) or as young adult (n = 1) (Group 2). Eight children were born before 1996, i.e. only had the possibility to receive upper-extremity treatment with BoNT-A in the wrist/finger flexors

and/or forearm pronators and interventions as adolescents or as young adults (Group 3). Of these, three children did not receive BoNT-A treatment due to passing away before the introduction of BoNT-A (n = 1), family declining treatment (n = 1), or vulnerability to BoNT-A for medical reasons (n = 1). All of the included children with dyskinetic CP, independent of group, had dystonia, none had athetosis. Participant characterization is given in Table 1 and details regarding participant treatment in Table 2.

The study was approved by the Umeå Regional Ethical Board (registration nr 2015–228–31M) and conducted in accordance with the Declaration of Helsinki. All parents and children whom had come of age at the time of data collection signed an informed consent form for participation. Medical information was recorded by investigators with patient care responsibilities (GA, BR) and is reported so that individual children cannot reasonably be identified.

Measures and Procedures

Measures of torque-controlled passive wrist extension/flexion with fingers extended, as quantified by goniometer measurements according to Norkin & White,[14] were extracted from the medical records of each participant. PWE-FE is very commonly impaired in children with severe CP.[15] Loss of passive wrist extension causes flexion deformity of the wrist, which is the most frequently observed pattern in children with severe CP. In this study, however, only one child (C6.3) had recorded measures of passive wrist flexion (due to a distinctive pattern of paresis in the flexors and overactivity in the wrist/finger extensors) and passive wrist flexion was consequently discarded from further examination and discussion. All measurements had been performed by the physiotherapist (BR and one additional physiotherapist between the years 2001–2005) and occupational therapist (GA) within the multidisciplinary team. As muscle tone is dependent of speed, the PWE-FE was obtained at low velocity by the physiotherapist, waiting for the child to relax as far as possible. This was done until the remotest distal joints began to bend, without hurting the child. At this position, the value in degrees was recorded by the occupational therapist. Note that the movement was stopped when the physiotherapist felt the resistance. Thus, PWE-FE is used as a proxy measure of resistance to passive movement caused by increased tone, and not as a measure of passive ROM or substitute for muscle length. Parallel conversation with assistants and/or caregivers ensured correct interpretation of children lacking own ability to communicate. For children born after 1999, additional measurements from the Cerebral Palsy Follow-Up Program (CPUP),[16] a Swedish national quality register for children with CP, were available for Västerbotten county from 2007 and added to the study. The mean amount of PWE-FE measurement occasions was 22.3 (range: 14–33) for Group 1, 6.5 (range: 0–19) for Group 2, and 10.5 (range: 2–19) for Group 3. Mean age of the first measure was 4.3 years (range: 1.5–7.3) for Group 1, 5.9 years (range: 1–17) for Group 2, and 13.1 years (range: 9.5–16.3) for Group 3. Mean age of last measure was 14.5 years (range: 10.8–18.3) for Group 1, 13.4 years (range: 2.8–21) for Group 2, and 19.3 years (range: 14.8–21.3) for Group 3.

For a measure of hand function, data regarding activity in the respective hand as assessed by House Classification,[17] Swedish version, were obtained. Hand function was classified on a scale ranging from 0 (no voluntary hand activity) to 8 (full spontaneous independent hand use). Lower classes 1 and 2, respectively, denote using the arm/hand without a grip (e.g. as stabilizing weight, pressing or pushing an object) and holding an object placed in the hand using an unstable grip. Medium classes denote the ability to hold onto object and stabilize it (class 3), actively grasp the object and hold it weakly (class 4), and actively grasp object and stabilize it well (class 5). As assessments using House Classification over the study period were irregular and judged as increasingly reliable over time, only the most recently available measurement for each child was included in the present study (i.e. representing "current hand function" in the respective group, see Table 1). These data points were extracted from entries in the medical records (n = 12) or from the CPUP register (n = 11). Alternatively, district occupational therapists responsible for a particular child/youth were asked to retrospectively perform an assessment specifically for the purpose of this study (n = 2).

Table 1. Participant characterization for the respective groups.

