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Upper Limb Assessment and Treatment in Cerebral Palsy

Izabela Blaszczyk

Department of Surgical and Perioperative Sciences,
Section for Hand and Plastic Surgery
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The most important thing is being passionate about what you're doing and always give it your all. That is the key to success.

Charlie White

To my patients with cerebral palsy

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ABSTRACT

Cerebral palsy (CP) is a heterogeneous group of neurological disorders caused by fetal or infant brain damage that often involves deficits in upper limb (UL) posture and function. Knowledge about effective methods of assessment and treatment of UL in CP is not extensive. In this thesis, different aspects of these two are explored.

In Paper I we retrospectively investigated the effect of a long-term treatment regime developed in Västerbotten county habilitation service. The treatment regime included intramuscular injections of botulinum toxin type A (BoNT-A) combined with occupational therapy (OT) and movement training. The results of passive extension of the wrist with fingers extended and the assessment of hand function in children with severe hand function impairment (initially House functional classification 0-1) were analyzed over time. Twenty-five children were divided into 3 groups depending on the treatment regime start age (before or after the age of 7) and treatment regime availability. We found significantly worse passive extension of the wrist with fingers extended in children who did not have a chance to benefit from therapy in early childhood. Additionally, an improvement in the passive movement of the wrists was noted in children who completed the treatment regime before the age of 7. Regarding hand function, a significant difference was found between children who received treatment in early childhood and those who received treatment as adolescents.

The injections of BoNT-A in CP are common, however the monitoring of eventual side effects and adverse events (AEs) after this treatment is difficult to perform in clinical practice. To facilitate this process, we created a new, no previously validated questionnaire (Paper II). The questionnaire was given to patients or their caregivers to be completed after each BoNT-A treatment. 94% of participants returned the questionnaire. 80 % were filled in completely which proves the effectiveness of the applied form and the ease of its use in clinical practice. 61% of patients reported one or more different AEs or sides effects. In addition, we analyzed the risk for generalized and focal distal AEs reported by 38% of patients. Those may indicate the spread of BoNT-A toxin to the whole body, therefore requiring special attention. We found that females had a 1.899 relative risk with significant association ($p=0.029$) of reporting generalized and focal delayed AEs compared to males. The use of the questionnaire helped to make the decision to change or discontinue BoNT-A injections in 8 cases (11%).

In some patients with dyskinetic type of CP (DCP) treated with BoNT-A to diminish the external rotation posture of the shoulders, a loss of treatment effect was observed, which contributed to the need to look for another method of treatment. In paper III, a surgical method to manage the external rotation posture of the shoulders is presented. The surgical

procedure consists of weakening the strength of the externally rotating muscles by cutting the attachment of one of them (release of the posterior deltoid) and complete denervation of the other (denervation of the infraspinatus). The third shoulder external rotator (teres minor) remains intact. The results of this procedure performed in 7 shoulders in 6 patients (age 14-24) were analyzed using satisfaction questionnaire and pre-/postoperative video-recordings. Five of 6 patients were very satisfied with the treatment, one was neither satisfied nor dissatisfied. Four patients had an obvious improvement in their shoulder position confirmed on video recordings. In one, overcorrection in the form of internal shoulder rotation was observed.

Assessment of the thumb in CP is important as the thumb impairment plays a crucial role in hand grip function. Paper IV presents a new tool called CP-thumb score, which addresses the occupational therapists to follow the changes in the thumb function and its posture. CP-thumb score has two parts: descriptive and score of the thumb's CMC joint radial abduction. Thirty thumbs in 19 patients with all types of CP were assessed with CP-thumb score. All assessments were made based on available video recordings. Additionally, all thumbs were assessed using the House's thumb-in-palm classification which has been shown to be unreliable. These two thumb assessments were compared with each other.

STRESZCZENIE

(ABSTRACT IN POLISH)

Mózgowe porażenie dziecięce (MPD) to heterogenna grupa zaburzeń neurologicznych spowodowanych uszkodzeniem mózgu płodu lub niemowlęcia. Upośledzenie funkcji kończyny górnej u pacjentów z MPD jest częste (60-80%). Wiedza na temat skutecznych metod oceny i leczenia kończyny górnej w MPD nie jest obszerna. Różne aspekty tych dwóch powyższych zagadnień są przedmiotem niniejszej pracy.

W pierwszej zaprezentowanej pracy badaliśmy retrospektywnie efekty terapii wypracowanej w ośrodku rehabilitacji dziecięcej w Umeå, którą zastosowaliśmy u dzieci ze znacznym upośledzeniem funkcji obu kończyn górnych (GMFCS IV-V, MACS IV-V). Terapia ta polegała na stosowaniu powtarzanych, w okresie wielu lat, domięśniowych iniekcji toksyny botulinowej typu A (BoNT-A) połączonych z zastosowaniem ortez i indywidualnie dobranym treningiem ruchowym. Przeanalizowaliśmy zmiany w wynikach pomiarów biernego prostowania nadgarstka z wyprostowanymi palcami oraz zmiany dotyczące funkcji ręki u dzieci ze znacznymi jej zaburzeniami na przestrzeni wielu lat (wyjściowa funkcja ręki wg klasyfikacji Housea 0-1). Zebraliśmy wyniki pomiarów od 25 pacjentów, których podzieliliśmy na 3 grupy w zależności od wieku rozpoczęcia leczenia (przed lub po 7 roku życia). Ponadto dzieci leczone we wczesnym dzieciństwie podzieliliśmy na dwie grupy ze względu na trudności w zastosowaniu pełnej terapii. Stwierdziliśmy znacznie gorszy wyprost bierny nadgarstka z wyprostowanymi palcami u dzieci, które nie miały szansy skorzystać z terapii we wczesnym dzieciństwie. Dodatkowo zaobserwowaliśmy poprawę w biernym ruchu nadgarstków u dzieci, które rozpoczęły leczenie przed ukończeniem 7 roku życia. Stwierdziliśmy istotną poprawę funkcji ręki u dzieci leczonych we wczesnym dzieciństwie w porównaniu z tymi, które rozpoczęły leczenie dopiero jako nastolatki.

Chociaż iniekcje BoNT-A w MPD są powszechnie stosowane, to monitorowanie ewentualnych skutków ubocznych i zdarzeń niepożądanych po tym leczeniu jest trudne do przeprowadzenia w praktyce klinicznej. Aby ułatwić ten proces stworzyliśmy nowy, niepoddany wcześniejszej walidacji kwestionariusz (praca nr II). Kwestionariusz ten był rozdawany pacjentom lub ich opiekunom do

wypełnienia po każdej iniekcji BoNT-A. 74 z 79 uczestników badania wypełniło kwestionariusz. 80% kwestionariuszy zostało wypełnionych w całości, co świadczy o skuteczności zastosowanego formularza i łatwości jego zastosowania w praktyce klinicznej. 61% pacjentów zgłosiło jedno lub więcej różnych zdarzeń niepożądanych lub skutków ubocznych. Przeanalizowaliśmy ryzyko uogólnionych zdarzeń niepożądanych które zgłaszało 38% pacjentów. Wystąpienie uogólnionych zdarzeń niepożądanych wskazuje na możliwość rozprzestrzeniania się toksyny poza mięśnie poddane leczeniu, dlatego wymagają one szczególnej uwagi. Stwierdziliśmy, że u pacjentów płci żeńskiej odnotowano prawie 1,9 ($p=0,029$) razy częściej wystąpienie uogólnionych zdarzeń niepożądanych niż u pacjentów płci męskiej. Zastosowanie kwestionariusza pomogło w podjęciu decyzji o zmianie lub o zaprzestaniu terapii iniekcjami BoNT-A w 8 przypadkach (11%).

U niektórych pacjentów z dyskinetycznym typem MPD leczonych BoNT-A w celu zmniejszenia dominującej pozycji barków w rotacji zewnętrznej zaobserwowano utratę efektu terapii, co spowodowało konieczność zastosowania innej metody leczenia. W pracy nr III przedstawiono chirurgiczną metodę korekcji pozycji rotacji zewnętrznej barków. Zabieg chirurgiczny polega na osłabieniu siły obracających zewnętrznie bark mięśni poprzez przecięcie przyczepu jednego z nich (uwolnienie mięśnia naramiennego tylnego), i całkowite odnerwienie drugiego mięśnia (odnerwienie mięśnia podgrzebieniowego). Trzeci z rotatorów zewnętrznych barku (teres minor) pozostaje nienaruszony. Wyniki tego zabiegu, przeprowadzonego na 7 barkach u 6 pacjentów (wiek 14-24 lata), przeanalizowano za pomocą kwestionariusza satysfakcji oraz porównania nagrań wideo wykonanych przed i po zabiegu. Pięciu z 6 pacjentów oceniło rezultat leczenia operacyjnego jako bardzo dobry. Jeden z pacjentów nie odczuł ani poprawy, ani pogorszenia. Czterech pacjentów miało wyraźną poprawę pozycji barku, potwierdzoną na nagraniach wideo. W jednym przypadku zaobserwowano nadmierną korektę rotacji zewnętrznej, co objawiało się nadmierną rotacją wewnętrzną barku.

W MPD niezwykle ważna jest ocena kciuka, ponieważ jego upośledzenie odgrywa kluczową rolę w funkcji chwytu dłoni. W pracy nr IV przedstawiono nowe narzędzie o nazwie CP-thumb score, które jest przeznaczone dla terapeutów w celu śledzenia zmian funkcji kciuka i jego ruchomości. Wynik badania składa się z części opisowej oraz skali

określającej zdolność zarówno aktywnego, jak i pasywnego odwodzenia promieniowego stawu nadgarstkowo-śródręcznego kciuka. Trzydzieści kciuków u 19 pacjentów z różnymi typami MPD oceniono za pomocą CP-thumb score. Wszystkie oceny zostały dokonane na podstawie dostępnych nagrań wideo. Ponadto wszystkie kciuki zostały ocenione przy użyciu dotychczas używanej klasyfikacji House'a. Wyniki oceny kciuka przy zastosowaniu tych dwóch narzędzi porównano ze sobą.

