Treatment with botulinum toxin A in children with cerebral palsy in Sweden

A Retrospective Cohort Registry Study

Botulinumtoxinbehandling av barn med cerebral pares i Sverige

En retrospektiv registerstudie

Maria Franzén

19920125-1569

Master's Thesis in Medicine

Supervisor: Ann Alriksson-Schmidt, PhD, MSPH

Co-supervisor: Gunnar Hägglund, MD, PhD

Examiner: Roland Andersson

LUND UNIVERSITY

Faculty of Medicine

Table of contents

Abstract

Introduction: Cerebral palsy (CP) is the most common childhood musculoskeletal disorder. Although symptoms, levels of functioning and comorbidities vary, spasticity is common in most and may cause bone and joint deformities. Injection with botulinum toxin A (BTX-A) is a well-documented treatment for spasticity, yet, lacking national guidelines, little is known about who receives BTX-A. Evaluation of the use of BTX-A is therefore necessary.

Aims: To analyse (1) the proportion of BTX-A treatment in children with CP related to age, sex, Gross Motor Function Classification System (GMFCS) level and healthcare region, (2) muscle group/s most often treated with BTX-A and (3) changes in the proportion of children treated with BTX-A over time.

Methods: Data from the last assessment of CPUP participants, a Swedish combined follow-up programme and national healthcare quality registry for individuals with CP, were used. Participants included children, born 2000-2015, with data recorded in the registry 2009-2010 or 2014-2015. Logistic regression was used to regress age, sex and GMFCS level on BTX-A treatment. Muscle group/s treated with BTX-A were assessed using cross tabs. Proportion of change in BTX-A treatment over a five-year period was analysed using chi-squares.

Results: We included 3028 children (57% boys; median age = 7 years) of which 26% received BTX-A. Significantly more boys (28%) than girls (23%) were treated with BTX-A (OR = 1.25, [95% CI 1.05-1.48]). There were significant differences based on age and GMFCS levels. A large spread in the proportion of BTX-A administered across healthcare regions (13-57%) was found. No significant change in the proportion of BTX-A administered during 2010 and 2015 was demonstrated.

Conclusion: BTX-A treatment differed based on age, sex and GMFCS level. Proportion of BTX-A treatment has remained stable the past five years. These results will be important in future discussions regarding who should receive BTX-A.

Populärvetenskaplig sammanfattning på svenska

Cerebral pares (CP) är den vanligaste orsaken till motorisk funktionsnedsättning hos barn. Mellan två och tre per 1000 födda barn får diagnosen, som uppstår till följd av en skada som drabbar den omogna hjärnan. Kända riskfaktorer är manligt kön, låg födelsevikt och förtidsbörd. Människor med CP är en heterogen grupp av individer där grad och svårighet av symptom, funktionsnivå och samsjuklighet varierar kraftigt. Spasticitet, ett resultat av hjärnskadan, är dock vanligt förekommande hos de flesta. Det innebär en onormalt förhöjd spänning i musklerna som kan, om det inte behandlas i tid, leda till felställningar, såsom muskelförkortning (kontraktur), skolios och höftluxation. Behandlingsarsenalen för spasticitet är bred. Ett alternativ är muskulär injektion av nervgiftet Botulinum toxin A (BTX-A) som hindrar signaler att gå från nerver till muskler och orsakar på så sätt en lokal relaxation i muskeln. Effekten är tillfällig och avtar efter tre till fyra månader. BTX-A har använts i över 20 år i detta syfte och anses vara en effektiv behandling. Trots detta betraktas BTX-användning inom CP fortfarande vara ett outforskat område då vi vet lite om vem som egentligen får BTX-A och vilken inverkan det kommer att få på människan i det långa loppet. En del forskare påstår att användningen av BTX-A kan vara skadligt. För att utreda detta vidare är det nödvändigt med en kartläggning av BTX-A-användningen, vilket var syftet med denna studie. Resultaten visade att användandet av BTX-A och vilken muskel som behandlades skiljde sig beroende på ålder, kön, svårighetsgrad av CP (baserat på grovmotorik) samt sjukvårdsregion. Barn i åldrarna fyra till nio år erhöll den största andelen BTX-A, fler pojkar än flickor erhöll BTX-A-behandling och hur ofta BTX-A användes i Sveriges 21 olika sjukvårdsregioner varierade stort. Den vanligaste muskeln som behandlades med BTX-A var vadmuskeln, vilket var känt sedan tidigare. Vidare såg vi att användandet av BTX-A i Sverige inte har förändrats de senaste fem åren. Vi anser att denna studie av BTX-A-användning hos barn med CP i Sverige kommer att vara väsentlig information i den fortsatta diskussionen om behandlingen, när studier om dess långtidseffekt föreligger.

Introduction

Cerebral palsy (CP) is the most common musculoskeletal disorder in children. The condition is a heterogeneous composition of neuromotor disorders resulting from an early-onset and non-progressive damage or lesion in the immature brain (1) occuring during pregnancy, delivery or before two years of age (2). Low birth weight, intrauterine infections, preterm delivery and multiple gestations are all important risk factors associated with the occurrence of CP (3) (4) (5). The reported prevalence of CP is 2.0-3.0 per 1000 live births (6) (7) and males are somewhat overrepresented in the condition, the ratio boys:girls is 1.4:1 (7) (8).

The hallmark of CP is the actual motor restriction, but accompanying impairments (i.e. comorbidities) and so called secondary conditions often make the disability more complicated and treatment more challenging. Comorbid impairments include disturbances affecting communication, perception, sensation, behaviour and cognition as well as epilepsy and problems related to feeding and nutrition (3). The secondary conditions are, in contrast to the primary brain injury, often progressive and may change over time. They are also, per definition, preventable. An example of a secondary condition is muscle contractures, often caused by spasticity. The surrounding environment and the characteristics of the individual (personal factors) affect and interact with these secondary conditions, which means they may take various forms in two persons with the same primary condition (9).

The traditional thinking about disabilities often included the notion that the individuals with disabilities should strive to be, learn and look “normal”. Over the past 15-20 years, a different perspective on disability has emerged where the focus is more on function and participation, culminating in the *International Classification of Functioning, Disability and Health* (ICF) from the World Health Organization (10). The ICF model consists of descriptive terms like “function”, “activity” and “participation”. However, it also considers the impact of contextual

factors, including environmental and personal factors, and as such it can be viewed as a merge between the medical and social models of disability. Although continually being revised, this model has helped to foster a new perspective with a different focus; not necessarily to cure (which in the case of many disabilities is not possible) or normalize the person but to increase functionality, improve capabilities and sustain health in particular related to locomotion, social interaction and independence (11).

There are alternate ways to classify the subtypes of CP. They may be classified by aetiology (if known), topographic distribution (e.g. hemiplegic, diplegic), in relation to the anatomical site of the brain damage (e.g. cerebral cortex, pyramidal tract) or symptoms and findings (spastic, ataxic, dyskinetic).

The Surveillance of Cerebral Palsy in Europe (SCPE) network constructed a classification of CP that is now used worldwide (12). The SCPE classifies the subtypes of CP into uni-or bilateral spastic, dyskinetic, ataxic or non-classified CP. The dyskinetic subtype can be further divided into dystonic or choreoathetotic CP. The spastic subtype is the most common, accounting for approximately 75% of all cases of CP (7). Many researchers and clinicians also classify individuals with CP in terms of their gross motor function.