Participant	First team visit (age)	CP diagnosis	GMFCS (level)	MACS (level)	House R/L
Group 1					
C1.1†	3 y 9 m	BSCP	5	5	0/0
C2.1	1 y 4 m	BSCP	4	4	5/5
C3.1	4 y 1 m	Dyskinetic CP	5	5	2/2
C4.1	6 y 4 m	BSCP	5	4	2/3
C5.1	3 y 6 m	BSCP	5	5	2/2
C6.1	1 y 11 m	BSCP	5	5	0/0
C7.1	1 y 5 m	BSCP	5	5	0/1
Group 2					
C1.2†	4 y 1 m	BSCP	5	5	0/0
C2.2†	6 y 5 m	Dyskinetic CP	5	5	1/1
C3.2	18 y	BSCP	5	5	0/0
C4.2	7 y 6 m	Dyskinetic CP	5	5	0/0
C5.2	7 y 6 m	Dyskinetic CP	5	5	2/2
C6.2	3 y 6 m	BSCP	5	5	0/0
C7.2	6 y 9 m	BSCP	5	5	0/0
C8.2	5 y 9 m	Mixed CP	5	5	2/2
C9.2	3 y	BSCP	5	5	3/1
C10.2†	1 y 6 m	Dyskinetic CP	5	5	2/1
Group 3					
C1.3†	11 y 5 m	BSCP	5	5	0/0
C2.3	13 y	BSCP	5	5	0/0
C3.3	13 y	Dyskinetic CP	4	4	0/1
C4.3	15 y	BSCP	5	5	0/0
C5.3	18 y 5 m	Mixed CP	5	5	0/0
C6.3†	10 y	BSCP	5	5	1/0
C7.3	15 y 4 m	Dyskinetic CP	5	5	0/1
C8.3	9 y 10 m	BSCP	5	5	0/0

Note. CP, cerebral palsy; R, right; L, left; MACS, Manual Ability Classification System; GMFCS, Gross Motor Function Classification System; C, child; †, deceased; y, years; m, months; BSCP, bilateral spastic cerebral palsy; Mixed CP, bilateral spastic and dyskinetic CP. House level denotes hand function at last measurement occasion, not initial hand function level at first team visit.

Spasticity-Reducing Treatment

The upper-limb BoNT-A treatment was done using BOTOX (concentration 100 u/1 ml) or DYSPORT (concentration 200 u/1 ml or 100 u/1 ml) with varying doses depending on the chosen muscle and number of muscles injected. Total dose by

Table 2. Spasticity-reducing treatment, movement training, and orthoses for the participants in the respective groups.

Participant	First BoNT-A upper-limb (age)	BoNT-A treatments (n)	BoNT-A treatment duration (y)	Surgery upper-limb (age 1st, n)	Passive movement training	Orthoses (age)
Group 1						
C1.1†	7 y	14	5.5	13 y 4 m, 1	Yes	4 y
C2.1	2 y 2 m	7	5	-	Yes	1 y
C3.1	4 y 6 m	6	4.5	-	Yes	17 y
C4.1	6 y 8 m	15	6.75	14 y, 1	Yes	6 y
C5.1	3 y 10 m	13	5.5	-	Yes	3 y
C6.1	2 y 2 m	21	10	-	Yes	2 y
C7.1	1 y 5 m	26	9.5	-	Yes	1 y
Group 2						
C1.2†	Waiting list	-		-	Yes	11 y
C2.2†	Waiting list	-		-	No	-
C3.2	21 y 6 m	5	4	-	Yes	18 y
C4.2	7 y 9 m	9	4.5	-	Yes	7 y
C5.2	14 y 7 m	4	1.5	-	Yes	14 y
C6.2	12 y 6 m	4	1.5	12 y 6 m, 1	Yes	5 y
C7.2	10 y	4	1	12 y 10 m, 1	Yes	7 y
C8.2	-	-		-	Yes	-
C9.2	-	-		-	Yes	3 y
C10.2†	Waiting list	-		-	No	-
Group 3						
C1.3†	-	-		14 y 1 m, 1	Yes	11 y
C2.3	16 y	15	8	20 y 7 m, 1	Yes	9 y
C3.3	13 y	20	16.3	21 y 7 m, 3	Yes	13 y
C4.3	15 y	8	4.4	19 y 6 m, 2	Yes	15 y
C5.3	23 y	3	3	-	Yes	23 y
C6.3†	17 y	8	2.9	-	Yes	12 y
C7.3	-	-		-	Yes	17 y
C8.3	-	-		18 y 4 m, 1	Yes	10 y

Note. Treatment duration refers to the time period when the participant received BoNT-A in one or more muscle groups affecting wrist/finger extension and/or wrist radial deviation. BoNT-A, botulinum neurotoxin type A; y, years; n, number; C, child; †, deceased; m, months

treatment did not exceed 600 u for BOTOX or 1000 u for DYSPORT. Injections were administrated under general anesthesia or topic anesthesia (EMLA) and/or conscious sedation (Midazolam) using electrical stimulation and/or EMG as a localization method. All seven children in Group 1 were treated with bilateral BoNT-A injections in the wrist/finger flexors and/or forearm pronators (100%), five children in Group 2 (50%), and five in Group 3 (62.5%). The mean number of bilateral BoNT-A treatments was 14.6 (range: 6–26) for Group 1, 5.2 (range 4–9) for Group 2, and 10.8 (range 3–20) for Group 3. Mean age of first BoNT-A treatment was 3.9 years (range 1.4–7) for Group 1, 12.9 years (range 7.8–21.5) for Group 2, and 17 years (range 13–23) for Group 3. The number of treated muscle groups varied as treatments were adjusted to individual need. At each treatment occasion, however, at least one muscle group affecting wrist/finger extension was treated with BoNT-A.