ABBREVIATIONS

ACP	Ataxic Cerebral Palsy
AEs	Adverse Events
AHA	Assisting Hand Assessment
ANOVA	Analysis of Variance
AROM	Active Range of Motion
BoNT-A	Botulinum Neurotoxin Type A
BSCP	Bilateral Spastic Cerebral Palsy
CIMT	Constraint-Induced Movement Therapy
CMC	Carpometacarpal
CP	Cerebral Palsy
CPUP	Cerebral Palsy Uppföljnings (follow-up) Program
CTS	Carpal Tunnel Syndrome
DBS	Deep Brain Stimulation
DCP	Dyskinetic Cerebral Palsy
DREZ	Dorsal Root Entry Zone
EMG	Electromyography
F	Female
GMFSC	Gross Motor Function Classification System
H-TIP	House Thumb-in-Palm classification
ITB	Intrathecal Baclofen
IP	Interphalangeal

M	Male
MACS	Manual Ability Classification System
MCP	Metacarpophalangeal
MRI	Magnetic Resonance Imaging
PROM	Passive Range of Motion
PWE-FE	Passive Wrist Extension with Fingers Extended
ROM	Range of Motion
SCPS	Surveillance of Cerebral Palsy in Europe
SPN	Selective Peripheral Neurotomy
SNAP25	Synaptosomal-Associated Protein, 25kD
SNARE	SNAP RE ceptor
TD	Thumb Deformity
UL	Upper Limb
USCP	Unilateral Spastic Cerebral Palsy
VAMP	Vesicle Associated Membrane Protein

ORIGINAL PAPERS

- I. Andersson G, Renström B, **Blaszczyk I**, Domellöf E.
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.
Dev Neurorehabil. 2020 Aug;23(6):349-358
- II. **Blaszczyk I**, Foumani NP, Ljungberg C, Wiberg M.
Questionnaire about the adverse events and side effects following botulinum toxin A treatment in patients with cerebral palsy. Toxins (Basel). 2015 Nov 6;7(11):4645-54.
- III. **Blaszczyk I**, Granström AC, Wiberg M.
Denervation of the infraspinatus and release of the posterior deltoid muscle in the management of dyskinetic external shoulder rotation in cerebral palsy. J Neurosurg Pediatr. 2015 Apr;15(4):438-44.
- IV. **Blaszczyk I**, Nordell S, Wiberg M.
CP-thumb score- A new Assessment of the Thumb Deformity in Cerebral Palsy. A pilot study.
In manuscript

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INTRODUCTION

CEREBRAL PALSY, TYPE, CLASSIFICATIONS

Cerebral Palsy (CP) is a heterogeneous group of neurological disorders of the development of movement and posture caused by fetal or infant brain damage. The prevalence of CP worldwide is around 1,5-3 per 1000 live births. In most cases (85-90%) brain damage occurs during pregnancy or birth. This form is called congenital CP. If the damage occurs more than one month after birth but before the second year of life, the CP is classified as acquired. Prematurity, low birth weight, multiple pregnancy and maternal infections are the strongest risk factors related to congenital CP. Trauma, brain infection, or stroke in early childhood leads to acquired CP. The injury to the developing brain in CP causes developmental deficiencies in motor, sensory and cognitive functions. Deficiencies in motor development in the early childhood are often the first observed symptoms raising the suspicion of CP. Concomitant impairment of vision, hearing and speech, epilepsy or intellectual disability can additionally affect the motor impairment. The basis for the implementation of any treatment is an early and correct diagnosis. In the case of CP, correct diagnosis is often difficult and a long-lasting process. It has been assumed in Europe that it takes 4-5 years of a child's life before the CP diagnosis is determined and classified. To guide in the diagnose of CP clinicians use strict guidelines in the form of a decision tree, consisting of inclusion and exclusion criteria. In about 75% of the cases brain damage can be identified using magnetic resonance imaging (MRI), however in several cases, no structural brain changes are found. Classification based on MRI results can still be considered under development (Franki 2020). The brain injury manifests differently in different parts of the pregnancy; ei brain injury in the first trimester will lead to maldevelopments, in the second or early third trimester will predominantly affect white matter whereas later injury predominantly affect grey matter.

According to Surveillance of CP in Europe, CP is divided into different types depending on the dominant movement disorder:

Spastic type is the most common (more than 80% of CP cases) and is characterized by increased muscle tone and pathological increased reflexes for stretch. Spastic CP is further divided into two subtypes,

unilateral spastic CP (USCP) if the motor impairment is observed in one side of the body, or **bilateral** spastic CP (BSCP) when both sides are involved. Spastic CP presents on MR-images as white matter lesion in form of periventricular leukomalacia or sequelae of intraventricular hemorrhage.

Dyskinetic CP type (DCP) is less common, only about 6-15% of all CP cases. DCP is a result of a lesion in the basal ganglia and/or thalamus and can affect one or more parts of the body. These changes can be identified using MRI. Depending on two major different movement disorder patterns, DCP is categorized as **dystonic** or **choreo-athetotic**. DCP is characterized by involuntary, uncontrolled movements and persistent primitive reflexes.

Ataxic CP type (ACP) is rare, about 4-10% of CP cases and caused by lesions in the cerebellum. ACP is characterized by abnormal patterns of posture, hypotonia and loss of muscle coordination.

The wide range of clinical symptoms makes the CP diagnosis challenging. Sometimes a mix of different movement disorders can be present causing difficulties to the classification of the CP type. In such cases the CP is classified as non-classifiable CP or mixed CP. The degree of motor impairment in CP varies from mild to severe problems. Different classification measures of function have been developed and validated. Together with CP subtype, they facilitate to predict the children's disability level during growth and help to plan possible clinical and habilitative interventions.

Gross Motor Function Classification System (GMFCS) is a widely used tool for classifying the level of motor impairment. It is an age-related five-level classification describing the ability and performance of movements such as sitting or walking (**Table 1**).

Manual Ability Classification System (MACS) is a five-level scoring system for assessing the ability to perform bimanual activities of daily living where level I indicate the best and level V the lowest level of manual ability. MACS assess both hands as a functional unit and describe how the patient with CP use the hands and how many assistances or adaptations are needed to perform self-initiated daily manual activities (**Table 2**).

Table1. Gross Motor Function Classification System (GMFCS)

Level I	Children walk at home, school, outdoors and in the community. They can climb stairs without the use of a railing. Children perform gross motor skills such as running and jumping, but speed balance and coordination are limited.
Level II	Children walk in most settings and climb stairs holding onto a railing. They may experience difficulty walking long distances and balancing on uneven terrain, inclines, in crowded areas or confined spaces. Children may walk with physical assistance, a handheld mobility device or used wheeled mobility over long distances. Children have only minimal ability to perform gross motor skills such running and jumping.
Level III	Children walk using a hand-held mobility device in most indoor settings. They may climb stairs holding onto a railing with supervision or assistance. Children use wheeled mobility when travelling long distances and may self-propel for shorter distances.
Level IV	Children use methods of mobility that require physical assistance or powered mobility in most settings. They may walk for short distances at home with physical assistance or use powered mobility or a body support walker when positioned. At school, outdoors and in the community, children are transported in a manual wheelchair or use powered mobility.
Level V	Children are transported in a manual wheelchair in all settings. Children are limited in their ability to maintain antigravity head and trunk postures and control leg and arm movements.

Table 2. Manual Ability Classification System (MACS)

Level I	Handles objects easily and successfully
Level II	Handles most objects but with somewhat reduced quality or speed of achievement
Level III	Handles objects with difficulty; needs help to prepare or modify activities
Level VI	Handles a limited selection of easily managed objects in adapted situations
Level V	Does not handle objects and has severely limited ability to perform even simple actions

MOVEMENT DISORDERS IN CP

Movement is the result of muscle activity that is initiated and controlled by the nervous system through various connections between the motor control structures of the central nervous system (cerebral cortex, basal ganglia, cerebellum, spinal cord, intermediate neurons) and the peripheral system (peripheral motor and sensory nerves, muscles, joints and bones). Many elements of this motor control system are not yet fully understood due to their complexity. The failures in this system that cause movement disorders in CP are known as upper motor neuron syndrome. Movement disorders of various types lead to reduced motor control in the affected body segments. The control over voluntary movement such as the ability to precisely move an extremity, eye or tongue, becomes difficult and sometimes impossible. In addition to losing control of voluntary movements, there are also disorders of automatic movements such as reflexes. Since each element of the motor control system can be affected to different degrees, there is a vast variety in the expression of the movement disorder, such as abnormal (increased or decreased) muscle tone, abnormal motor planning and balance (dystonia, athetosis, chorea, tremor and ataxia). Furthermore, several movement disorders may coexist at the same time in varying degree of intensity.

In spastic CP, **spasticity/hypertonia** or the recently promoted term, **hyper-resistance** is present. There are disagreements not only about terminology of this symptom, but even its definition and assessment are controversial. Hyper-resistance is described as increased neuromuscular response to passive muscle stretch. Hyper-resistance is considered to consist of neural and non-neural components. The neural component consists of velocity dependent pathological, hyperactive stretch reflex (stretch hyperreflexia) observed during fast movement, due to lack of inhibition which is related to the upper motor neuron injury and non-velocity dependent involuntary muscle contraction (involuntary background activation) which is observed during slow passive stretch. The non-neural component is considered a secondary impairment, as a result of tissue adaptation to the pathological neural regulation in form of changes in elasticity (stiffness), viscosity and shortening of the muscle, ligaments and other soft tissues (van den Noort 2017). The difficulty in distinguishing these components makes it difficult to assess hyper-resistance therefore commonly used qualitative clinical measurements

(modified Ashworth scale, Tardieu scale) are unfortunately not valid and reliable. So far, instrumented quantitative assessments, such as electrophysiological and biomechanical measures used in research, are difficult to apply in clinical practice. In addition, there are indications of a low correlation between qualitative clinical measurements and quantitative electrophysiological assessments (Fleuren 2010).

Also, hyper-resistance may impair the function by weakening antagonist muscles. This will over time contribute to increased stiffness in affected muscles and joints. Flexion posture of the joints are more frequently observed, although extension postures may also occur.

It is important to mention the phenomena of co-contraction which is a physiological simultaneously contraction of the agonist muscles and inhibition of the antagonist muscle around one joint. The pathological stretch reflex and abnormal co-contraction influence each other (Rosa 2015).

Hypotonia is a less frequently recognized type of movement disorders. It manifests as lower than normal muscle tone causing muscle weakness and affects the level of physical activity. Low physical activity has in turn a negative effect on the development of muscle mass, cause skeletal changes such as osteopenia, and therefore pathological fractures and bone deformities. Hypotonia can affect one or more of the body segments, for example the muscle of the trunk or the neck.

In DCP two major movement disorders are present simultaneously: dystonia and choreoathetosis. The pathophysiology behind dystonia and choreoathetosis is not known but seems to be generated by damaged basal ganglia and/or thalamus.

Dystonia is observed more often and characterized by abnormal posture with hypokinesia and involuntary, repetitive, twisting movements caused by sustained or intermittent muscle contractions.

Choreoathetosis is characterized by hyperkinesia, involuntary rapid muscle tone changes (chorea) or involuntary slow writhing or contorting movements (athetosis).

Common characteristics of dystonia and choreoathetosis are the movement involuntariness, resulting in major difficulties to perform and develop voluntary movement of the affected extremity (Monbaliu 2017).

In ACP, the postural control (balance) is impaired causing inability to control the body's position in space especially during gait. Movements are performed with abnormal rhythm, force and accuracy. Tremor in the upper limb is common. ACP type is unusual and therefore we are lacking accurate description of mechanisms of **ataxia** in CP (Dan 2020).

MOTOR DYSFUNCTION OF THE UPPER LIMB IN CP

Upper limb (UL) motor dysfunction affect about 60-83% of the population with CP (Arner 2008, Makki 2014). The pattern and level of motor dysfunction varies depending on the CP type, the lesion degree and the individual's age. The brain lesion in CP affects the use of the UL already after birth. In USCP, a clear asymmetry in the hand use can be observed already during the first months of life. The child's ability to grasp with the affected hand is worse than in healthy side, and the sign of an adducted thumb (thumb in-palm) with flexed fingers around the thumb is more frequently seen. In mild cases, the impairment is limited to one movement of the arm, for example difficulty to supinate the forearm or only few small movement limitations in a some segments of the UL are evident. These kinds of small limitations are often difficult to recognize and may only be seen during more complex bimanual hand activity. Therefore, repeated evaluation with validated and reliable tools are of great importance for early detection of these deviations. Paper IV is dedicated to this topic. In more severe cases (GMFCS IV-V) the child does not use the affected UL at all and the ability to reach and grasp is severely impaired. Therapeutic challenges related to the UL therapy of this group are the subject of paper I.

In DCP, the UL function is severely impaired in most cases. Effective reaching and gripping are extremely difficult to perform as muscle tone varies uncontrolled during the task, not only in the UL but often in the whole body. Stabilizing the UL and keeping the arm in a functional position is difficult to sustain long enough to perform the intended action, even with the hand's gripping function preserved. Paper III is devoted to this problem.