The Gross Motor Function Classification System (GMFCS) is a five-level ordinal scale describing gross motor function, with different descriptions for children of different ages (13). GMFCS is based on the children's self-initiated movement with focus on sitting, walking and mobility. Level I describes the highest level of gross motor function and level V the lowest. Children at GMFCS I are able to walk independently, without mobility aids, but the coordination and balance may be limited. Those at GMFCS V are dependent on a wheelchair for mobility and transportation. It has been demonstrated that the individual GMFCS level in most children with CP remains stable over time (14), although there are exceptions (15). The

GMFCS scale was expanded and revised in 2008 to include five age-bands up to the age of 18 years (16).

A major problem for individuals with CP has been the development of hip dislocations and scoliosis due to abnormal forces caused by spasticity, muscle imbalance and gravity. This will impair the function of the individual, who, in time, might need orthopaedic surgery. To prevent the emergence of these, a follow-up program for children with CP (CPUP) was initiated in 1994, in Skåne, Sweden with early detection and prevention of these complications as its primary purpose (17). Since 2007, this follow-up program has been used throughout Sweden while also serving as a national healthcare quality registry.
Following a concerted effort, Sweden now has more than 100 quality registers with the primary purpose to improve the quality of Swedish healthcare and to detect inequalities, and more recently also to serve as a basis for research.
Currently, the CPUP structure is used in Norway, Denmark, Iceland, Scotland and also in parts of Australia. Additional aims of CPUP include to conduct research, to increase awareness of the condition, to evaluate the efficacy of treatments and to improve the collaboration among professionals working with individuals with CP (17).

Spasticity is one symptom of the upper motor neuron syndrome found in CP and can be defined as a velocity-dependent hyper excitability of muscles to stretch, featured by overstated tendon reflexes, augmented resistance to passive movement and hypertonia resulting from loss of upper motor inhibitory control (18).
As previously mentioned, spasticity may lead to secondary conditions, including muscle contractures, scoliosis and hip dislocations, if not treated and prevented in time. There are various ways to prevent or reduce spasticity; physical therapy, e.g. muscle stretching, surgical

interventions, e.g. selective dorsal rhitzotomy (SDR) or intrathecal baclofen pump (ITB pump) and medications, e.g. oral baclofen or intra muscular injection of botulinum toxin A (BTX-A).

BTX-A is a potent neurotoxin found in clostridium botulinum, a gram-positive bacterium. The toxin produces paralysis by blocking the presynaptic release of the neurotransmitter acetylcholine in the neuromuscular junction (19). BTX-A reduces the hyperactive activity and spasticity in the muscle. It is recommended for children with CP as it can improve function and prevent or delay the formation of fixed contractures and deformities and reduce the need of surgical interventions (20). The chemical denervation of BTX-A is reversible and consequently has only temporary effects lasting for three to four months (21) (22).

BTX-A was registered as a pharmacological drug in 1989 and it was first used for treatment of spasticity in individuals with CP in 1993 (23). It is given as an intramuscular injection in the spastic muscle. A local anaesthetic creme, e.g. EMLA creme, or sedation with Midazolam or similar substance is usually given as premedication before the injection. Ultrasound or electromyography (EMG) is often used to make sure the needle is in the right position in the muscle.

BTX-A is generally considered a safe treatment. Side effects are rarely reported and when they are, they tend to be minor. Documented side effects include pain at the injection site, local muscle weakness and mild flu-like symptoms (24) (25).

Although BTX-A has been used for treating spasticity in individuals with CP for a long period of time it is still considered an unexplored area. It is well documented that BTX-A has a spasticity-reducing effect (26), but the major focus has been on BTX-A and its spasticity-reducing effect in either specific muscle groups or specific subtypes or GMFCS levels in CP. However, evidence is lacking regarding the long-term use and effect of BTX-A (27) (28) and

some reports have suggested that the long-term use of BTX-A might be detrimental (29). Little is known about how, and to what extent, BTX-A is used in clinics and habilitation centres in Sweden. Moreover, it is not well established who receives it. To our knowledge, there are no published studies describing this. This information is needed because it can facilitate the development of national guidelines once evidence regarding the long-term effects of BTX-A in children with CP has been accumulated.

The overall purpose of the study was to investigate to what extent BTX-A treatment was used and who received BTX-A treatment in a total population of children with CP in Sweden.

The specific aims were to analyse:

1. the proportion of children with CP in Sweden treated with BTX-A in relation to age, sex, GMFCS level and healthcare region,
2. the most common muscle group/s treated in relation to the same variables listed in Aim 1. and,
3. changes in the proportion of children with CP treated with BTX-A over time (2010 and 2015).

Methods

Procedure

This study was based on data from the CPUP (17). Families with a child with CP are informed about CPUP and have the option of not participating. They also receive the information that choosing not to participate will not affect the healthcare received. When choosing to participate in CPUP, the families are told that data recorded in the registry may be used for research and quality improvement projects, and that the data will be handled and presented in a non-identifiable manner in accordance with current legislation (30). In Sweden, more than 95% of all children with CP participates in CPUP and are included in the registry (17).

The children are regularly examined by their local physiotherapists (PTs) and occupational therapists (OTs). The interval between two clinical examinations varies depending on the child's age and the GMFCS level (Figure 1). Children at GMFCS level I are examined once a year until the age of six years, then every second year. Children at GMFCS levels II-V are examined twice a year until the age of six and thereafter once a year. A separate assessment schedule is used for radiographic follow-ups of the hips and the spines. The results from the examinations are entered into the registry. Examples of what are examined by the PTs and OTs at each assessment are gross motor function, hand function, mobility, range of joint motion, postural ability in standing, sitting and lying, muscle spasticity, pain and pain sites. In addition to the physical assessment, whether or not the child received treatment with BTX-A since the last examination is also recorded.

Participants

Participants in CPUP born 2000 or later were eligible for inclusion, however, those who had undergone SDR or had an ITB pump inserted were excluded. For the purpose of this study**,** three age cohorts were constructed (referred to as Cohort 1, Cohort 2 and Cohort 3 hereon

after). Cohort 1 was used in Aims 1 and 2 and consisted of all eligible participants recorded in the registry during 2014-2015 (n = 3119). Ninety-one children did not meet the inclusion criteria and were therefore excluded from the analyses; 17 had undergone SDR and 31 had an ITB pump resulting in a total number of 3028 children in Cohort 1.

Cohorts 2 and 3 were used in Aim 3 to investigate changes in BTX-A treatment over time (2009-2010 versus 2014-2015). A total of 736 children in Cohort 2 and 649 children in Cohort 3 were included. These cohorts were assembled to create two independent groups, where a participant should only be able to be in one group. The age-span three to five years was chosen because this grouping did not result in overlap of participants.

Cohort 2 consisted of children aged three to five years, recorded in the registry 2014-2015 (n = 739). Three children were excluded, of whom one had undergone SDR and two had an ITB pump resulting in a total number of 736 children in Cohort 2. Cohort 3 consisted of children of the same age as in Cohort 2 but recorded in the registry 2009-2010 (n = 655). Six children were excluded, of whom three had undergone SDR and three had an ITB pump resulting in a total number of 649 children in Cohort 3. Figure 2 illustrates how the three cohorts were assembled.

Measures

Some of the children had up to five assessment points recorded, and the data regarding age, sex, GMFCS level and healthcare region from the first of these individual assessments were used.