Bilateral upper-limb surgery was performed by the team hand surgeon in two participants of Group 1 (at age 13 and 14 years, respectively), in two participants of Group 2 (at age 12.5 and 13 years), and in five participants of Group 3 (at ages ranging from 14 to 21.5 years).

Statistical Analyses

Analyses of group differences regarding the background data were carried out by ANOVA, with follow-up t-tests, or chi-square analyses. Chi-square was also employed for analyzing group differences in the distribution of PWE-FE values between groups. Tests of group differences in hand function were carried out by Kruskal–Wallis analyses, with follow-up Mann-Whitney U tests.

Results

A main effect of group for age when first visiting the multidisciplinary team was revealed, $F(2,22) = 16.78$, $p < .001$, characterized by Group 3 (M_{age} = 13.3 years, SD = 2.9) being evidently older than Group 1 (M_{age} = 3.2 years, SD = 1.8) and Group 2 (M_{age} = 6.4 years, SD = 4.6). A main group effect was also found for age when first receiving orthoses, $F(2,20) = 5.78$, $p = .01$. Follow-up testing showed that this effect was driven by Group 3 (M_{age} = 13.8 years, SD = 4.5) receiving orthoses significantly later than Group 1 (M_{age} = 4.9 years, SD = 5.6) but not than Group 2 (M_{age} = 9 years, SD = 5.2). Of the children in need of orthoses, independent of group, those with a diagnosis of dyskinetic CP (n = 7) generally received their orthoses significantly later (M_{age} = 13.9 years) than those with a diagnosis of BSCP (n = 16; M_{age} = 7.4 years), $t = 2.64$, $p = .02$. Although between-group analyses regarding the number of children receiving surgical procedures revealed no significant differences, a greater amount of (repeated) surgery in Group 3 can be noted.

Passive Wrist Extension with Fingers Extended (PWE-FE)

Figure 1 shows the individual outcomes regarding right and left PWE-FE for the respective group over time, with dotted lines denoting the limits for critical to normal values according to the CPUP "traffic light system" (red: ≤ −20°,