Another factor that may limit motor activity of the UL is pain. It is known that pain increases the amplitude of the stretch reflex, which impairs the ability to perform movements. The limited motion can contribute to pain, for example the flexion posture of the wrist can lead to median nerve entrapment (Carpal Tunnel Syndrome, CTS), with neuralgia and skin sensation disturbance. The coexisting impairment of vision and/or skin sensory perception result in further obstacles for UL function development.

UPPER LIMB DEFORMITIES IN CP

Initially in childhood, full normal passive range of motion (PROM) is noted in all joints of UL. Impaired use of the UL and movement disorders can lead to gradual secondary changes in the muscles, joints and connective tissue manifested by limited PROM. There is a lack of consensus how and why limitation of PROM develops in CP. Many studies on histology, morphology and biomechanics of the muscles in CP have yet to date not given any convincing answers. Interestingly no correlation has been found between increased hyper-resistance and limited PROM. Probably since the reasons for limited PROM in CP are complex and multifactorial (de Bruin 2012). Limited PROM can in some be manifested already in the first year of life, whereas in others it develops first in their teens. Once developed, reduced PROM often increases over time and ultimately results in a fixed joint posture. Overall, about 35% of children with CP develop limitation of PROM in UL (Makki 2014, Hedberg-Graff 2019). The reduced PROM in wrist extension with extended fingers seems to occur most often, in about 19% of patients with spastic CP at age of 4 year. The evaluation of changes in this parameter is the subject of the analysis in paper I. Other common restrictions in PROM occur in the shoulder (14%), forearm supination (13%), wrist extension with flexed fingers (10%) and elbow extension (9%) at the age of about 7 years (Hedberg-Graff 2019). Individuals with a major level of impairment (GMFCS IV-V) show a higher risk of developing limitations in PROM. In cases with minor level of impairment (GMFCS I-III) the risk of PROM limitation is higher in USCP than BSCP.

Sometimes the PROM limitation never occurs, and even joint hypermobility can be observed. This especially in individuals with DCP in which uncontrolled, involuntary, repetitive and sometimes very powerful

movements can cause ligament injuries that in some even may cause painful instability of the affected joints. We present two such cases in paper III. Other ligamentous changes causing joint instability in UL in CP are hyperextension of the thumb metacarpo-phalangeal (MCP) joint or swan-neck deformity in the fingers. These deformations are the result of disturbed balance between various muscle groups operating these joints. Within the elbow, the radial head can luxate, or their cartilage may be destroyed. Within the shoulder, glenohumeral subluxation or dislocation can occur.

Skeletal deformities may occur as well. In cases with significant impairment of forearm supination during the limb growth, pathological bending of the radius can be observed, and in cases with major flexion contracture of the wrist, significant deformations in the wrist bones can occur. These changes often lead to the destruction of the articular cartilage and thus cause pain.

In some cases, impaired UL growth is manifested by skeletal shortening and poorly developed muscle mass. This can be observed especially in patients with USCP while in patients with DCP subtype the muscle mass is often very well developed.

HISTORICAL REVIEW OF THE NATURE, ASSESSMENT AND TREATMENT OF CP.

The first who studied and defined cerebral palsy was the British physician **William John Little**. In his lectures from 1843-44, printed in 1853 and titled "*Nature and Treatment of the Deformities of the human frame*" we find the first descriptions of CP and suggestion for treatments. Dr Little was the first to describe the deformities as a result of *universal rigidity of the muscular system in newborn infants* and calls them *universal or congenital spasmodic rigidity which induces development of spastic contracture*. He described that in the case of spastic contracture, *the muscular and nervous systems are unable to perform slow, steady, well ordered action*. He noted the variability of the symptoms; *...in some cases, the rigidity can be observed immediately or after several months or years, when rigidity became complicate with structural shortening*. He was the first to suspect a relationship between spastic contracture and premature birth or asphyxia during a difficult delivery. In 1861, after about 25 years of clinical experience, research and reflections, he presented his findings to the Obstetrical Society of London. Since then, the disease is called Little's disease. Unfortunately, his theory was not accepted by colleagues until about one hundred years later. Another important name that should be mentioned is **Sigmund Freud**. He stated that cerebral palsy may occur already before delivery due to abnormalities in the development of the fetus. However, his theory was rejected by his contemporaries.

Little recommended early prophylaxis of contractures. He advocated the use of mechanical extension to remove the structural shortening by manipulations, stretching and mechanical instruments in correction of spastic deformities. On failure, he recommended tenotomy if structural shortening of muscle existed, but he warned that a relapse should be expected especially in the growing child. *In the cases of failure of mechanical instruments, the tenotomy can be consider as a dernier ressort....the relief is not permanent... and return of the original deformity may be expected.*

Tenotomy was discovered and popularized in form of subcutaneous tenotomy by the German orthopedist **Louis Stromeyer** in 1830 and was dedicated originally for the treatment of clubfoot. This method became

widely used by numerous orthopedists to correct all kind of deformities of different origin in every part of the body. Before the popularization of the subcutaneous tenotomy, major deformities of the fingers, feet or whole extremities were treated not uncommonly by amputation performed by general surgeons. It should be remembered that at that time, it was orthopedics who dealt with non-surgical correction and prevention of deformities by using manipulations, stretching, gymnastics and mechanical instruments. Surgical treatment was reserved only for surgeons. Notably, Little himself suffered from clubfoot as a remnant of poliomyelitis at the age of four. He met Stromeyer during his licentiate ship in Germany and his foot was successfully operated by Stromeyer. Little imported this method to England and considered himself as the “Apostol of tenotomies”. He used Stromeyer’s procedure, however, warned and pointed out that the success of tenotomy depends on the etiology and pathology of the treated deformity. He observed that many of his colleagues used the subcutaneous tenotomy without understanding that different deformity natures existed. Little’s intention was to warn against the belief that tenotomy gave a permanent solution for spastic deformity, but he was obviously far from completely rejecting this treatment. Unfortunately, his statement that *tenotomy can be considered as a dernier ressort* has been misunderstood by his successors. Little died in 1894 at the age of 84. (Accardo 1989) Just a few publications appear for the next 50 years, and we do not see many continuators of Little's ideas. (Bradford 1890, Mansel 1890, Hunder 1892).

In 1913 Dr Little’s son **Ernest Muirhed Little** presents developments of surgical treatment methods, however he mentions that *treatment of spastic palsy received very little attention and many physicians and especially neurologists condemned all operations*. Despite these negative trends, some advances took place, most of them regarding the treatment of the lower extremity. Orthopedists are beginning to use tendon lengthening instead of subcutaneous tenotomy. Long-lasting splinting after tendon elongation with early training and multilevel tendon surgery at one sitting are reported (Lorenz, Vincent, Gigney). The bone deformities in CP are successfully corrected by joint arthrodesis or rotation osteotomy combined with tenotomy (Soulié, Debet).

The first attempts to perform surgery of nerves were made using total neurotomy of the ischiatic nerve (Nutt 1908), rhizotomy (Foerster 1908), intraneural alcohol injection into the nerves (Allison and Schwab 1909), selective motor branch neurotomy (**Stoffel** 1911) and nerve transplantation (Vulpinus 1911). All these kinds of interventions were probably performed sporadically and did not gain widespread use. The infamous effects of surgical treatment of CP seem to last until the 1950s or even longer. *Failures led to the discard of surgical treatment, and the conservative school of nonsurgical treatment grew in favor...The surgical approach in general was held in disrepute...* wrote Robert Carroll in 1950. Margaret Jones in her article titled: What's New in Cerebral Palsy in 1953 wrote: *Little reference is made today to these excellent articles revealing an understanding of the problem which has not changed too greatly in the succeeding 65 years.* She summarizes the current knowledge about CP and the therapeutic methods used at the time.

The treatment of seizures, behavior problems and mental retardation seems to be in the center. The use of sedative, hypnotic and antiepileptic drugs such as Benzedrine (Amphetamine), chloral hydrate, alcohol, paraldehyde and phenobarbital are widely recommended as relaxants. In case of failure neurosurgery of the brain such as lobotomy, topectomy, gyrectomy was recommended. Orthopedic surgery began to develop slowly again with an emphasis on being only a supplement to rehabilitation therapies.

There is a very small number of publications concerning the treatment of the UL in CP before the Second World War, and those produced had in common the opinion that surgical treatment of the spastic hand is rarely indicated and often disappointing (Burman 1938). There are only two papers published before 1950 which present successful surgical treatment. Both focused on the treatment of pronation deformity of the forearm and flexion deformity of the wrist. First is **Max Page's** muscle-sliding operation from 1923 and the second is **Green's** tendon transplantation of the flexor carpi ulnaris to wrist radial extensor from 1942.

In the fifties we see a return to the idea of surgical treatment in the musculoskeletal system. The message from the authors of these publications is the same: Surgical procedures are seldom indicated. In

selected cases, possibly in about 10%-20% of all CP cases, the hand function or appearance can be improved. Many hand deformities cannot be treated surgically, and many patients can be improved by splinting, stretching and re-education. There were recommendations to perform selective tenotomies and different tendon transfers or joints arthrodesis. The most frequently described surgical procedures focused on deformities of the wrist and the thumb (Carroll 1951, Goldner 1955, Cooper 1952). In the sixties a number of publications present several surgical procedures addressed to improve the hand function in the patients with USCP grew (Pollock 62, Green 62, Matev 63, Samilson 64, Swanson 64, Mortens 65). These surgical procedures included pronation deformity of the forearm, flexion deformity of the wrist, thumb-in-palm deformity and swan-neck deformity of the fingers. Many used different tendons transfers. The results of often multiple procedures were unstable, with a high rate of recurrence. However, in 1966 Inglis presented promising results on treatment of elbow flexion, forearm pronation and wrist flexion deformity using two-stage surgery; the pronator-flexors release (the Page's procedure from 1923) during the first seance and thumb deformity correction in the second. He interestingly concludes: *the principal errors in surgical treatment.... are excessively ambitious goals and too optimistic expectations of restored function.... Goals in CP must be more modest.*

In parallel with surgery in the musculoskeletal system surgical methods of the neurologic system develops. In 1983 **Brunelli** promoted the idea of reducing hypertonia in the UL by performing hyponeurotization now called selective peripheral neurotomy (SPN). Although the idea was not new, it was most often used for hypertonia treatment in the lower limb. The first who performed neurotomy of a hypertonic muscle was Stoffel in 1911. He performed total denervation of hip adductor muscle by cutting the obturator nerve. SPN is one of the neuroablative treatment methods like selective dorsal rhizotomy or DREZ (dorsal root entry zone) surgery but performed more distally thus giving the possibility of a more selective denervation. The basis of neuroablative surgery is the hypothesis that reduction of number of afferent Ia sensitive fibers which transmit impulses from muscle stretch receptors (muscle spindles, Golgi tendon organs) decrease pathological stretch reflexes. In the case of SPN, section of both afferents and efferent fibers are performed at the level of motor nerve branches. SPN can be done in different ways. Neurotomy if the

surgeon just cut the nerve. Neurectomy involves cutting and removing part of a nerve, making a gap of at least 5mm or more. Neurotomy or neurectomy can be performed at the different level of the nerve. To distinguish the level, the selective or hyper selective terms are used. Neurectomy can be done totally 100% or partially (usually 75% or more) Until today there is no consensus on which technique is most appropriate. The idea of the partial hyperselective neurectomy is based on animal studies showing that the nerve motor endplate from intact (25%) motoneurons sprouts and recruits more motor units of the muscle and on this way reinnervates previously denervated muscle, whereas regrowing of afferent, sensory Ia fibres is disorganised and don't reinnervate the muscle spindle and Golgi tendon organs. Since the end of the twentieth century, there are sporadic publications of the use of SPN in selected cases of focal spasticity or dystonia in the upper extremity (Maarrawi 2006, Sindou 2007, Sitthinamsuwan 2010, Gras 2017, Leclercq 2021).