Age was calculated based on the date of birth and the date of examination, then rounded to whole years and treated as a continuous variable. Sex was recorded as a dichotomous variable where boys were coded as 0 and girls as 1. The gross motor function was classified according to the extended and revised version of the GMFCS (16) and was recorded as an ordinal scale

from I to V, where I indicated the least and GMFCS V the most affected gross motor function, respectively, then treated as a categorical variable. The 21 different healthcare regions in Sweden, in which the children were examined, were treated as a categorical variable. The muscle groups treated with BTX-A at any assessment during 2014-2015 were coded as categorical variables. The muscle groups included were categorized as the gastrocnemius, the hamstring or the adductor muscles alone, or the combinations of the gastrocnemius and the hamstring muscles, the gastrocnemius and the adductor muscles, the hamstring and the adductor muscles and finally the gastrocnemius, the hamstring and the adductor muscles. Additional muscles or other combinations of muscles treated (or missing data) were combined into one group, for a total of eight groups. The total number of treatments in the gastrocnemius, the hamstrings and the adductors muscles, based on these eight groups, were also calculated. For all aims (all cohorts), BTX-treatment was coded as yes if the participants had received BTX-A at any assessment during 2009-2010 or 2014-2015 and no if the participant had not received BTX-A at any of the assessments. If participants had missing data on this specific item they were subsequently analysed as not having received BTX-A treatment.

Data analysis

Distributions of the data were inspected and continuous variables are presented as medians and standard deviations (SD) and categorical variables as frequencies (n) and percentages (%). Ninety-five percent confidence intervals (95% CIs) to assess statistical significance among age, sex and GMFCS level on BTX-A treatment and for the same variables on most common muscle group/s treated with BTX-A.

For Aim 1, the proportion of BTX-A treatment in relation to age, sex GMFCS level and healthcare region were assessed using cross-tabs and 95% CIs for binomial proportions. Aim

1 was also analysed using logistic regression. Prior to performing the analysis, a statistician assessed the assumptions for logistic regression to ensure that specification, model fit and multicollinearity were acceptable. Initially, the specification of the model was not satisfactory. This was in relation to the age variable, which was originally entered as a continuous variable. To improve specification age was recoded as a categorical variable with five age categories; 1-3 years, 4-6 years, 7-9 years, 10-12 years and 13-15 years respectively, which did improve specification. Moreover, Pearson's residuals were plotted. As a rule of thumb, in large samples, the residuals should be within the -3 (or -2) and 3 (or 2) range, which was the case for the data in this study. Both main effects (age, sex and GMFCS levels) and interactions were tested (age X sex; age X GMFCS level; sex X GMFCS level). Given the number of levels (21), healthcare region was not included in the logistic regression. Even if the omnibus test would have been significant, and we would know which healthcare regions were statistically significantly different in relation to the reference group, we would not know (without the inclusion of some type of post-hoc follow-up test) which additional pair-wise comparisons differed statistically. Recoding the healthcare regions to fewer levels was considered (for instance five larger regions) but decided against because of the lack of a theoretical rationale for doing so. Therefore, differences between healthcare regions on use of BTX-A were not tested using a statistical test of significance.

Aim 2 involved the injection of BTX-A into certain muscle groups and combinations of muscle groups. The relationships between the different muscle groups treated with BTX-A (%) in relation to age, sex and GMFCS level were calculated using cross-tabs and 95% CIs for binomial proportions.

In Aim 3, chi-square tests (χ^2) were used to compare differences in use of BTX-A between 2010 and 2015.

IBM SPPS version 22 (31) and Stata 13 (32) were used for all analyses.

Ethical considerations

An open discussion about potential differences in BTX-A treatment may induce concerns in individuals with CP and their families. Nevertheless, it is important that this becomes highlighted, because assessing potential inequalities in healthcare (which is one of the goals of national quality registers) is a first and required step to be able to remedy it should it be required.

The impact of BTX-A use cannot be determined until additional longitudinal studies on the long-term effects of BTX-A have been performed. If future studies will indicate that BTX-A has mostly positive effects, differences in BTX-A use, perhaps mostly in relation to sex or healthcare region, will be interpreted as disparities or inequalities in healthcare. However, if the opposite is found (that BTX-A treatment will have significant negative effects), those residing in regions where BTX-A is administered more liberally might be upset that they have been given a “harmful” treatment.

The study was approved by the Ethics Board at Lund University (LU 443-99, revised 2009).

Results

A total of 3028 children in Cohort 1, with a median age of 7 years (SD = 4 years), ranging from 1 to 15 years were included. The age, sex and distributions of GMFCS levels are presented in Table 1.

In Cohort 1, 776 children (26%) were recorded to have received BTX-A treatment at least once since the previous assessment. The proportion of children treated with BTX-A varied with age (Figure 3), peaking at the age of four to six years. Boys were more likely to have received BTX-A treatment (28%, [95% CI 25.5-29.8]) than girls (23%, [95% CI 20.8-25.4]). Children at GMFCS level I received the lowest proportion of BTX-A treatment while the proportion was highest at GMFCS levels III-IV. Children at level II and V received a higher proportion than GMFCS level I but lower than GMFCS levels III and IV (Figure 4). The logistic regression analysis was conducted to estimate the effect of age, sex and GMFCS level on treatment of BTX-A for the 3028 participants (interactions were found not to improve the model and were therefore not included). A test of the full model against a constant only model was statistically significant, indicating that the predictors as a set reliably distinguished between those receiving or not receiving BTX-A, as shown by chi square test, χ^2 (3, N = 3028) = 148.18, p = .001. The odds ratios and 95% CIs for logistic regression are presented in Table 2. The proportion of children treated with BTX-A across healthcare regions varied from 13% to 57% (Figure 5), with a median of 27%.

Data on specific muscle group/s treated with BTX-A were missing in 242 children (31%) and in nine children (1%) there were other muscle groups or combinations of muscles treated than tested for in the analyses (e.g. m. rectus femoris, m. iliopsoas, m. tibialis posterior). Data on muscle group/s treated with BTX-A were available for 525 of the 776 children (68%) who

received BTX-A in Cohort 1. Of those, 198 children (38%) had received BTX-A injections in more than one muscle groups. This calculation did not include data from the group of missing data/other muscles because it was not possible to determine if these children were treated in one or multiple muscle groups. The proportions of BTX-A treatment in relation to muscle groups and 95% CIs are presented in Table 3. In all age categories, except in 13-15 year-olds where treatment in the hamstring muscles were equally common, the gastrocnemius muscle was the most common muscle treated, and especially in children four to nine years of age. Injections in the hamstring and adductor muscles were more common at older ages (10-15 year-olds) compared to younger children. The most common muscle group/s treated with BTX-A in relation to age is presented in Figure 6. For both boys (n = 269, 57%) and girls (n = 146, 49%) the gastrocnemius muscle was the most common muscle group/s treated with BTX-A. The proportion of the other muscle group/s treated with BTX-A did not change substantially between the sexes; 136 boys (29%) and 72 girls (24%) had received BTX-A treatment in the hamstring muscles, while 82 boys (17%) and 57 girls (19%) were treated in the adductor muscles. Children at GMFCS I-III most often received treatment with BTX-A in the gastrocnemius muscle, whereas children at GMFCS IV were more likely to receive BTX-A treatment in the hamstring muscles and children at GMFCS V in either the hamstring or the adductor muscles (Figure 7). The proportion of children treated with BTX-A in the gastrocnemius muscle decreased with GMFCS level (Figure 7).

A total of 248 children (34%) in Cohort 2 and 228 children (35%) in Cohort 3 had received BTX-A at least once since the last assessment. No statistical significant differences were found in the proportion of BTX-A treatment between 2009-2010 and 2014-2015 as shown by chi square test, χ^2 (1, N = 1385) = 0.32, p = .575.

Discussion

This study was based on a total population of children with CP in Sweden aged one to fifteen years and described the epidemiology of the use of BTX-A. About one fourth of all children with CP were recorded to have received BTX-A treatment at least once since the last assessment. The use of BTX-A varied with age, sex, gross motor function and healthcare region.