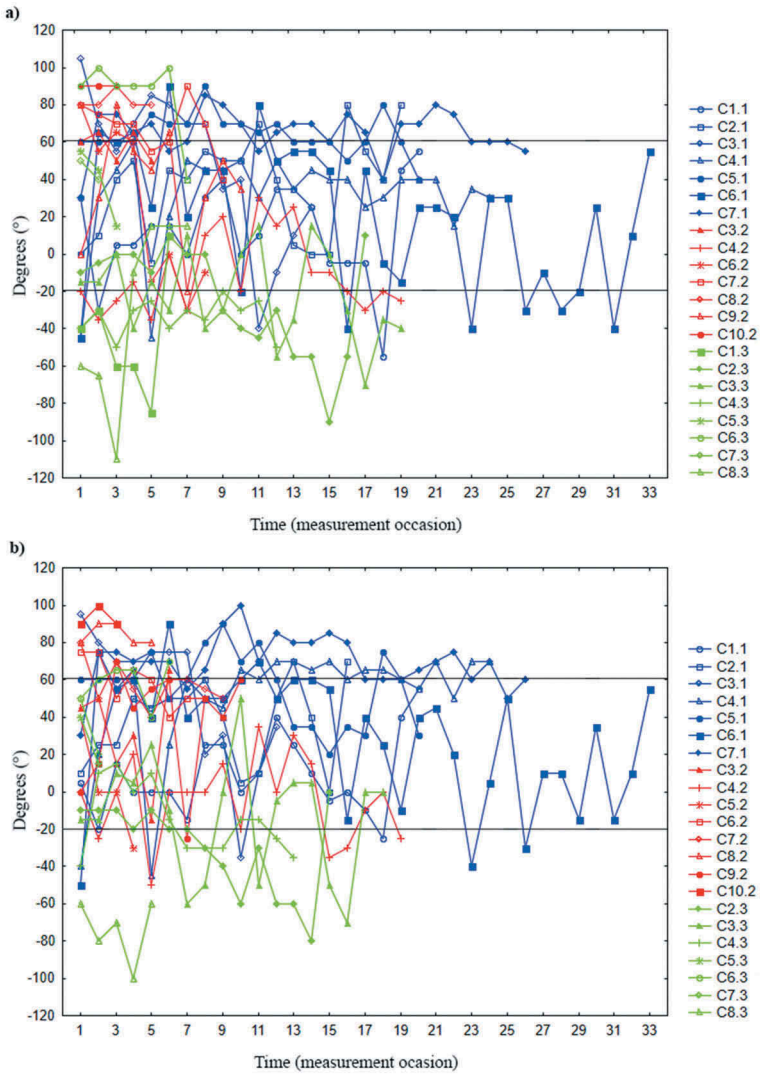

Figure 1. Line plots of passive wrist extension with fingers extended (PWE-FE) values in degrees for each individual child within Group 1 (blue), Group 2 (red) and Group 3 (green) over measurement occasions for (a) the right wrist (Group 1, n = 7; Group 2, n = 7; Group 3, n = 8), and (b) the left wrist (Group 1, n = 7; Group 2, n = 8; Group 3, n = 7). The black lines denote the borders between "red" values (≤−20°, critically below normal extension), "yellow" values (>−20° to <60°, below normal extension), and "green" values (≥60°, normal extension).

critically below normal extension; yellow: > −20° to < 60°, below normal extension; green: ≥ 60°, normal extension).[18] Overall, there was a main group difference in the distribution of critical values (right wrist: chi^2 = 62.3, p <.001; left wrist: chi^2 = 62.7, p < .001), mainly characterized by Group 3 having evidently more critical (red) and less normal (green) values for both the right and left wrist compared with Group 1 and 2 (Figure 2). Further, comparing mean PWE-FE data at the endpoints of the timelines (i.e. degrees at first vs. last measurement occasion) for the respective group generally suggested a positive increase in degrees for Group 1, a slight decrease for Group 2, and no evident change for Group 3 (Figure 3). A critical comparison of mean PWE-FE for Group 1, last measurement occasion (M_{age} = 14.5 years, SD = 2.86), and Group 3, first measurement occasion (M_{age} = 13.6 years, SD = 2.13), revealed a significant difference for the left wrist, F(1,12) = 8.18, p < .05, and a near significant difference for the right wrist, F(1,13) = 4.29, p = .059. Thus, at a comparable age, Group 1 had more favorable PWE-FE values than Group 3 for both hands, the left one in particular.

As seen in Figure 1, there are rather pronounced intra-individual oscillations in PWE-FE within Group 1, with positive changes often associated with BoNT-A treatment in particular for the children with BSCP (C1.1, C4.1, C6.1, C7.1). Two of the children (C1.1, C4.1) received surgery in early adolescence, also resulting in improved PWE-FE. Of importance is that BoNT-A treatment (sometimes with the addition of surgery) facilitated the use of orthoses, likely contributing to the positive changes. Reversely, a clinical observation is that negative changes are generally associated with the effect of BoNT-A wearing off, with corresponding problems using orthoses. For many children, this meant that the orthoses had to be adjusted in a less efficient manner in waiting for the next BoNT-A treatment. Over time, there could also be various obstacles to performing planned BoNT-A treatments such as diseases (infections, pathological fractures) or competing surgical procedures (scoliosis, hip).