For a long time, experienced hand surgeons pointed out that careful evaluation and adequate patient selection is crucial to obtain good surgical treatment results (Samilson 66 ,67, Goldner 68). We need to remind ourselves that the evaluation tools of UL function were very limited. The most often used methods were repeated observations of the patient during activity, assessment of the active and passive range of motion, stability of the joints and sensibility of the hand. Swanson (1964) mentioned the role of the experienced occupational therapist in determination of the indications for surgery and role of pre- and post-surgical video registration for evaluation of the treatment's results. Zuk (1961) and Samilson (1964) tried to use EMG in planning of surgery. Samilson (1966, 1967) was first to utilize a "hand evaluation sheet" and found it useful if the same observations were made in serial examinations. His goal to evaluate the whole extremity including the shoulder and elbow must be considered quite unique for that time.

The lack of quantitative methods for evaluation of the different treatment methods was clearly a problem during the next few decades and plausibly explain that the scientific level of the publications from this period was low. Additionally, factors such as heterogeneous population and short follow-up time make it difficult to draw conclusions from the presented treatment results from this time. In 1969 the hand function test was developed by Jepsen at al. (Jepsen-Tylor hand function test).

Unfortunately, this kind of evaluation was not used to assess the treatment results during the next decades. In the 80's Dr James House (1981) published his classification of the hand, House's functional classification and thumb-in-palm classification (**Table 3,4**). Both are widely used until today, however, their usefulness for evaluating treatment outcome is limited (Smeulders 2005).

Class	Designation	Activity level
0	Does not use	Does not use
1	Poor passive assist	Uses as stabilizing weight only
2	Fair passive assist	Can hold onto object placed in hand
3	Good passive assist	Can hold onto object and stabilize it for use by other hand
4	Poor active assist	Can actively grasp object and hold it weakly
5	Fair active assist	Can actively grasp object and stabilize it well
6	Good active assist	Can actively grasp object and then manipulate it against other hand
7	Spontaneous use	Can perform bimanual activities easily and occasionally uses the hand spontaneously
8	Spontaneous use	Uses hand completely independently without reference to the other hand

Table 3. House's functional classification system

Type of Deformity	Primary Deforming Muscles	Thumb Position
Type 1	Adductor pollicis	Adduction of the first ray across the palm
Type 2	Adductor pollicis and thenar muscles	Adduction of the first ray across the palm, MCP flexion
Type 3	Adductor pollicis	Adduction of the first ray with secondary volar plate laxity (MCP hyperextension)
Type 4	Adductor pollicis, thenar muscles, FPL	Adduction of the first ray; MCP flexion, IP flexion

IP = interphalangeal joint, MCP = metacarpophalangeal joint, FPL= Flexor pollicis longus

Table 4. House Thumb-in-palm classification

With the development of neonatal intensive care in the 1980s and 1990s, the mortality rate of children with severe disabilities decreased. The number of children with CP has increased and research into the origin of CP and CP management becoming a priority. Cooperation between several CP centres begins in Europe under the name of Surveillance of Cerebral Palsy in Europe (SCPE 2000). One of the effects of this cooperation is a new CP definition, classification and strict inclusion criteria into various CP subtypes. Terminology such as spastic hemiplegia, diplegia or quadriplegia are replaced by unilateral and bilateral spastic CP. Gross Motor Functional Classification System (GMFCS) and Manual Ability Classification System (MACS) are developed and recommended for use as a complement to the CP subtype. Used together with CP subtype, they help to form more homogeneous groups in research projects. Continued monitoring of the individuals with CP is recommended to gain more knowledge about the various conditions of CP. For example, in Sweden a surveillance program called Cerebral Palsy Uppföljning Program (CPUP) started in 1994. It became a national quality register in 2005 and almost all (95%) individuals with CP participate in it.

On the same time different evaluation tools for assessment of UL are developed such as: Quality of Upper Extremity Skills Test (DeMatteo 1992), Shriners Hospital Upper Extremity Evaluation (1996), Melbourne Assessment of Unilateral Upper Limb Function (Randal 1999) or Assisting Hand Assessment (2003). Several activity interventions for UL in CP were developed by occupational therapists and physiotherapists such as Constraint-Induced Movement Therapy (CIMT), Bimanual training, Goal-directed training, occupational therapy by using splint and strength training.

In the early 2000's new treatments to reduce the increased muscle tone were introduced: Peroral or intrathecal Baclofen therapy and intramuscular Botulinum toxin type A injections (BoNT-A). The later, gained popularity and began to be widely used in the treatment of UL in CP. In Sweden, the use of BoNT -A injections in the UL started to be used by hand surgeons in almost all hand surgery departments already in the 2000 and in 2008 the national strategy on use of BoNT-A in UL was published in the Swedish Medical Association Journal ("Läkartidningen", Arner 2008). In a systematic review of interventions for children with CP, the BoNT-A injections in the upper extremity combined with occupational

therapy showed strong effectiveness (Nowak 2013), whereas, effectiveness of surgical interventions could not be shown, probably due to the low number of publications of a good quality devoted to this subject. Surgery of the UL in CP is challenging and the number of hand surgeons dealing with this issue is not large. In 2020, the Swedish national register of CP hand surgical interventions was introduced. I hope that this data, combined with data from CPUP, contributes to a better understanding of the effectiveness of hand surgical procedures.

ASSESSMENT OF THE UPPER LIMB IN CP

A careful assessment of the entire UL as well as each UL is crucial for planning and evaluating the results of the interventions. There are many different assessment tools to evaluate hand function in patients with CP. Some of them are validated, some are not, and new assessment tools are constantly being developed. In the section below, I present the evaluation tools that were used in my research.

House functional classification of the hand (paper I, III, IV) is a nine-level classification, describing separately grip quality in each hand (**Table 3**). Level 0 for no used hand, level 1-3 for a hand with poor, fair or good passive grip of assist hand, level 4-6 indicates a hand with poor, fair or good quality of active grip, level 7-8 a hand which is used spontaneous partial or complete. House functional classification is validated, and reliable classification widely used to assess the hand function level in all CP types.

Measurement of the Range of motion (ROM) (paper I, IV)
Range of motion (ROM) is a measure of joint movement expressed in degrees (°) of a circle. Measurement performed with help of goniometers is reliable and validated. Each body joint has a different ROM for each type of movement. For example, in the wrist, four types of movements are possible to perform: extension, flexion, radial deviation, and ulnar deviation. The ROM for the wrist extension is 0 to 70 degrees, for the flexion 0 to 70 degrees, for radial deviation 0 to 20 and for ulnar deviation 0 to 45 degree. The wrist ROM depend on condition of different muscle groups such as wrist flexors/extensors and fingers extrinsic flexors/extensors including the thumb extrinsic muscles. Therefore, measurement of the wrist ROM should be performed with different positions of the fingers to evaluate the different conditions between

different muscle groups. The ability of wrist flexion/extension is assessed twice, with fingers in extension and flexion. Movement can be performed passively (passive range of motion - PROM) by the investigator, or actively (active range of motion - AROM), by the patient himself. PROM measurement should be performed with very slow speed to avoid eliciting of stretch reflex during measurement.

House thumb-in-palm classification (H-TIP) (paper IV) is a classification describing the thumb deformity in CP (**Table 4**). It is a four-level score, type 1, most common, if only the adduction of the thumb's carpometacarpal (CMC) joint is noted, type 2 if type 1 and flexion of the thumb's metacarpophalangeal (MCP) joint is noted, type 3 if type 1 and hyperextension of the thumb's MCP joint is noted, and type 4 if type 2 with flexion of thumb's interphalangeal (IP) joint is noted. This classification has its limitation because not all possible CP thumb deformities can be classified.

Video recording (paper III, IV) is an excellent tool to collect the data about UL function in the patients with CP. They can be re-played and repeated. The repeated video recordings of the same activity of the UL can be assessed and compared with each other. The observed changes can be assessed. The most important is that the hand function we are interested in is captured in proper aspects. Even measurement of joint AROM and PROM can be assessed based on video recording. Video recording can be standardized or individualized and adapted to the functional level of each patient. However, for the best benefit the person recording must be familiar with the issue. **Assisting Hand Assessment (AHA)** is standardized tests where video recording is used. **AHA** assesses how effectively the patients use their impaired hand during bimanual activity. The session of hand activity is recorded, and 22 items are scored using a 4-point rating scale. Each scale step represents quality of observed performance according to precisely defined criteria.

Questionnaire (paper II, III, IV) is a research instrument that consists of several questions that aim to collect information from participants. Questions can be close-ended where the answer is predefined, for example dichotomous question, YES/NO. These kinds of questions are used to collect quantitative data. Open-ended questions give participants the possibility to answer in open text. They open unlimited response options and are most often used with a small group in qualitative

research. **Satisfaction questionnaire (paper III)** is used to evaluate satisfaction after any service or treatment. The answers to questions are formulated in the form of degree of satisfaction/dissatisfaction or in the form of scale for example from 0-10. Standardized answers of close-ended types (multiple choice questions) help to compile the data. Well-designed questionnaires help to collect a lot of data in a short time. The questions must be easy to read and understand for participants. The number of questions and their content must be related to the research topic. The simplicity of filling out the questionnaire and clear instructions on how to collect it ensures high participation.

Follow-Up survey program for people with Cerebral Palsy (Cerebral Pares Uppföljningsprogram, CPUP) (paper I, IV) is a Swedish national quality register for people with CP. The survey includes a standardized, follow-up assessments of UL. Assessments are done by occupational therapists twice a year up to 6 years of age and after that once a year. The following assessments are repeatedly performed: MACS, House functional classification of the hand, PROM of almost all UL's joints except elbow and wrist flexion, AROM of the forearm's supination, Zancolli classification, House thumb-in-palm classification (until 2016). The aim of this monitoring is prevention and early intervention in cases with signs of worsening in any of the assessments. The result of the subsequent assessment is always compared with the previous assessment. To detect significant changes in assessment of the PROM the "traffic light system" is used. Green level means good/normal PROM, yellow level indicates warning that PROM decreased from normal and red indicates severe limitation of PROM (**Table 5**). In addition to assessments of UL, CPUP collects information on applied interventions, movement therapy, orthoses type and botulinum toxin injections.