BTX-A treatment was administrated most often in the four to six year-olds. This corresponds to a previous study (33) describing the development of spasticity of the gastrocnemius muscle in relation to age. The study showed an increase in muscle tone up to four years of age in children with spastic CP, up to six years of age in children with dyskinetic CP, followed by a reduction in muscle tone at later ages. Our results thus indicate that most children receive BTX-A treatment when they have the highest degree of spasticity.

Boys were significantly more likely to be treated with BTX-A than girls. Although a small difference, this has, to our knowledge, not been demonstrated before. It is well documented that the ratio boys:girls in CP is dominated by boys (7) (34), but the distribution of the severity of CP, in terms of gross motor function, has not been found to differ significantly between the sexes, as shown by two studies based on data from the CPUP (7) (35). In one of those studies (35), there was no statistically significant difference between the distribution of boys and girls in relation to subtype, although when inspected one subtype at a time there was a male predominance in all subtypes of CP except ataxic CP, where 54% where girls. That boys appear more likely to receive BTX-A treatment than girls does not seem to be explained by differences in the distribution of sexes in relation to GMFCS levels or subtypes. This is further supported by the result in our study that there were no sex-differences found in terms of what muscle groups were most commonly treated with BTX-A. A possible explanation, not

related to physiology, might be a biased perception of the treating provider that boys are supposed to be more physically active than girls and therefore administer BTX-A to a higher extent in boys.

Children at GMFCS levels II to V were more often treated with BTX-A compared to children at GMFCS level I. Children with higher levels of gross motor function (i.e. lower levels of GMFCS) frequently belong to the unilateral spastic subtype (7), which often includes individuals that function well in terms of activities of daily life. The spasticity in these children is generally less severe (33) and not interacting with the levels of functioning to the same extent. Children with lower gross motor function might have a higher degree of spasticity and might therefore be at an increased risk of developing muscle contractures, which is in line with higher proportions of BTX-A treatments in these children.

The large differences in BTX-A administered in the different healthcare regions (13 to 57%) might primarily be predicative of the individual experiences and preferences of the treating providers. Given that BTX-A is an expensive treatment, it is possible that the large differences are also related to how individual healthcare regions allocate their funds, and how BTX-A and habilitation services are prioritized within the different regions. Future national guidelines of BTX-A use in CP might help guide the providers in terms of who might benefit the most from receiving the treatment.

Overall, the gastrocnemius muscle was the most common muscle treated with BTX-A. This has been reported previously, as equinus foot (due to spasticity in the gastrocnemius muscle) is the most common deformity in children with CP (36). That more than half of the children received treatment in multiple muscle groups (more often in children at higher GMFCS

levels) highlights the fact that CP is not a single symptom disorder, but a musculoskeletal condition with several different muscle groups involved.

Younger children (four to nine year-olds) were more likely to receive BTX-A in the gastrocnemius muscle, which is in accordance with how spasticity changes with age in this muscle (33), and that the development of muscle contractures is greatest in the gastrocnemius muscle at younger ages (37). The preponderance of older children (13 to 15-year olds) in BTX-A treatment of the hamstring and the adductor muscles might be explained by that the development of muscle contractures is highest in the hamstring and adductors muscles at these ages (37). Furthermore, children at GMFCS IV-V were also more often treated with BTX-A in the hamstring and the adductor muscles. Children with lower gross motor function are often found in the bilateral spastic or dyskinetic subtypes of CP (7). Why these muscles were more often treated in these children may be explained by the more proximal involvement of spastic muscle groups in the bilateral subtype of spastic CP (38), referred to as crouch gait, due to spasticity in the hamstring muscles. This implies a greater limitation of activity, corresponding to a higher level of GMFCS (7). Children at GMFCS levels I-III were more likely to receive BTX-A treatment in the gastrocnemius muscle, which corresponds to the typical gait pattern often seen in children with higher gross motor function (i.e. lower GMFCS levels) and unilateral spastic CP; true equinus foot at younger ages (38) (39).

The proportion of children treated with BTX-A did not change between the two time periods 2009-10 and 2014-15. This indicates that although some authors in recent years have been in favour of a more restrictive approach of BTX-A use (27) (40), the quantity of BTX-A treatment has not been affected in Sweden.

There were a number of limitations to this study. Children in CPUP primarily receive BTX-A to prevent secondary complications due to spasticity, but the long-term intention of the treatment was not documented in all cases, and not analysed. This information would have allowed for a better understanding of the differences in proportions of BTX-A treatment in the healthcare regions in Sweden. The classification of subtype, according to the SCPE classification, was missing in several cases and therefore not included in this study. If the information of subtype would have been available a better understanding of the results regarding different muscle groups treated might have been possible. Additional variables that would have been interesting to analyse in relation to BTX-A treatment in children with CP would have been if one or both legs were treated at the same time and what dose of BTX-A was used. When performing secondary analyses, the investigator is limited to the variables included in the registry. Moreover, registers, by necessity, cannot include too vast a number of varibles because that might compromise compliance and by extension coverage rates. On the other hand, what make registry studies so powerful is the large patient inclusion, a sample of a total population, which strengthens generalizability and allows for external validity. By using data from CPUP we were able to include all GMFCS levels, even those children less likely to receive BTX-A because they are all followed-up annually or every second year, which reduced the risk of selection bias in the study.

This study was the first step in identifying the pattern of BTX-A treatment in a total population of children with CP. The potential impact of differences in the proportion of BTX-A administered is difficult to determine, because the long-term effect of BTX-A is still unknown, although no obvious or serious side effects seen to be present. The use of BTX-A will eventually be guided by what future studies determine regarding BTX-A and its long-term effects. Most likely, we will end up in a “grey zone”, where the positive and the negative

effects of BTX-A will need to be weighed in to make an informed decision for each individual child. The results that use of BTX-A treatment changed with age, sex, GMFCS level and healthcare region will be a useful tool in the development of national guidelines and in the needed discussion about who should or should not receive BTX-A in this population.

Conclusion

Treatment with BTX-A in Sweden varied in relation to age, sex and GMFCS level. Muscle group/s treated also varied with age and GMFCS level and corresponded to the development of spasticity and muscle contractures. The proportion of BTX-A treatments given has not changed over the past five years.

Acknowledgements

I would like to thank Tomasz Czuba for great assistance with the statistical analyses of this project. I sincerely thank my supervisors Ann Alriksson-Schmidt and Gunnar Hägglund for all their support and for the opportunity to work on this project.