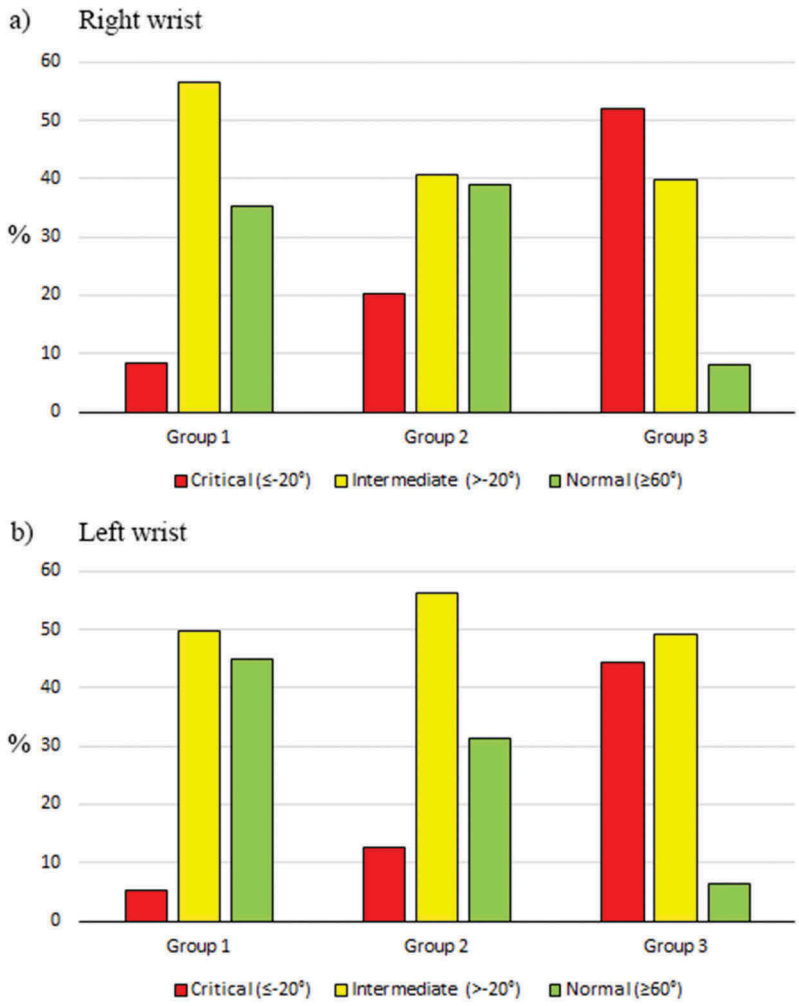

Figure 2. Bar charts showing frequency of critical to normal values for passive wrist extension with fingers extended (PWE-FE) as a function of group for (a) the right wrist, and (b) the left wrist.

During such periods, parents and assistants were instructed to increase movement training/stretching.

Of the children in Group 2 represented in Figure 1, one child (C10.2) only corresponds to three measurements occasions due to passing away while on the waiting list for BoNT-A treatment. Three of the children (C3.2, C6.2, C7.2) received BoNT-A treatment first when passive wrist extension grew increasingly worse during childhood/adolescence (10–21 years old), from this point providing a similar oscillating pattern as the children in Group 1. One child (C4.2) received BoNT-A treatment at early school age, benefitted from BoNT-A during 5 years but eventually had to stop this treatment due to respiratory problems. Despite continued movement training and orthoses, this child's PWE-FE worsened to critical values (−25°, bilaterally).

As shown in Figure 1, the initial PWE-FE values for the children in Group 3 are generally lower than those for the children in Group 1 and 2. Three children (C5.3, C6.3, C7.3) are exceptions, although to be noted is that two of these (C5.3, C7.3) have a dyskinetic CP diagnosis (i.e. changing muscle tone between joint flexion-extension and thus relatively preserved PWE-FE values), and one (C6.3) has deformity of the wrist extensors (i.e. displaying a reversed pattern regarding PWE-FE). Five children (C2.3, C3.3, C4.3, C5.3, C6.3) received BoNT-A treatment and interventions from the age of 13–23 years, although seemingly not improving values to the level of the children in Group 1 and 2 over time. One child (C8.3) was forced to go through surgical intervention of the right hand at 18 years old as elbow/hand spasticity caused the hand to disturb the individual's tracheostomy tube. The surgery led to an improvement in this case, but can be perilous for children with airway issues.

Hand Function

Regarding hand function, no main group effect was found for either the right-hand House classification (mean Group 1 = 1.6, SD = 1.8; mean Group 2 = 1.0, SD = 1.2; mean Group 3 = 0.1, SD = 0.4; p = .10; Figure 4a) or the left (mean Group 1 = 1.9, SD = 1.8; mean Group 2 = 0.7, SD = 0.8; mean Group 3 = 0.3, SD = 0.5; p = .07; Figure 4b). Follow-up testing did, however, show a significant difference for the left-hand House Classification between Group 1 and 3 (U = 11.0, p <.05).

Discussion

In general, the data derived from the present descriptive study support previous findings of positive effects of BoNT-A