	RED	YELLOW	GREEN
Shoulder abduction	$\leq 120^\circ$	$>120^\circ$ $<160^\circ$	$\geq 160^\circ$
Shoulder flexion	$\leq 120^\circ$	$>120^\circ$ $<160^\circ$	$\geq 160^\circ$
External shoulder rotation	$\leq 0^\circ$	$>0^\circ$ $<45^\circ$	$\geq 45^\circ$
Internal shoulder rotation	$\leq 0^\circ$	$>0^\circ$ $<40^\circ$	$\geq 40^\circ$
Elbow extension	$\leq -30^\circ$	$>-30^\circ$ $<-10^\circ$	$\geq -10^\circ$
Elbow flexion	x	x	x
Forearm supination	$\leq 45^\circ$	$>45^\circ$ $<80^\circ$	$\geq 80^\circ$
Forearm pronation	$\leq 45^\circ$	$>45^\circ$ $<80^\circ$	$\geq 80^\circ$
Wrist extension	$<0^\circ$	$\geq 0^\circ$ $<60^\circ$	$\geq 60^\circ$
Wrist extension with fingers extended	$\leq -20^\circ$	$>-20^\circ$ $<60^\circ$	$\geq 60^\circ$
Wrist flexion	X	x	x
Wrist ulnar deviation	$\geq 45^\circ$, $<0^\circ$		$<45^\circ$, $\geq 0^\circ$
Wrist radial deviation	$<0^\circ$	$\geq 0^\circ$ $<20^\circ$	$\geq 20^\circ$

Table 5. Values of Passive range motion (PROM) for the UL joints: critical (red), warning (yellow) and normal (green) according to the CPUP “traffic light system”

TREATMENT OF THE UPPER LIMB IN CP

Today there is no consensus about the treatment of UL in CP. Several different treatment methods are used with or without scientific evidence (Nowak 2020). One of the main reasons for so little knowledge about the effectiveness of the applied interventions is the lack of good and reliable outcome measurements. Another reason is the great diversity and inhomogeneity in the CP population. The multitude of uncommonly comorbid neurological symptoms such as hyper-resistance, hypotonia, dystonia, chorea, compensatory movements, co-contractions or paralysis often cause mistakes or inaccuracies in pre-intervention assessment and diagnosis. This, in consequence, leads to difficulties in assessing the applied treatment method.

The following treatment methods were used in my research: passive stretch therapy, orthoses and chemo denervation using intramuscular injections of BoNT-A which are noninvasive interventions and invasive treatments: tendon release and surgical denervation using total neurectomy.

Passive stretch therapy (paper I) is a noninvasive intervention. Passive stretching exercises are the most common used type of movement therapy in the patients with limited ROM. Regular stretching movements of the muscles, tendons and joints can be performed by caregivers or the patient themselves a few times a day. Little is still known about the stretching effect on muscles and tendons in CP. The evidence for stretching effectiveness is limited, however in combination with BoNT-A treatment it is recommended in management of hyper-resistance in CP (Nowak 2020).

Orthosis treatment, also called hand splint treatment, **(paper I)** is a noninvasive occupational therapeutic intervention. Different orthosis models are used for different purposes. In paper 1, we used non-functional orthoses that position the fingers and the wrist in a functional position. They are usually used at night so as not to interfere with the voluntary function of the hand, and for at least 6 hours a day or more. The purpose of their use is continuous stretching of tissues (muscles, tendons, ligaments). It is believed that their use prevents contracture. The effectiveness of orthosis treatment in preventing contracture in CP is unclear (Jackman 2014, 2018).

Botulinum toxin's mechanism of action and therapeutic application. (paper I, II, III)

Botulinum toxin type A (BoNT-A) is a protein produced by bacterium *Clostridium botulinum* which together with other toxins serotypes (B,E,F) in human cause a food poisoning called botulism. One of the symptoms of botulism is flaccid paralysis of the muscles. Muscle contraction is a result of stimuli transmitted from the nerve to the muscle and it occurs in the neuromuscular junction in so called motor endplates. The signal transmission is mediated by acetylcholine. BoNT-A inhibits the release of acetylcholine from motor endplate. Motor endplates consist of a pre-synapse membrane, synapse cleft and a post-synapse membrane. In the pre-synapse membrane (nerve end) there are vesicles containing acetylcholine. Electrical impulse that travels through the nerve and reaches the motor endplate causes the release of acetylcholine found in vesicles at the pre-synapse membrane. Vesicles open and release acetylcholine to the synaptic cleft thanks to the SNARE protein complex (SNAP25, VAMP, syntaxin). On the other side of motor endplate, at the post-synaptic membrane, there are acetylcholine receptors which, when bound with acetylcholine, activate channels for potassium and sodium ions (K⁺, Na⁻). Movement of these ions causes depolarization that spreads to muscle fibers and leads to muscle contraction.

BoNT-A acts by reaching the pre-synapse membrane and enters the nerve cell thanks to specific receptors (gangliosides). BoNT-A consists of a heavy (Hc) and a light chain (Lc). BoNT-A bind to gangliosides using Hc and form a vesicle and by this way the BoNT-A come into the nerve end (endocytose). Then the Lc, which is a protease, leaves the endocytic vesicle and cuts (like a pair of scissors) the protein SNAP25 which is a part of the SNARE protein complex. The SNARE complex loses its activity and vesicles containing acetylcholine cannot reach the synaptic cleft. By this way the lack of acetylcholine in the synapse interrupts the muscle contraction. BoNT-A causes a temporal chemical denervation of the injected muscle.

There are three available medical preparations of BoNT-A: BOTOX, DYSPORT and XEOMIN. The injections technique, dose, concentration and volume applied to the injections side play an important role in obtaining the desired effect. The injected muscle became weak and due to this, it is easier to move the joint and perform movement and training of

antagonist muscles. BoNT-A effect is long-lasting but not permanent. It usually takes about 3 days before the toxin starts to act, and it takes about 3 months before muscle tone returns. To maintain the effect, treatment with BoNT-A needs to be repeated. Some patients are treated with botulinum toxin every 3-6 months for several years. There is strong scientific evidence showing effectiveness of BoNT-A treatment in spasticity and dystonia management in CP.

Treatment with botulinum toxin injections is not free of side effects and adverse events as the toxin can spread. Small amounts of the toxin can reach circulation and thus move to other parts of the body, to other muscles and organs. However, the high affinity binding to neuronal membrane especially for hyperactive neurons which express higher rate of receptors contribute to treatment safety. The mechanism of degradation and eventual distribution of BoNT-A to another part of nerve cell by retrograde transport through the axon to other cells and further to the central nervous system, has not been clarified so far. The block of acetylcholine releases by BoNT-A can occur in all cholinergic nerve fibers. For example, the production of saliva in the salivary gland or sweat production in the sweat glands can be reduced in the same way as muscle activity. As the BoNT-A is a protein, an autoimmune reaction antibody production may occur which can lead to resistance. The risk of resistance and consequently, the disappearance of the BoNT-A effect seems to increase with the intensity and frequency of injections.

Surgical interventions (paper I, III)

As mentioned above in the historical review, there is still no consensus regarding indications for the use of various surgical methods and the evidence of their effectiveness have not yet been confirmed. There are many different surgical techniques available to correct the various deformities found in the UL in the patients with CP. The surgical treatments can be divided in two major groups: surgery at the musculoskeletal system and surgery at the neurological system. The aim of all of them is to decrease, redirect, rebalance or eliminate the muscle forces around the affected joints. The reduction in muscle tone improves joint mobility and by this improved function can be expected.

It is believed that surgery diminishes the pathologic stretch reflex. In the case of muscle-tendon unit lengthening it is achieved by decreasing

tension in the intrafusal muscle spindle and in the case of selective peripheral neurectomy it is achieved by a reduction in the number of afferent Ia fibers innervating muscle spindles. Below I will describe the methods that I used in my research.

Surgical treatment of major restriction in wrist PROM in patients with very limited hand function.

The goal of treatment is to reduce the flexion contracture of the wrist to facilitate hygiene, dressing and improve appearance. In severe cases, wrist flexion contracture can cause pain due to entrapment of the median nerve (carpal tunnel syndrome) or due to damage to the cartilage of the radiocarpal joint. Wrist flexion contracture can be treated with a variety of surgical techniques:

tendon lengthening can be carried out in various ways, through so-called Z-tendon lengthening, muscle slide (release of the muscle proximal insertion) or fractional lengthening. The latter is performed by single or multiple incision of the tendon in its intramuscular course. In most cases, it is necessary to lengthen multiple tendons of the wrist and finger flexors. Sometimes the extensor tendons contribute to wrist flexion deformity, e.g., extensor carpi ulnaris and/or abductor pollicis longus can flex the wrist in cases of concomitant severe pronation deformity of the forearm.

tenotomy means cutting the tendon. The cut tendon can be left or moved and sutured to another place, so-called transferred.

tendon transfer means moving the distally cut tendon to a different location and changing the function of a given muscle, e.g., flexor carpi ulnaris can be cut at the wrist level (pisiforme) and moved around the ulna dorsally to the extensor carpi radialis brevis and sutured to it (Green transfer). The flexor becomes an extensor by changing the passage and attachment of the tendon. The results of this transfer are uncertain and difficult to predict due to the varying quality of this not so uncommonly spastic muscle.

tenodesis- the elongated and weak tendons of the wrist extensors can be shortened which increases their static extension action.

carpectomy is a resection of the wrist's proximal row bones (scaphoid, lunate and triquetrum).

wrist arthrodesis is the fusion of the wrist with a plate and screws.

carpal tunnel release is recommended in cases of suspicion of nerve pain, caused by carpal tunnel syndrome. Due to the limited ability to communicate, information about this disease is difficult to obtain. Patients with carpal tunnel syndrome often protest when touched, they do not tolerate gloves or hygienic procedures and they do not tolerate the use of orthoses.

Treatment of external shoulder rotation deformity in patients with dyskinetic type of CP (DCP)

The patients with DCP suffer from involuntary movements which are particularly troublesome when they involve the muscles of the shoulder. Involuntary movements initiated in this area can cause voluminous movements of the entire UL. Sometimes they are so strong that they damage the ligaments, leading to joint instability and even damage to the cartilage of the joint. All of this can cause severe pain. Involuntary movements result from alternating activity of antagonistic muscle groups along the entire UL. Muscle activity varies with time and force and can change rapidly under the influence of a variety of stimuli, for example, sound. In some patients, one muscle group dominates others. One possible pattern is movement where external shoulder rotation is dominant. It is not known whether this is the result of pure involuntary movement or the result of a mixture of involuntary movement and persistent primitive reflexes. On top of this, there may be overlapping compensatory muscle activity consciously induced by the patient to reduce the force of movements beyond control. It seems that the patient who does not want to let her/his arm move uncontrollably, tightens other muscles over which she/he has some degree of control, which makes the entire UL difficult to move. Consequently, the number of muscles that can be used for any intended movement is diminished. This fact indirectly contributes to the low level of UL functionality. It is known that patients with DCP have a very high energy demand. This is because many of their muscles are in constant motion, and this requires a lot of energy. We can compare this effort to that of an athlete. Therefore, the patients with DCP are often simply tired. Positioning the shoulder in the external rotation cause the entire UL to be kept out of sight. When this pattern occurs in both UL, the hands cannot get close to each other, and any bimanual activity is impossible. Therefore, most of the patients with this kind of

problem have a severe impairment in UL function. It is possible to affect involuntary movement by using BoNT-A injections in the external rotator muscles of the shoulder: posterior deltoid, infraspinatus and teres minor. The aim of treatment is to reduce involuntary movement power by weakening of the muscular strength in the injected muscles. This treatment can improve the position of the UL, protects the joint from dislocation, although over-treatment may provoke joint instability. Sometimes there is improvement in the UL function or only pain reduction. Some patients notice improvement in their sitting position on a wheelchair, or it is easier to pass through the door, making it easier to dress or simply calming involuntary movements, which is felt as a relief. In a few of my patients with DCP, that were repeatedly treated with BoNT-A in the external rotators of the shoulder, I saw a loss of BoNT treatment effect over time or severe adverse events. Despite promising effects in the functional results, this made the BoNT-A treatment impossible to continue for these patients, forcing me to find some alternative treatment method. I decided to use **total selective peripheral neurectomy (SPN)**. Total SPN acts like BoNT-A; disrupting signals from nerve to the muscle we want to get rid of. Out of the three external rotators of the shoulder, I decided to totally denervate only one of them, namely the infraspinatus muscle which is the most powerful external rotator of the shoulder. Another reason for choosing the infraspinatus muscle, were anatomical conditions: the muscle is innervated by the terminal branch of the suprascapularis nerve which is easy to locate. Another advantage is the possibility of making a gap between the ends of the cut nerve using the natural barrier which is the acromion located nearby and thus avoid the possible regeneration and return of muscle innervation. Total SPN can even be compared to a tenotomy. In both techniques, we obtain elimination of the activity of the given muscle however in my opinion the advantage of SPN is the intactness of the muscle attachments provides a certain degree of stabilization (passive tenodesis) and reduces the risk of joint instability and its dislocation. To reach the infraspinatus nerve, tenotomy of the posterior deltoid muscle is required. In my observations the posterior deltoid release does not guarantee the complete lack of influence of this muscle on the external rotation of the shoulder. The results of infraspinatus denervation and release of the posterior deltoid muscle are presented in paper III.