References

1. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol. 2007; 109: p. 8-14.
2. Bass N. Cerebral palsy and neurodegenerative disorders. Curr Opin Pediatr. 1999; 11(6): p. 504-7.
3. Odding E, Roebroeck M, Stam H. The epidemiology of cerebral palsy: incidence, impairments and risk factors. Disabil Rehabil. 2006; 28(4): p. 183-91.
4. O'Callaghan M, MacLennan A, Gibson C, et al. Epidemiologic associations with cerebral palsy. Obstet Gynecol. 2011; 118(3): p. 576-82.
5. Tronnes H, Wilcox A, Lie R, Markestad T, Moster D. Risk of Cerebral Palsy in relation to pregnancy disorders and preterm birth: a national cohort study. Dev Med Child Neurol. 2014; 56(8): p. 779-85.
6. Colver A, Fairhurst C, Pharoah P. Cerebral palsy. Lancet. 2014; 383(9924): p. 1240-9.
7. Westbom L, Hägglund G, Nordmark E. Cerebral palsy in a total population of 4–11 year olds in southern Sweden. Prevalence and distribution according to different CP classification systems. BMC Pediatr. 2007; 7(41).
8. Nordmark E, Hägglund G, Lagergren J. Cerebral palsy in southern Sweden I. Prevalence and clinical features. Acta Paediatr. 2001; 90(11): p. 1271-6.
9. Simeonsson R, McMillen J, Huntington G. Secondary conditions in children with disabilities: Spina Bifida as a case example. Ment Retard Dev Disabil Res Rev. 2002; 8(3): p. 198-205.
10. World Health Organization. Official website of the World Health Organization. [Online].; 2016 [cited 2016 November 16. Available from: http://www.who.int/classifications/icf/en/.
11. Rosenbaum P, Stewert D. The World health Organization International Classification of Functioning, Disability and Health: A model to guide clinical thinking, practice, and research in the field of Cerebral palsy. Semin Pediatr Neurol. 2004; 11(1): p. 5-10.
12. Cans C. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE). Dev Med Child Neurol. 2000; 42(12): p. 816-24.
13. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system, to classiffy gross motor function in children with cerebral palsy. Dev Med Child Neurol. 1997; 39(4): p. 214-23.
14. Palisano R, Cameron D, Rosenbaum P, Walter S, Russell D. Stability of the gross motor function classification system. Dev Med Child Neurol. 2006; 48(6): p. 424-8.
15. Alriksson-Schmidt A, Nordmark E, Czuba T, Westbom L. Stability of the Gross Motor Function Classification System in Children and Adolscents with Cerebral Palsy - A Retrospective Cohort Registry Study. Dev Med Child Neurol.. In press.
16. Palisano R, Rosenbaum P, Bartlett D, Livingstone M. Content validity of the expanded and revised Gross Motor Function Classification System. Dev Med Child Neurol. 2008; 50(10): p. 744-50.
17. Alriksson-Schmidt A, Arner M, Westbom L, et al. A combined surveillance program and quality register improves management of childhood disability. Disabil Rehabil. 2016; 0(0): p. 1-7.
18. Lance J. The control of muscle tone, reflexes, and movement: Robert Wartenberg Lecture. Neurology. 1980; 30(12): p. 1303-13.

19. Kumar R, Dhaliwal H, Kukreja R, Singh B. The botulinum toxin as a therapeutic agent: molecule structure and mechanism of action in motor and sensory systems. Semin Neurol. 2016; 36(1): p. 10-19.
20. Graham H, Aoki K, Auii-Rämä I, al e. Recommendations for the use of botulinum toxin type A in the management of cerebral palsy. Gait Posture. 2000; 11(1): p. 67-79.
21. de Paiva A, Meunier F, Molgó J, Aoki K, Dolly J. Functional repair of motor endplates after botulinum neurotoxin type A poisoning: biphasic switch of synaptic activity between nerve sprouts and their parent terminals.. Proc Natl Acad Sci U S A.. 1999; 96(6): p. 3200-3205.
22. Aoki K. Pharmacology and immunology of botulinum toxin type A.. Clin Dermatol. 2003; 21(6): p. 476-480.
23. Koman L, Mooney 3rd J, Smith B, Goodman A, Mulvaney T. Management of cerebral palsy with botulinum-A toxin: preliminary investigation. J Pediatr Orthop. 1993; 13(4): p. 489-95.
24. Boyd R, Graham J, Nattrass G, Graham H. Medium term respone characterisation and risk factor analysis of botulinum toxin A in the management of spasticity in children with cerebral palsy. Eur J Neurol. 1999; 6(4): p. 37-45.
25. Delgado M. The use of botulinum toxin type A in children with cerebral palsy: a retrospective study. Eur J Neurol. 1999; 6(4): p. 11-18.
26. Wong V. Evidence-based approach of the use of Botulinum toxin type A (BTX) in cerebral palsy. Pediatr Rehabil. 2003; 6(2): p. 85-96.
27. Gough M, Fairhurst C, Shortland A. Botulinum toxin and cerebral palsy: time for reflection? Dev Med Child Neurol. 2005; 47(10): p. 709-12.
28. Ade-Hall R, Moore A. Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy. Cochrane Database Syst Rev. 2000; 2(CD001408).
29. Schroeder A, Ertl-Wagner B, Britsch S, et al. Muscle biopsy substantiates long-term MRI alterations one year after a single dose of botulinum toxin injected into the lateral gastrocnemius muscle of healthy volunteers. Mov Disord. 2009; 24(10): p. 1494-503.
30. CPUP. CPUP uppföljningsprogram för cerebral pares. [Online].; 2013 [cited 2016 November 21. Available from: http://cpup.se.
31. IBM Corp. [IBM SPSS Statistics for Windows, Version 22.0]. 2013..
32. StataCorp LP. [Stata Statistical Software: Release 13.1]. 2013..
33. Hägglund G, Wagner P. Development of spasticity with age in a total population of children with cerebral palsy. BMC Musculoskelet Disord. 2008; 6(9).
34. Johnson A. Prevalence and characteristics of children with cerebral palsy in Europe.. Dev Med Child Neurol.. 2002; 44(9).
35. Chounti A, Hägglund G, Wagner P, Westbom L. Sex differences in cerebral palsy incidence and functional ability: a total population study. Acta Paediatr. 2013; 102(7).
36. Kedem P, Scher D. Foot deformities in children with cerebral palsy. Curr Opin Pediatr. 2015; 27(1): p. 67-74.
37. Nordmark E, Hägglund G, Lauge-Pedersen H, Wagner P, Westbom L. Development of lower limb range of motion from early childhood to adolescence in cerebral palsy: a population-based study. BMC Med. 2009; 28(7).
38. Rodda J, Graham H. Classification of gait patterns in spastic hemiplegia and spastic diplegia: a basis for a management algorithm. Eur J Neurol. 2001; 8(5): p. 98-108.
39. Hägglund G, Wagner P. Spasticity of the gastrosoleus muscle is related to the

development of reduced passive dorsiflexion of the ankle in children with cerebral palsy: a registry analysis of 2,796 examinations in 355 children. Acta Orthop.. 2011; 82(6): p. 744-748.

40. Carr L, Cosgrove A, Gringas P, Neville B. Position paper on the use of botulinum toxin in cerebral palsy. Arch Dis Child. 1998; 79(3): p. 271-273.