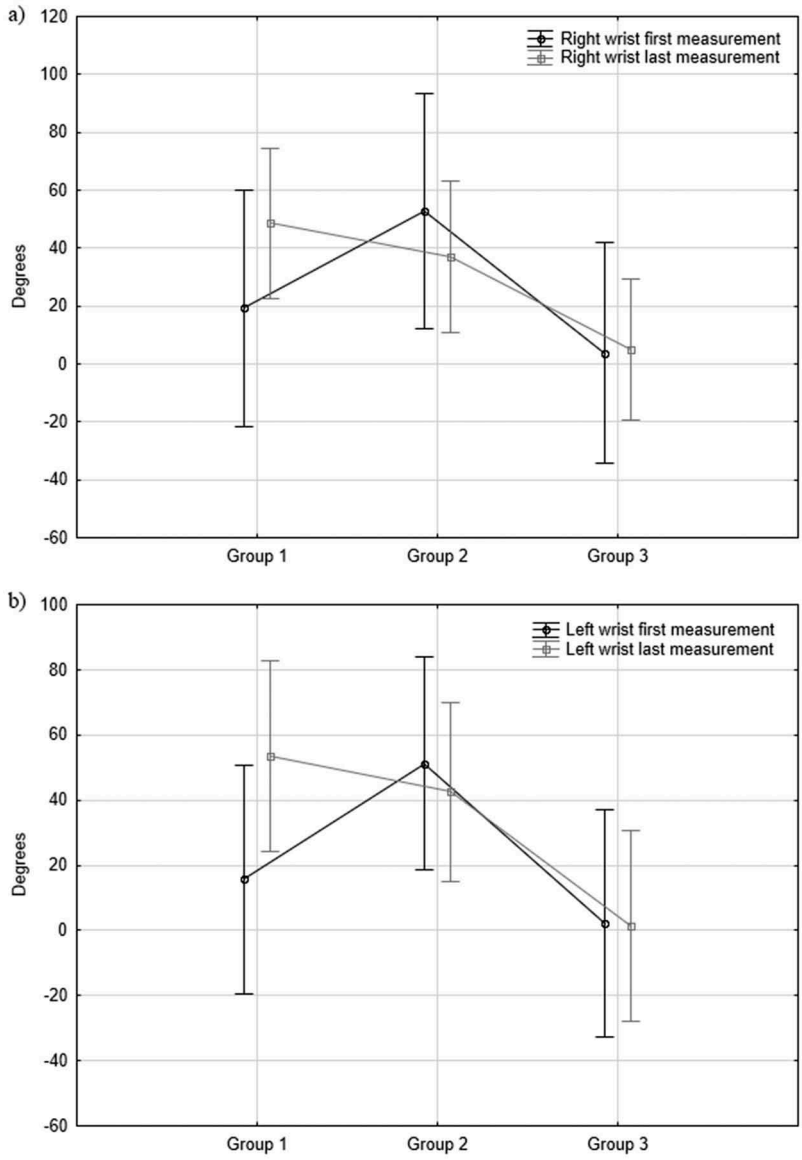

Figure 3. Mean group values for passive wrist extension with fingers extended (PWE-FE) at the first and last measurement occasion, respectively, for (a) the right wrist, and (b) the left wrist.

combined with training for the upper-extremity in children and adolescents with severe CP.[9–11] Findings reported here expand on previous research by cautiously indicating that repeated treatment over a long-lasting time period may regulate critical values of PWE-FE which, in turn, may promote hand function development. At start of the treatment regime for Group 1, the aim of treatment was only to preserve passive wrist and finger extension. As a result, at least some of the participants were observed to develop a (limited) hand function promoting participation, which was not initially expected. Positive treatment effects of BoNT-A together with rehabilitation therapy on upper-limb function in children with severe CP have previously been found to be relatively long-lasting,[11] also as described in individual cases.[19,20] Here, it is shown that, as treatment effects eventually wear off, repeated treatment may continue to be of importance for these children. Although there may be a risk for unwanted side effects for some individuals,[21] the use of BoNT-A is regarded as a comparatively safe addition to rehabilitation paradigms for the upper-extremity.[22] In the present long-term perspective, the combination appears effective in promoting activity and participation. Apart from positive functional effects, caregivers and assistants have also mentioned that the treatment has led to reduced pain, improved hygiene and cosmetic appearance, and relief in caregiver burden.

With regard to hand function/activity, it should be noted that, even though statistical group differences were minor, there is a big difference for the individual child between not being able to use the upper-extremity at all (House Classification 0) or to be able to put it to use (House Classification 1). In Group 3, five of eight children (62.5%) had no hand function at all, as opposed to two out of seven (28.6%) in Group 1. Two children in Group 1 are presently able to operate a powered wheelchair. Two additional children in Group 1 achieved the ability to steer a versatile mobility platform (Akka Smart) at the respective ages of 11 and 13