AIMS OF THE THESIS

The overall aim of this thesis was to study different aspects of the assessment and treatment of the UL in patients with CP.

Specific Aims

Paper I

To describe the worked-out regime of long-term spasticity-reducing treatment applied in children with severe CP (GMFCS/MACS IV,V).

To investigate if implemented treatment improves mobility of the wrist and fingers and whether the age at treatment start affects treatment effectiveness.

To assess changes in hand function using House's functional classification assessment.

Paper II

To evaluate the questionnaire for collection of data on side effects and adverse events (AEs) after BoNT-A in patients with CP. Here, the second aim was to investigate the risk for side effects and AEs due to BoNT-A injection in the UL muscles.

Paper III

To present a surgical approach to perform denervation of the infraspinatus muscle.

To investigate the effects and usefulness of infraspinatus muscle denervation and posterior deltoid release in patients with DCP and external rotation pattern of shoulder.

Paper IV

To develop a new tool (CP-thumb score) for assessment of the thumb in the patients with CP. The second aim was to compare the new assessment with already existing House's thumb-in-palm classification.

HYPOTHESES OF THE STUDIES

Paper I

Spasticity-reducing treatments in combination with orthoses and movement training utilized by multidisciplinary team in Västerbotten habilitation service since 2001 prevent the development of wrist flexion deformities and promote the development of hand function in children with severe CP.

Paper II

The questionnaire facilitates the collection of information about side effects and AEs and can increase the safety of the BoNT-A treatment.

Paper III

The surgical denervation of the infraspinatus muscle combined with release of the posterior deltoid muscle improve position of the UL in cases of dyskinetic external shoulders rotation pattern and can improve quality of life in patients with DCP for whom treatment with BoNT-A is no longer available.

Paper IV

All types of thumb deformations in CP can be easy accessed by occupational therapist using CP-thumb score.

MATERIALS AND METHODS

PAPER I

This is a retrospective review of changes in passive wrist extension with fingers extended (PWE-FE) and changes in hand function in the patients with severe CP (GMFCS/MACS IV-V) and bilateral very limited hand function (House 0-1) who had access to worked-out treatment regime consist of BoNT-A intramuscular injections, orthosis and movement training used since 2001 by multidisciplinary team in Västerbotten county habilitation service. Detailed information on applied interventions such as: BoNT injections in the muscle affecting wrist/fingers flexion, the type of hand orthosis prescribed and its use, passive movement training, and hand surgical procedures were collected. All information was extracted from medical records or from CPUP register. PWE-FE measurements values were collected according to the CPUP “traffic light system” where red correspond to value $\leq -20^\circ$ which is major impaired (critical), yellow correspond to value $> -20^\circ$ to $< 60^\circ$ moderate impaired (intermediate) and green $\geq 60^\circ$ which is normal value.

Participants in paper I

Twenty-nine children fulfilled inclusions criteria. The final study group comprised of 25 children (16 with BSCP, 7 with DCP, 2 with MIX CP) who gave consent to participate in the study. They were divided into 3 groups depending on the age they received the first BoNT-A treatment and/or other intervention in the wrist/finger flexors and/or forearm pronators. Group 1 (7 patients) received full therapy according to the regime worked out ≤ 7 years age. In group 2 (10 patients) participants who, for various reasons, could not be fully treated according to the worked-out regime and received BoNT-A treatment after the age of 7. Group 3 (8 patients) included participants born before 1996, i.e., at least 6 years before the introduction of the worked-out regime, which consequently means that they did not have a chance to benefit from therapy in early childhood (**Table 6, 7**).

Participant	First BoNT-A upper-limb (age)	CP diagnosis	GMFCS (level)	MACS (level)	House* R/L
Group 1					
C1.1 [†]	7y	BSCP	5	5	0/0
C2.1	2y 2m	BSCP	4	4	5/5
C3.1	4 y 6m	DCP	5	5	2/2
C4.1	6 y 8 m	BSCP	5	4	2/3
C5.1	3 y 10 m	BSCP	5	5	2/2
C6.1	2 y 2 m	BSCP	5	5	0/0
C7.1	1 y 5 m	BSCP	5	5	0/1
Group 2					
C1.2 [†]	-	BSCP	5	5	0/0
C2.2 [†]	-	DCP	5	5	1/1
C3.2	21y 6m	BSCP	5	5	0/0
C4.2	7 y 9 m	DCP	5	5	0/0
C5.2	14 y 7 m	DCP	5	5	2/2
C6.2	12 y 6 m	BSCP	5	5	0/0
C7.2	10 y	BSCP	5	5	0/0
C8.2	-	Mix CP	5	5	2/2
C9.2	-	BSCP	5	5	3/1
C10.2 [†]	-	DCP	5	5	2/1
Group 3					
C1.3 [†]	-	BSCP	5	5	0/0
C2.3	16 y	BSCP	5	5	0/0
C3.3	13 y	DCP	4	4	0/1
C4.3	15 y	BSCP	5	5	0/0
C5.3	23 y	Mix CP	5	5	0/0
C6.3 [†]	17 y	BSCP	5	5	1/0
C7.3	-	DCP	5	5	0/1
C8.3	-	BSCP	5	5	0/0

*House level denotes hand function **at last** measurement occasion, not initial hand function level at first team visit.

Table 6. Participant Characterization for the Respective Groups, paper I

Group (N)	First PWE-EF measure <i>mean age</i>	Last PWE-EF measure <i>mean age</i>	PWE-EF measures <i>mean number</i>	First BoNT treatment <i>mean age</i>	Patients treated with BoNT <i>N (%)</i>	BoNT Treatments number <i>Range (mean)</i>	Patients treated with orthoses/ passive movement training <i>N</i>	Patients treated with hand surgery <i>N (age range)</i>
1 (7)	4,3	14,5	22,3	3,9	7 (100)	6-26 (14,6)	7/7	2 (13-14)
2 (10)	5,9	13,4	6,5	12,9	5 (50)	4-9 (5,2)	7/10	2 (12-13)
3 (8)	13,1	19,3	10,5	17	5 (62,5)	3-20 (10,8)	8/8	5 (14-21)
(Total 25)					17		22/23	9

Table 7. Assessment and treatment in respective groups

PAPER II

This is a prospective data collection. The incidence of AEs and side effects after BoNT treatment in the UL or UL and lower limb in patients with CP were collected using a novel, not previously validated questionnaire (**Figure 1**). Patients/caregivers were given the questionnaire with an enclosed pre-stamped envelope directly after the BoNT-A treatment. They were informed about the aim of study and were instructed how to fill it. If no posted answer was received at 4 weeks after treatment, a reminder was sent by letter. All answers, comments and missing answers were discussed at the follow-up visit 1-3 months after BoNT-A treatment. All reported AEs and sides effect were divided into two subgroups depending on the severity of the health consequences:

- 1). generalized and focal distant
- 2). focal local and procedural.

Otherwise, the following information was collected: level of motor impairment (GMFCS), age, gender, body weight, total dose and type of used BoNT-A (BOTOX or DYSPORT), number of treated body parts.

Seventy-nine patients with CP were in total treated 123 times with BoNT-A in the UL or UL and lower extremities in the Hand and Plastic Surgery department in Umeå from February 2010 to May 2011 and all received the questionnaire. Hundred five (85%) questionnaires were returned from 74 (94%) patients. Three patients were treated 3 times and filled out the questionnaire 3 times, 25 patients 2 times and 46 only once. Participants were grouped according to level of motor impairment (GMFCS level IV-V, with GMFCS I-III), gender (F/M), age (<10y/≥10y), body weight (<45kg/≥45kg), BoNT-A total dose by treatment (<400U/≥400U for BOTOX, respective <800U/≥800U for DYSPORT), BoNT-A dose/body weight by treatment (<10U/≥10U for BOTOX respective <20/≥20 for DYSPORT) and number of treated body parts (<6/≥6).

BOTULINUM TOXIN TREATMENT ADVERSE EVENTS REPORT

DATE OF BIRTH _____ NAME _____ WEIGHT _____

CARE UNIT _____ DATE OF TREATMENT _____ PHYSICIAN _____

DRUG _____ TOTAL DOSE _____ TREATED LIMB _____

We ask that the carer to the above-mentioned patient help us gather information on side effects of botulinum toxin treatment. This form should be completed within 2-4 weeks after the treatment and submitted no later than 4 weeks after treatment in the enclosed stamped envelope to our department. Please note if any of the following symptoms have occurred, they may have been associated with botulinum toxin treatment (mark X for each question).

SYMPTOMS	NO	YES	IF "YES" PLEASE COMMENT
GENERAL WEAKNESS			
FATIGUE			
FLU LIKE SYMPTOMS			
PNEUMONIA			
BREATHING DIFFICULTIES			
SWALLOWING DIFFICULTIES			
SPEECH DIFFICULTIES			
DRY MOUTH			
DIARRHOEA			
URINARY INCONTINENCE			
LOCAL MUSCLE WEAKNESS			
PAIN			
ITCH			
RASH			
HEMATOMA ON INJECTION SITE			
OTHER SYMPTOMS			

If a serious health condition occurs and urgent treatment is required, ask the responsible care facility to contact us

Figure 1- Adverse events questionnaire.

Participants in paper II

74 patients with all types of CP (USCP 18, BSCP 38, DCP 16, MIX 2) and all CP degree (GMFCS I-III 28, IV-V 46) aged from 1.5 to 47.5 years (mean age 13.5 years, SD 7y 8m) finally participated in the study (**Table 8**).

<i>n</i>	<i>Sex (M:F)</i>	<i>Age (y:mo)</i>	<i>Weight (kg)</i>	<i>CP^a type</i>		<i>GMFCS^f</i>	
74	41:33	13:6 (SD 7:8)	37 (SD 20)	USCP	18		
				BSCP	38	I-III	28
				DYSK	16	IV-V	46
				MIX	2		

M: male; F: female; y: year; mo: months. CP: cerebral palsy; USCP: unilateral spastic cerebral palsy; BSCP: bilateral spastic cerebral palsy; DYSK CP: dyskinetic cerebral palsy; MIX CP: mixed type of cerebral palsy; GMFCS: Gross Motor Function Classification System.

Table 8: Characteristics of participants, paper II

PAPER III

This is a case series study with description of surgical approach, surgical technique of infraspinatus muscle denervation and posterior deltoid muscle release which were made in the patients with DCP with external rotation pattern of shoulders. All had previously been treated with BoNT-A injections in external shoulder rotators with improvement. In all, BoNT-A treatment could not be continued because the loss of treatment effect or sides effects caused by BoNT-A. Pre- and postoperative video-recordings and patient satisfaction questionnaire were used minimum 6 months after surgery as outcome measurements. Additionally, in one patient the AHA could be used to assess the outcome.