Figures and Tables

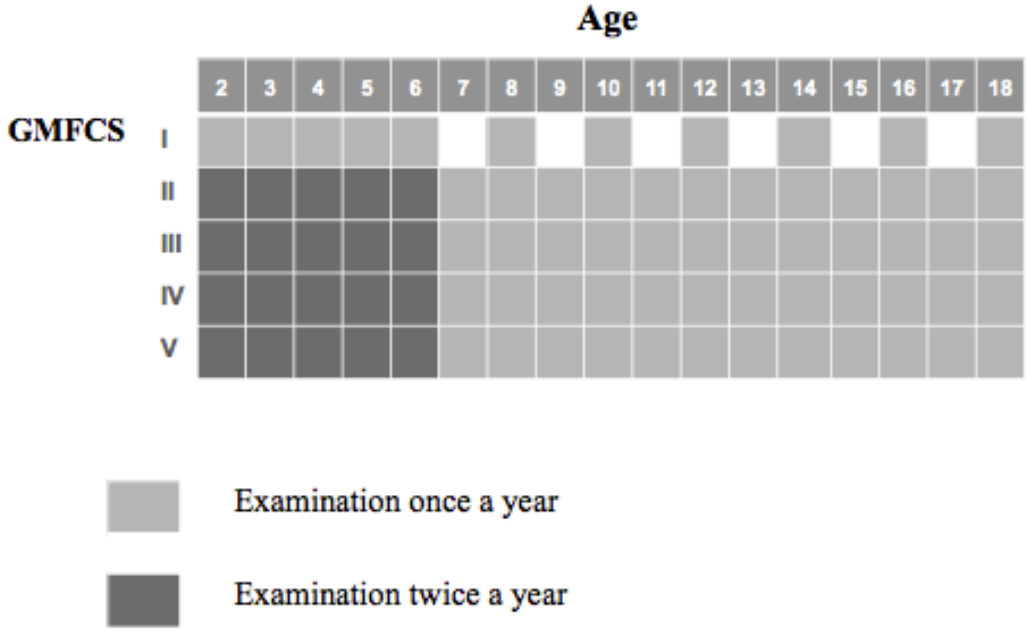


Figure 1. Assessment schedule for CPUP

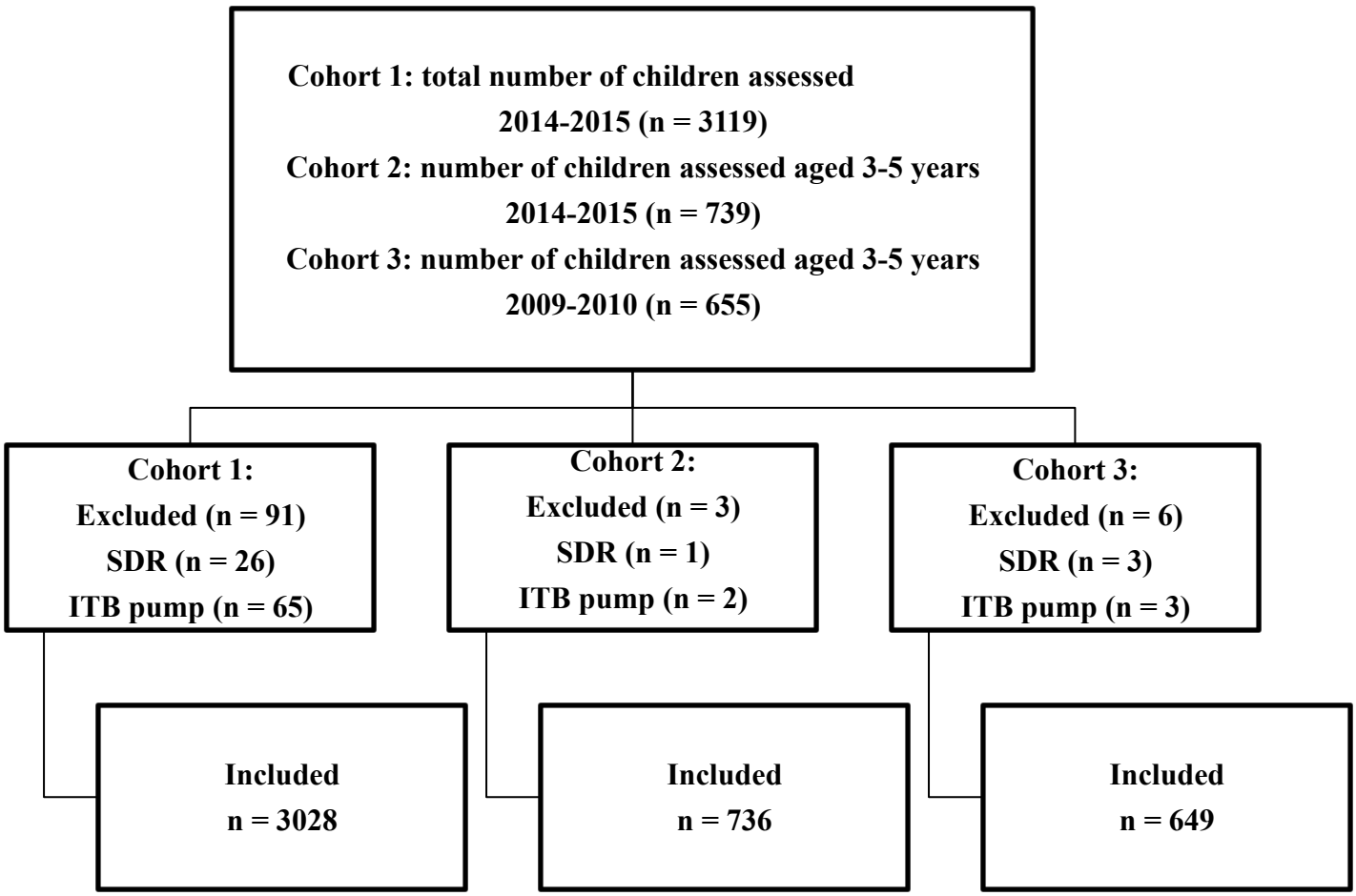


Figure 2. Flowchart of a decision tree for study inclusion.
SDR = Selective dorsal rhitzotomy.
ITB pump = Intrathecal baclofen pump.

Table 1. Number of children, n (%), in relation to sex, age and Gross Motor Function Classification System (GMFCS) level in Cohort 1 (children born 2000 or later and registered in CPUP 2014-2015).

	Boys n (%)	Girls n (%)	Total n (%)
Age (years)			
1-3	334 (19)	279 (21)	613 (20)
4-6	416 (24)	287 (22)	703 (23)
7-9	393 (23)	270 (21)	663 (22)
10-12	371 (22)	291 (22)	662 (22)
13-15	211 (12)	176 (14)	387 (13)
GMFCS level			
I	748 (43)	589 (45)	1337 (44)
II	310 (18)	206 (16)	516 (17)
III	165 (10)	118 (9)	283 (10)
IV	263 (15)	197 (15)	460 (15)
V	239 (14)	193 (15)	432 (14)
Total	1725 (57)	1303 (43)	3028 (100)