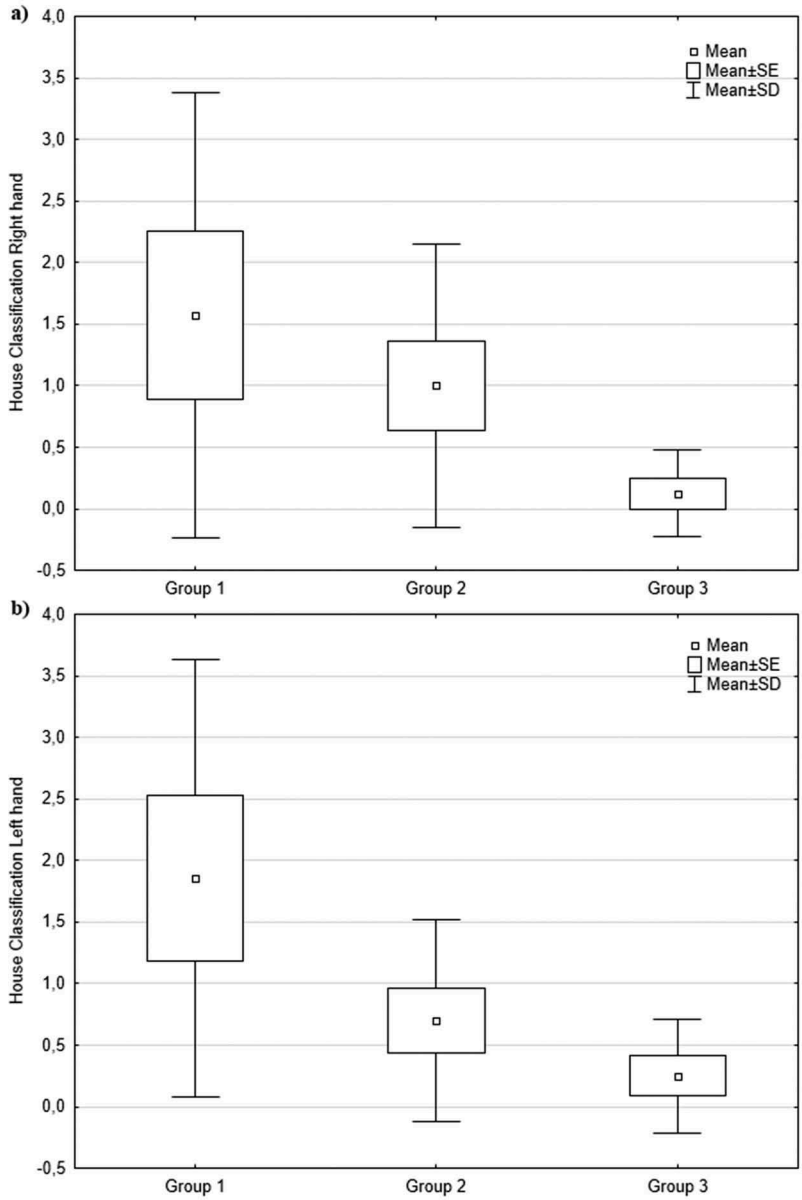

Figure 4. Box plots showing the mean house classification at the last measurement occasion as a function of group for (a) the right hand, and (b) the left hand.

years old, not previously being able to use the hands for activity. It should be noted that, in these cases, a supportive interchange between the multidisciplinary team, the child's habilitation team, caregivers and school has played an important part in the positive development. Still, it is plausible that maintaining passive wrist extension capacity and the premises for manual activity over an enduring time period is of importance, even if the functional relevance is not revealed until later.

In accordance, starting treatment at a young age seems more beneficial than starting treatment later during childhood/adolescence for children with early treatment indication. In this study, five of the eight children in Group 3 first came to the multidisciplinary team when deficits in multiple joint passive range of motion were already manifested. This induces a risk that structures beyond the muscular level are affected, which may lead to a reduced effect of BoNT-A treatment and consecutive obstruction of movement training and the manufacturing and use of orthoses to help improve passive range of motion. In support of this statement, all of these five individuals have eventually been submitted to one or several multilevel surgical procedures as BoNT-A treatment did not achieve expected target. Only one of them had some preserved hand function (C3.3), in the four other cases, the surgery was performed to facilitate daily care. Targeted treatment during the upbringing, or even relatively preserved movement capacity during childhood, may however not guarantee that surgical interventions will not be needed at later ages. Two children in Group 2 (C6.2, C7.2) received surgery when it became evident that BoNT-A injections could not stop a negative development of limited passive elbow extension. In Group 1, two children underwent surgery due to a late adverse reaction to BoNT-A (C4.1) and the need for BoNT-A exceeding the recommended maximum dosage (C1.1). It should be noted that well-founded and opportune surgery may be an important treatment addition and an

effective prerequisite for hand function development. Continued follow-up is however required to tell whether the need for surgery, and the nature of such procedures, will be different for the children in Group 1 compared with children receiving surgery at later ages without prior systematic treatment. Increased general knowledge of worsened passive upper-extremity movement capacity at adolescence in children with severe CP, and how to best combat this, is also warranted. In all groups, there are examples of reduced PWE-FE starting at adolescence, suggesting an increased risk for developing loss of passive ROM during this period of major bodily changes (see also ref. 15). Apart from dedicated research studies, follow-up programs such as CPUP are clearly of importance (even if passive ROM during childhood has been adequate) but could be intensified around adolescent age to enable timely interventions.