Participants in paper III

Six patients with DCP (5 female), ages 14-24 years participated in the study. Five of them had Dystonic subtype of DCP and GMFSC/MACS IV-V levels and one had choreo-athetotic subtype of DCP and GMFCS II and MACS III levels (**Table 9**).

Patient No.	Type of DCP	GMFCS	MACS	House R/L	Oral Baclofen	ITB	Previous Orthopedic Intervention	No. of BTX-A before shoulder surgery
1	Dystonic	IV	IV	1/4	No	No	S, H	12
2	Dystonic	IV	IV	2/4	Yes	Yes	S	30
3	Choreoathetoid	II	III	2/4	No	No	—	3
4	Dystonic	IV	V	1/0	No	Yes	S, H	9
5	Dystonic	IV	V	0/4	No	No	M	7
6	Dystonic	V	V	0/0	Yes	Yes	Rh	10

House = House's functional classification system; S = scoliosis surgery; H = hip surgery; M = multilevel surgery in the lower limbs; Rh = radial head resection.

Table 9. Clinical characteristics of the patients, paper III

PAPER IV

Paper IV presents a new instrument called CP-thumb score for assessing the thumb in the patients with CP. The CP-thumb score had two parts (**figure 2**). The first is descriptive and requires answer (yes, no or can't be assessed) to four questions. This should be done by the examiner after observing the thumb during activity. The second part is a score of the thumb's CMC joint radial abduction movement. Active radial abduction is expressed by number 1-4 and passive radial abduction is expressed by letter A-D. The result of score called radial abduction score consist of the combination of the number and the letter that corresponds the specified radial abduction value of the thumb in degrees.

The results of thumb assessment using the CP-thumb score were presented and compared with House's thumb-in-palm classification. All thumbs' assessments were performed on patients whose hands were previously videotaped during another assessment and available in medical documentation. All assessments were done together at the same time by one OT and one hand surgeon.

Part 1 CP-thumb, descriptive	Right			Left		
<i>Assessment during activity</i>	Yes	No	Can't be assessed	Yes	No	Can't be assessed
Signs of thumb-in palm can be observed						
Hyperextension of MCP-joint can be observed						
Hyperextension of IP-joint can be observed						
Can actively move IP-joint while MP-joint is stabilized.						
Comment:						

Part 2 CP-thumb CMC-joint radial abduction	Right		Left	
Active radial abduction				
1) Active radial abduction >45°				
2) Active radial abduction 45°-30°				
3) Active radial abduction <30°				
4) Active radial abduction can't be observed				
Active radial abduction can't be assessed				
Passive radial abduction				
A) Passive radial abduction >45°				
B) Passive radial abduction 45°-30°				
C) Passive radial abduction <30°				
D) Passive radial abduction can't be observed				
Comment:				
Radial abduction score:				
(Number (1-4) for active and letter (A-D) for passive radial abduction)	_____	_____	_____	_____
	Active	Passive	Active	Passive

Figure 2: CP-thumb score

Participants in paper IV

19 patients with all types of CP (USCP 7, BSCP 5, DCP 5, Mixed CP 2) and all MACS degree (MACS I-1, II-6, III-3, IV-5, V-4), ages 1.5-45 years and different impairment of hand function (House 0-7) were selected for the study (**Table 10**). Eight thumbs from hands not impaired (House 8) were excluded resulting in analysis of a final number of 30 thumb assessments.

<i>N</i>	<i>CP type</i>	<i>GENDER</i>	<i>AGE (y)</i>	<i>GMFCS</i>	<i>MACS</i>	<i>HOUSE R/L</i>
1	USCP	M	1,5	3	3	3/8
2	USCP	M	2	2	2	8/2
3	USCP	M	5	1	2	8/5
4	USCP	F	7	2	1	6/8
5	USCP	F	9	1	2	4/8
6	USCP	M	9	1	2	5/8
7	USCP	F	19	1	2	8/7
8	BSCP	F	5	4	4	5/2
9	BSCP	F	7	4	4	5/2
10	BSCP	F	8	5	4	5/4
11	BSCP	M	13	5	5	0/1
12	BSCP	M	45	4	5	2/2
13	DCP	M	7	4	4	1/2
14	DCP	F	9	5	4	3/2
15	DCP	M	11	1	2	6/7
16	DCP	F	18	5	5	2/2
17	DCP	F	24	5	5	3/4
18	MIX CP	M	13	2	3	5/4
19	MIX CP	M	17	2	3	3/8

USCP- Unilateral Spastic Cerebral Palsy, BSCP-Bilateral Spastic Cerebral palsy,
DCP- Dyskinetic Cerebral Palsy, MIX CP- Mixed form of Cerebral Palsy
F-female, M- male, Y- age in years, GMFCS-Gross Motor Function Classification
System, MACS-Manual Ability Classification System, House-House's functional classification
system, R-right, L-left

Table 10. Participant's description, paper IV

ETHICAL CONSIDERATIONS

Paper I

The study was approved by the Umeå Regional Ethical Board (Dnr 2015–228–31M) and conducted in accordance with the Declaration of Helsinki. All parents and children who 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 and is reported so that individual children cannot reasonably be identified.

Paper II

All patients and caregivers had given informed consent. The Regional Ethical Review Board of Umeå, Sweden, approved the study (Dnr 2013-386-31).

Paper III

All patients/parents signed an informed consent form for participation. The Swedish Ethical Review Board approved the study (Dnr 2013-34-31M)

Paper IV

The Regional Ethical Review Board of Stockholm, Sweden, approved the study (Dnr 2018/1464-31)

STATISTICAL ANALYSIS

Paper I

Analyses of group differences regarding background data were carried out by ANOVA, with follow-up t-tests, or chi-square analyses. Differences of the distribution of PWE-FE value between groups were analyzed using Chi-square test. Analyses of group differences in hand function were carried out by using Kruskal-Wallis test, with follow-up Mann-Whitney U tests.

Paper II

SPSS Statistics 18 were used to analyze the collected data. Incidence of AEs and side effects are presents as risk, odds ratio, 95%CI and p value.

Paper III

not applicable

Paper IV

not applicable

RESULTS

PAPER I

The following finding were found in paper I

Significant differences was found regarding values for PWE-FE (right wrist: $\chi^2 = 62.3$, $p < 0.001$; left wrist: $\chi^2 = 62.7$, $p < 0.001$) in the Group 3 where more frequently, critical (red) and less normal (green) values of PWE-FE measurements was noted that in the groups 1 and 2 (**Figure 3**).

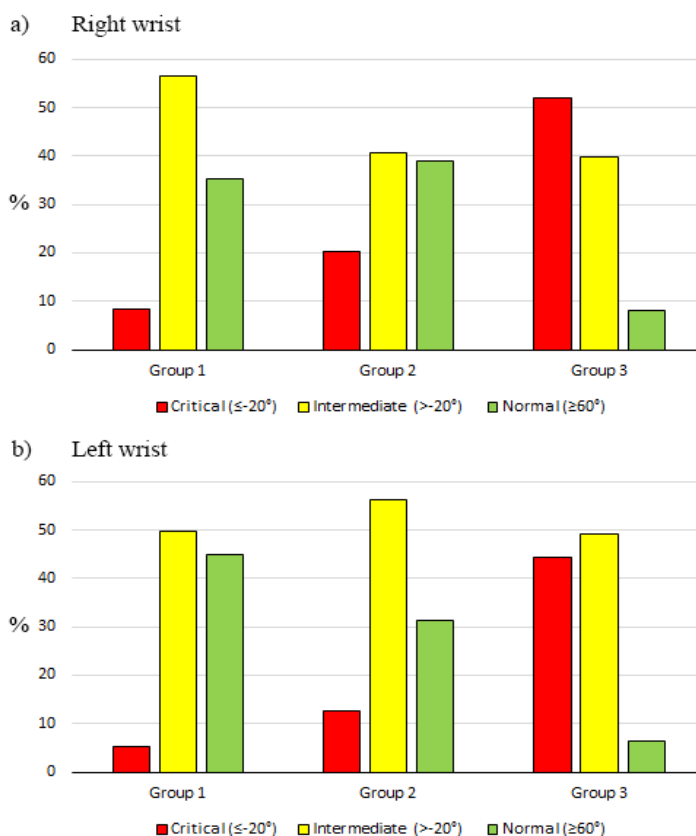


Figure 3. Frequency of critical to normal values for PWE-FE as a function of group for the right (a) and left (b) wrist.

Comparing mean PWE-FE data (mean changes in degrees between first versus last measurement occasion) for the groups suggest improvement in wrist movement for group 1, slight decrease in wrist movement for group 2 and no evident changes for group 3 (**Figure 4**).

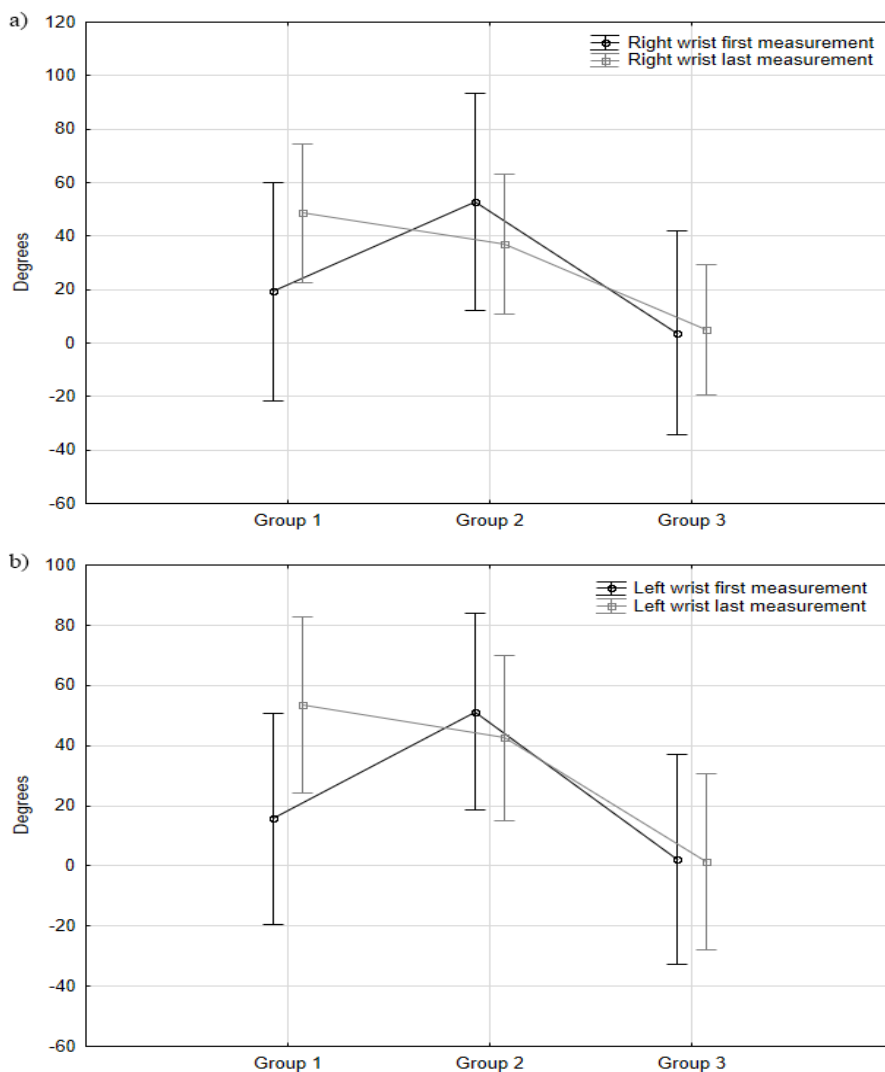


Figure 4. Mean group values for PWE-FE at the first and last measurement occasion for the right (a) and left (b) wrist.