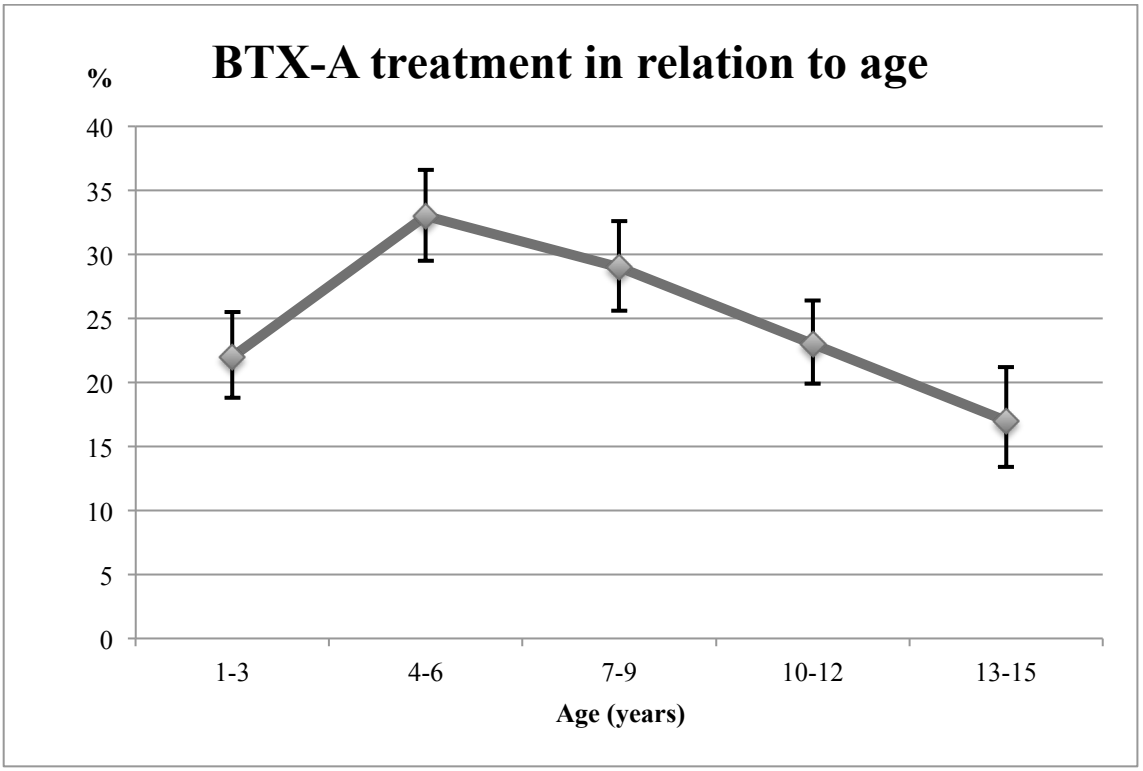
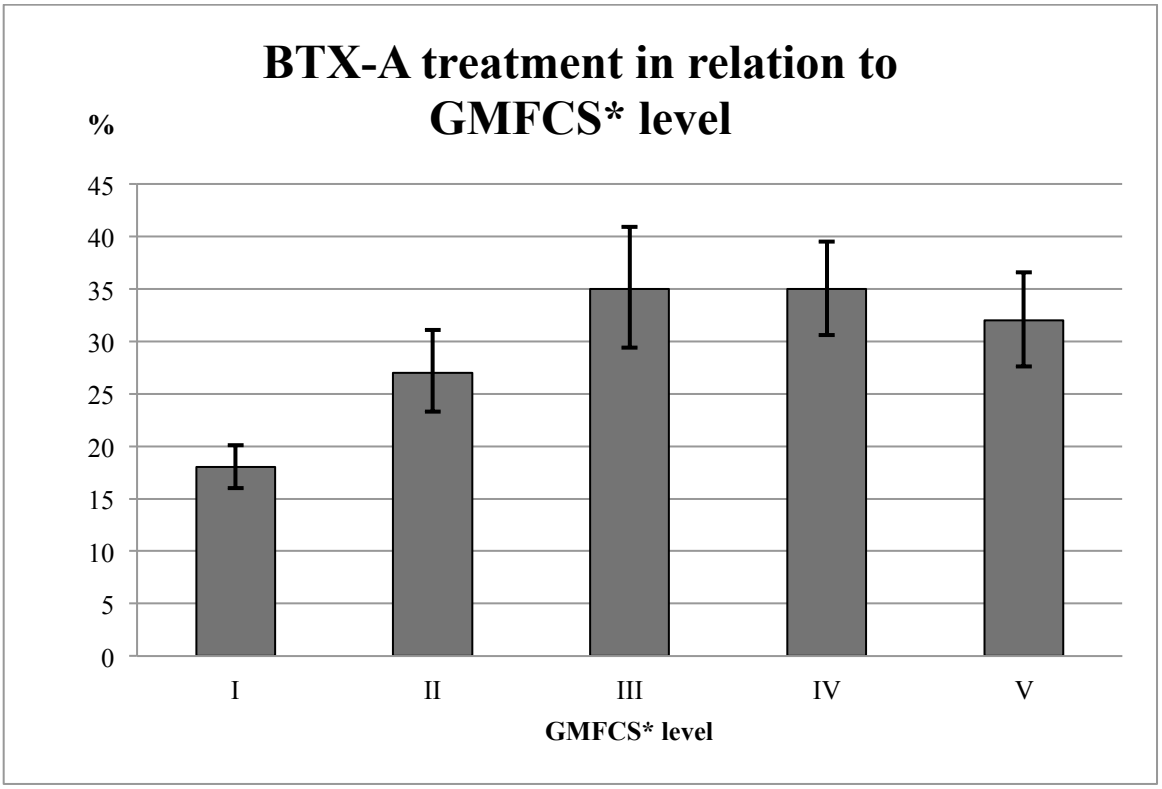


Figure 3. Proportion of children treated with botulinum toxin A (BTX-A) based on age. N = 3028. The line segments represent the upper and lower bounds of the 95% confidence intervals.



* GMFCS = Gross Motor Function Classification System

Figure 4. Proportion of children treated with botulinum toxin A (BTX-A) based on GMFCS* level. N = 3028. The line segments represent the upper and lower bounds of the 95% confidence intervals.

Table 2. Odds ratios and 95% CIs of children with cerebral palsy treated with botulinum toxin A in relation to age, sex and Gross Motor Function Classification System (GMFCS) level.

Variable (reference group)	Odds ratio (95% CIs)
Age (1-3 years of age)	
4-6 years of age	2.02 (1.57-2.61)
7-9 years of age	1.53 (1.18-1.99)
10-12 years of age	1.14 (0.87-1.50)
13-15 years of age	0.81 (0.58-1.13)
Sex (Girls)	
Boys	1.25 (1.05-1.48)
GMFCS level (Level I)	
Level II	1.75 (1.37-2.24)
Level III	2.59 (1.94-3.45)
Level IV	2.58 (2.02-3.28)
Level V	2.27 (1.77-2.92)

CIs = confidence intervals.

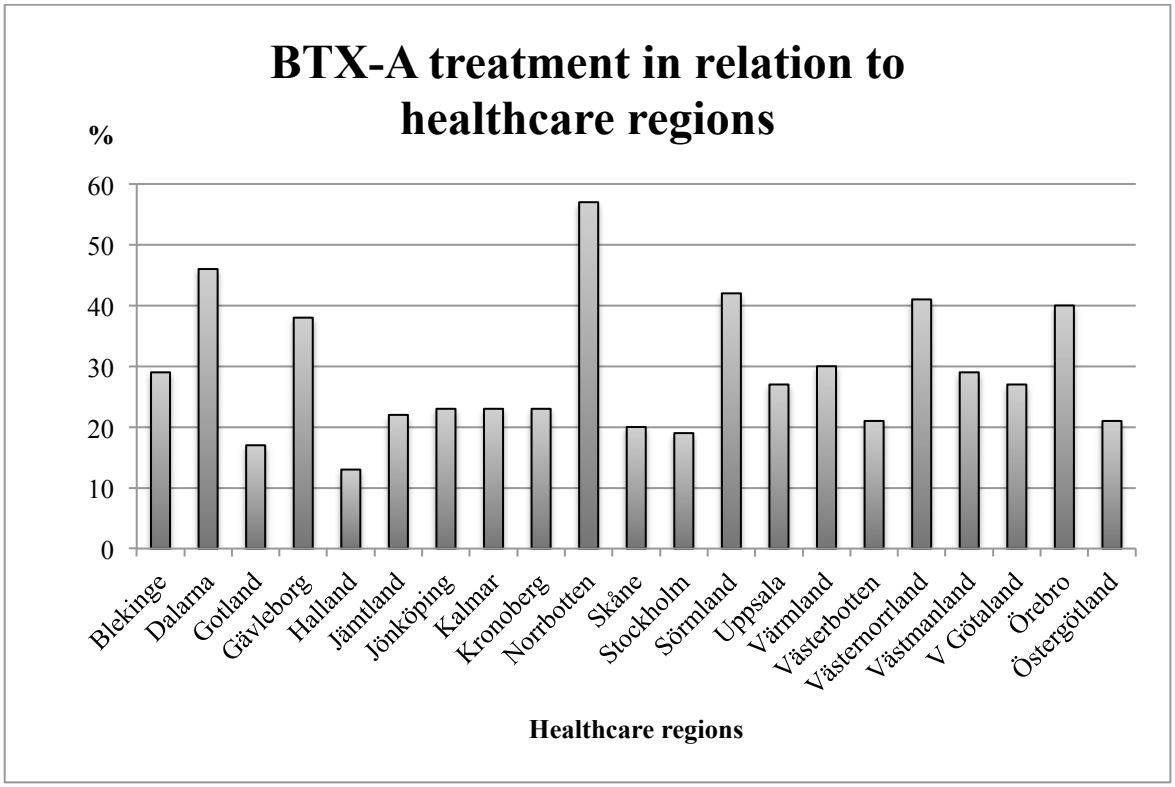


Figure 5. Proportion of children treated with botulinum toxin A (BTX-A) based on healthcare regions. N = 3028.