With regard to the different types of diagnoses represented in the present sample (dyskinetic CP vs. BSCP), it can be noted that it is commonly accepted that children with BSCP benefit from stretching and movement interventions from a young age. The potentially positive effect of orthotics in early childhood has also been increasingly recognized for these children. In contrast, a similar practice is not generally the case for children with dyskinetic CP as it is conventionally believed that they do not develop loss of passive ROM due to frequent changes in muscle tone (i.e. providing a natural prophylaxis). In this study, however, passive ROM appears to deteriorate at adolescent age for many of these children, and a sudden need for medical treatment (including BoNT-A), training and orthotics may emerge. In the present sample, it was also found that orthoses were given at a considerably later age for children with dyskinetic CP than for children with BSCP. Both of these findings are in keeping with results from a recent Swedish longitudinal population-based study investigating the development of a passive upper-limb range of motion in a large sample of children with CP.[15] If upper-extremity treatment and interventions have been assumed unnecessary, such unexpected negative change may be difficult for the child's caretakers to accept. Thus, at least when approaching adolescence, training/orthotics for the upper-extremity also for children with dyskinesia could be openly considered as an option in treatment programs for children with severe CP.

It should be noted that the extreme measurement variability associated with treatment response in the young children with severe CP in this study is not due to measurement error or poor reliability. The measurement of PWE-FE employed gives indirect information about muscle tone. If the child does not have joint contractures, large changes in passive wrist motion are probable following BoNT-A treatment as the treated muscles relax, although the extreme fluctuations observed were unexpected. The most extreme fluctuations appeared when measurements were carried out at the peak of BoNT-A effect (2 weeks-2 months after injection depending on the child). As the treatment effect wears off, muscle tone increases and PWE-FE values are worsened. Still, with repeated treatment, the positive effect returned in our sample. Thus, a normal value (green) is to be taken as an indication that the passive movement is still possible to attain, while repeated below normal (yellow) or critical (red) values are signs of difficulty to attain movement due to muscle/tendon/ligament resistance. As for children with dyskinetic CP, muscle tone fluctuates on a daily basis even without treatment, which may be represented in the measurements.

There are several obvious limitations to this study that needs to be addressed. As the study concerns children with the most severe type of CP and multiple disabilities in a relatively sparsely populated Swedish county, sample sizes are inevitably limited. The grouping of participants originated from a clinical question of whether children with severe CP receiving treatment before 7 years of age seemingly benefitted more from this treatment than those who did not receive treatment and older children who did not have the same treatment option when they were younger. However, there is substantial heterogeneity between and within groups in terms of age, diagnoses, training programs, orthotics, BoNT-A injection sites, amounts, dosages and intervals, intervention frequency and spacing, the presence of co-interventions such as intrathecal baclofen therapy, and surgical procedures (including hip- and/or back surgery). Thus, between-group comparisons are jeopardized by many confounders, making it challenging to evaluate the effect of BoNT-A in adjunct to upper-limb training/orthotics in this population in this way. The conclusions drawn must, therefore, be interpreted with care as there is a risk that our findings, at least in part, may have been the result of other factors than the treatment. Of particular concern is the age difference between groups. An evident, steady decline in PWE-FE values from early childhood to late adolescence has been reported for Swedish children with CP.[15] Thus, age is to be regarded as a potentially powerful confounder in the present report. Still, it should be noted that at a comparable age of approximately 14 years, Group 1 had evidently more positive PWE-FE values than Group 3. Moreover, due to the global heterogeneity involved in the present data set, there were unfortunately too many missing values to enable the use of a more coherent statistical approach such as growth curve modeling. Data are thus presented mainly on a descriptive level. All of these restrictions warrant the results and interpretations to be taken with caution. The study is, however, unique in its description of early and late upper-extremity treatment in children with severe CP over a long time period. Hedberg-Graff and colleagues[15] showed that the start of a significant decline in PWE-FE in their sample, particularly implicating children at higher GMFCS and MACS levels, occurred at 4–6 years of age, and stressed the importance of prevention to avoid functional consequences. Our results support the notion that introducing a treatment regime including BoNT-A treatment in the wrist/finger flexors and/or forearm pronators in adjunct to training/orthotics for the upper-extremity at this early age, upheld over time, might be a rewarding intervention strategy to this end. Continued follow-up of the children in Group 1 will tell whether the age-related decline is inevitable or if positive effects might be maintained. In general, there is an established need for continued research regarding the effects of spasticity-reducing treatment in adjunct to upper-extremity rehabilitation interventions in children with severe CP.[22] Future studies will expectantly confirm and expand the tentative findings presented here.

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Declaration of interest statement

The authors have no conflicts of interest to disclose.

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