Table 3. Distribution of muscle group/s treated with botulinum toxin A (BTX-A).

Muscles groups treated with BTX-A	Total n (%, 95% CIs)
Single muscle groups	
Gas alone	254 (33, 29.4-36.2)
Ham alone	43 (6, 4.0-7.4)
Add alone	30 (4, 2.6-5.5)
Combinations of muscle groups	
Gas+Ham	89 (12, 9.3-13.9)
Gas+Add	33 (4, 2.9-5.9)
Ham+Add	37 (5, 3.4-6.5)
Gas+Ham+Add	39 (5, 3.6-6.8)
Other combinations or missing data	251 (32, 29.1-35.8)
Total number of treatments	
Gas	415 (54, 49.9-57.0)
Ham	208 (27, 23.7-30.1)
Add	139 (18, 15.3-20.8)

N = 776
Gas = the gastrocnemius muscle, Ham = the hamstring muscles, Add = the adductor muscles.
CIs = confidence intervals.

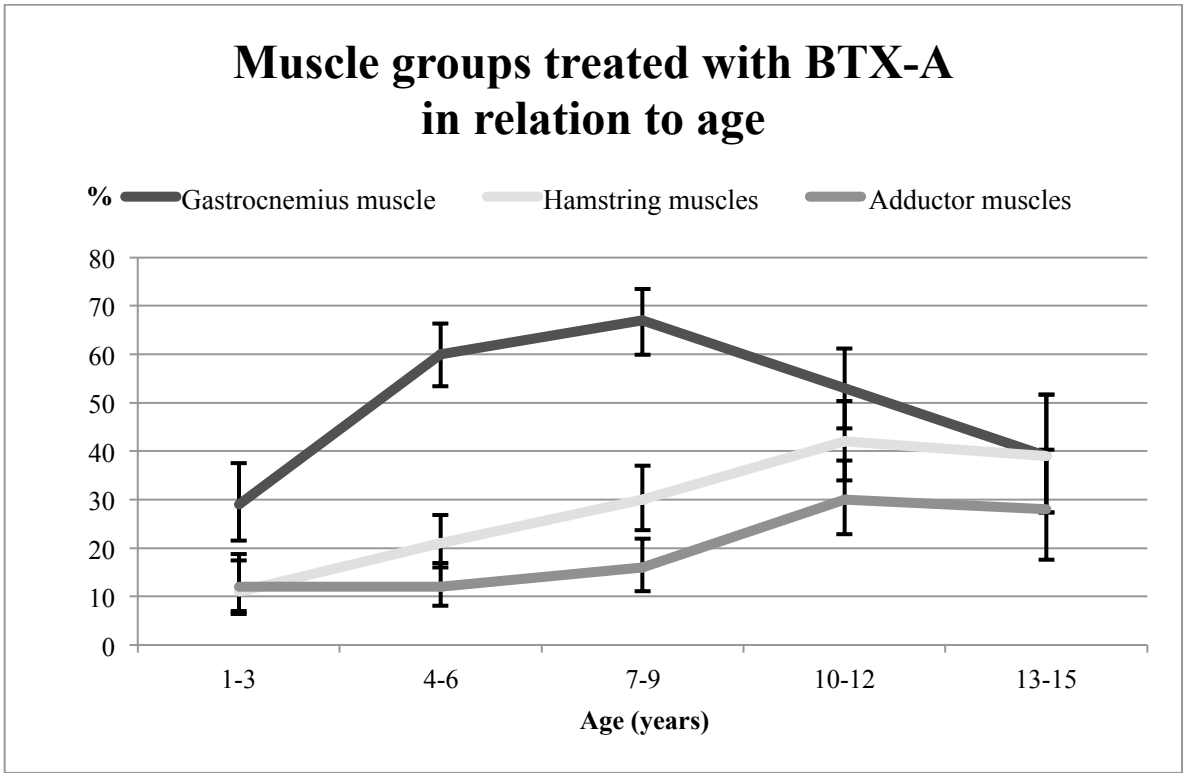
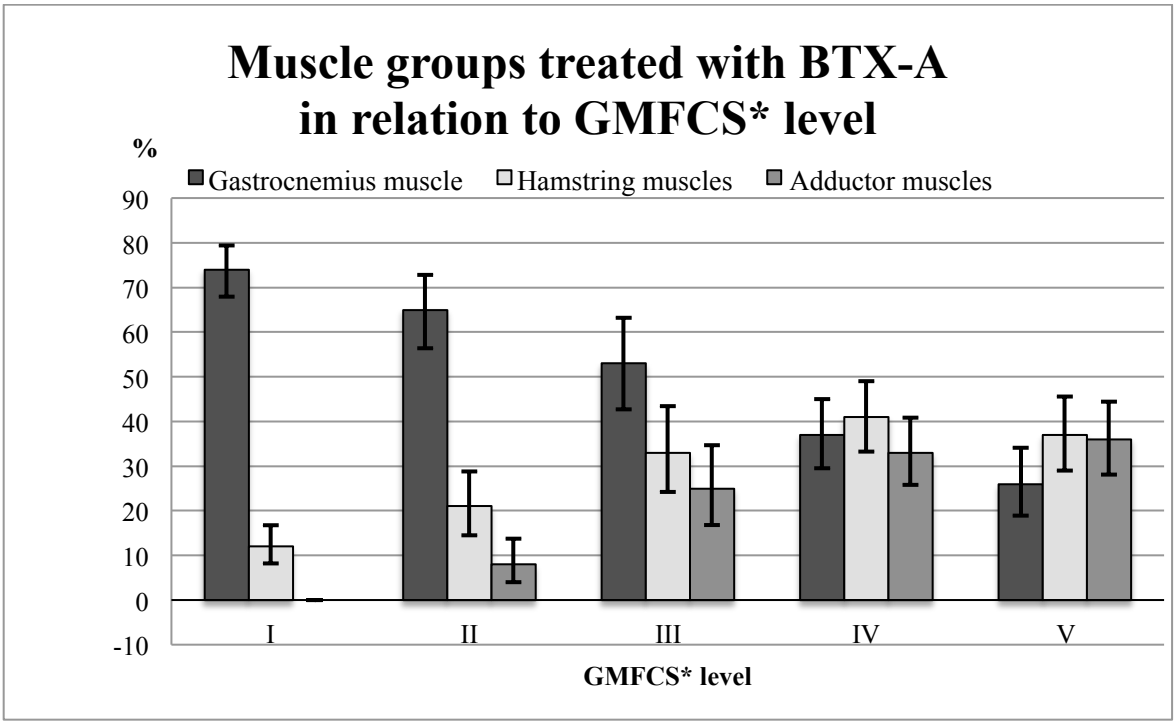


Figure 6. Proportion of children treated with botulinum toxin A (BTX-A) based on muscle groups and age. N = 776. The line segments represent the upper and lower bounds of the 95% confidence intervals. The muscle group treated may be treated alone or in combination with one or both of the other muscle groups in the diagram.



* GMFCS = Gross Motor Function Classification System

Figure 7. Proportion of children treated with botulinum toxin A (BTX-A) based on muscle group/s and GMFCS* level. N = 776. The line segments represent the upper and lower bounds of the 95% confidence intervals. The muscle group treated may be treated alone or in combination with one or both of the other muscle groups in the diagram.