Comparison of mean PWE-FE data for group 1, last measurement occasion (mean age=14.5y, SD=2.9) and group 3, first measurement occasion (mean age =13.6y, SD=2.1), showed a significant difference for the left wrist ($F(1,12) = 8.18, P < 0.05$) and near significant difference for the right wrist ($F(1,13) = 4.29, p = 0.059$). It shows that at a comparable age, group 1 had better PWE-FE value than group 3.

In group 1, major oscillations in PWE-FE value were noted. The positive changes were often associated with BoNT-A treatment or after received hand surgery. On the other hand, negative changes in PWE-FE were associated with the disappearance of the BoNT-A effect (see example in **Figure 5**).

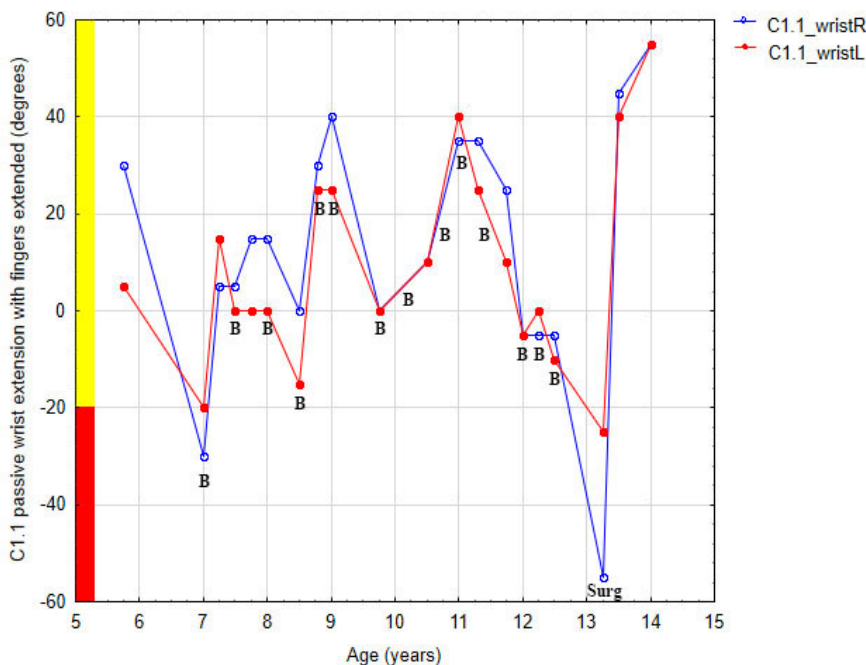


Figure 5. Changes in PWE-FE associated with BoNT-A treatment or surgery (patient C1.1.).

Regarding hand function, significant difference was found in follow-up testing for left hand House functional classification between group 1 and 3 ($U = 11.0$, $p < 0.05$ (**Figure 6**).

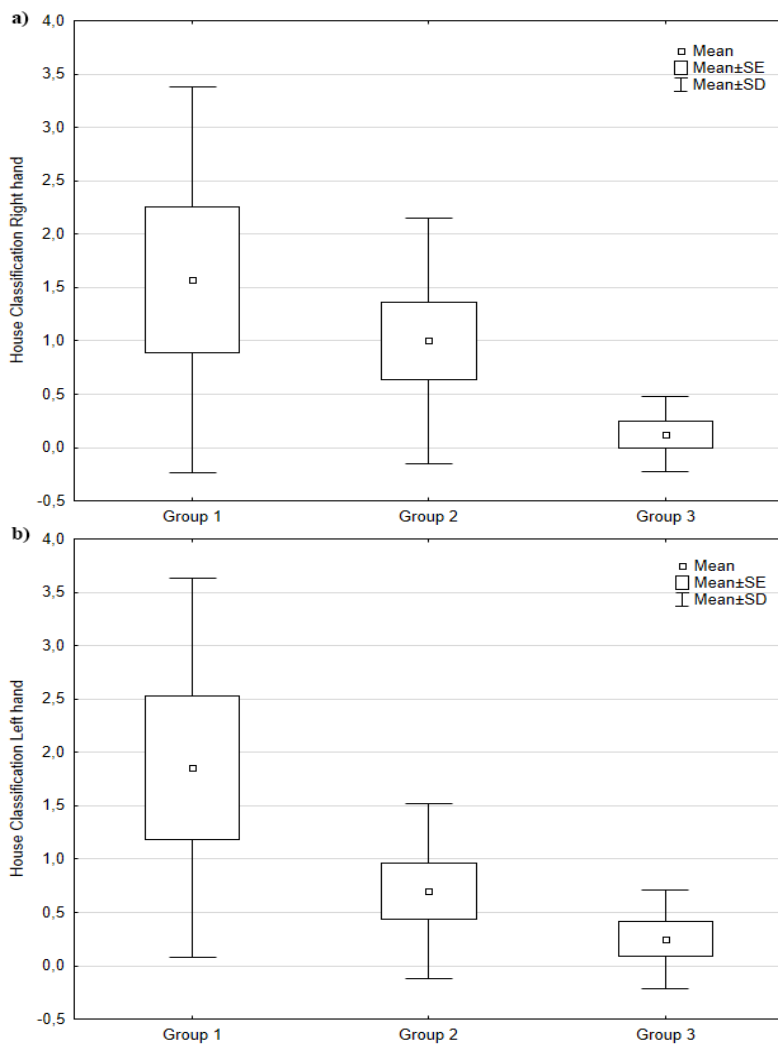


Figure 6. Box plots showing the mean House functional classification at the last measurement occasion as a function of group for the right (a) and left (b) hand.

Significant differences ($F(2,22) = 16.78$, $p < 0.001$) was found between the groups according to age in which children's UL were assessed by multidisciplinary UL-CP-team. For Group 1 mean age of first assessment was 3.2 years, (SD = 1.8), for Group 2 it was 6.4 years, (SD = 4.6) and for Group 3 it was 13.3 years (SD = 2.9).

Significant differences ($F(2,22) = 5.78$, $p = 0.01$) was found for age when first receiving orthoses. Participants in group 3 received orthosis significantly later (mean age = 13.8 y, SD = 4.5) than group 1 (mean age = 4.9 y, SD = 5.6) or group 2 (mean age = 9 y, SD = 5.2).

The other finding according to the use of orthosis was that generally the patients with DCP received their orthosis significantly later (mean age = 13.9 y) than the participants with BSCP (mean age = 7.4 y), $t = 2.64$, $p = 0.02$.

A greater but not significant amount of repeated hand surgical procedures was noted in Group 3.

PAPER II

Participation and deficiencies in the optimal completion of the questionnaire.

There was a high percentage of participation in the study. 94% of participants (74 of 79) returned 85% of used questionnaires (105 of 123). Some patients participated in the study several times (max 3 times). Only 16 of 74 returned after a reminder letter. Eighty-four of 105 were filled in completely and of them 33 without any observed side effects or AEs. Only 53 answers were missing in 21 questionnaires. Twenty-seven of 53 missing answers concerned speech disorders and urinary incontinence problems. It turned out that the lack of answers to these questions was because these patients either had no speaking skills or were using diapers and therefore it was not possible to observe changes in these functions. All the other missing answers resulted from the caregivers' uncertainty and were discussed with them during follow-up visit 1-3 months after treatment.

Collecting information about AEs and side effects with help of a questionnaire.

The main observation of paper II was that the use of the questionnaire by the patient or caregiver to capture AEs and side effects following BoNT-A treatment helps to ensure that they were not overlooked. The reporting of AEs and side effect was greater than expected. Forty-five patients (61%) reported 95 AEs and side effects after 54 (51%) of BoNT-A treatments. Of these 50 (53%) belonged to the generalized (systemic) and focal distant AEs. All results are presented in **Table 11**.

Adverse Event's Type (n)	n (%) AEs	n (%) * Treatments	n (%)** Patients	n (%) Female	n(%) Male
All adverse events	95 (100)	54 (51)	45 (61)	21 (64)	24 (59)
<u>Generalized (systemic) adverse events (26):</u> generalized muscle weakness (18), fatigue (3), flu-like symptoms (5) <u>Focal distant adverse events (24):</u> swallowing troubles (5), speech disorders (3), dry mouth (4), drooling (2), respiratory troubles (2), pneumonia (1), diarrhoea (1), nosebleeds (2), hot flashes (1), urinary incontinence (3)	45 (47)	33 (31)	28 (38)	17 (51)	11 (27)
<u>Focal local adverse events (22):</u> local muscle weakness (15), pain at the site of injection (3), itching (1), rush (1), swelling at injection site (1), cold hands (1) <u>Procedural adverse events (23):</u> bruising (19), leakage (2), no effect of treatment (2)		30 (29)	27 (37)	12 (36)	15 (37)

AEs, adverse events. * % of all 105 treatments, ** % of all 74 participants

Table 11. Incidence of adverse events (number of treatments=105, number of patients=74, F/M=33:41)

Association of AEs and side effects with different variable (Table 12)

The second observation was the significant associations ($p = 0.029$) in the reported frequency of generalized (systemic) and focal distant AEs with gender. Female had 1.899 ($p=0.029$) relative risk (Rr) of reporting AEs compared to males. We also found a trend of association to total used dose of BoNT-A per treatment ($Rr=1.65$, $p= 0.095$). We did not find any association with body weight, number of treated body parts, GMFCS level, age or used BoNT-A dose by body weight.

Variable	Odds ratio	<i>p</i> -value	95% CI	Relative risk	95% CI
Gender: F/M	2.564	0.029	1.101-5.973	1.899	1.060-3.400
Total dose (U): ≥400/<400	2.171	0.095	0.875-5.390	1.651	0.945-2.885
Body weight (kg): ≥45/<45	1.662	0.285	0.654-4.223	1.432	0.725-2.831
Number of treated body parts (n): ≥6/<6	1.214	0.667	0.501-2.940	1.141	0.631-2.063
GMFCS level: IV-V/I-III	1.080	0.866	0.442-2.636	1.054	0.568-1.955
Age (y): ≥10/<10	0.975	0.952	0.424-2.242	0.982	0.554-1.741
Dose (U/kg): ≥10/<10	0.809	0.618	0.352-1.859	0.866	0.492-1.523

F: female; M: male; CI: confidence interval; GMFCS: Gross Motor Function Classification System.

Table 12. Risk for generalized and focal distant adverse events after BoNT-A treatment.

Consequences of the observed side effects on the future course of treatment

In 8 patients due to the reported AEs and side effects, a decision was made to change the plans for the next treatment. One patient was treated surgically due to the loss of BoNT-A effects, 4 patients had their treatments postponed and 2 had their dose reduced. In 3 patients, the AEs and side effects were found to be so serious that the risks associated with them outweighed the benefits of treatment. In two of these, respiratory problems were assessed as severe. The third patient had swallowing difficulties.

PAPER III

The results of infraspinatus muscle denervation in 6 patients with DCP are presented in paper III. In 5 of these patients, the posterior deltoid muscle was also released. In one patient, the procedure was performed on both sides.

Safety of surgical procedure

No early postoperative complications were observed in any of the patients. However, the patient who underwent bilateral surgery developed after a few months a complication in the form of an internal rotation pattern in one shoulder which needed to be treated with BoNT-A in the shoulder's internal rotators.

Satisfaction and subjective improvement

Five of six patients were very satisfied with the received treatment, one was neither satisfied nor dissatisfied. Five patients reported that their arm was more relaxed at rest. Four patients noticed improvement while passing through doors. Three patients reported an ease in reaching their mouth with the hand and improvement in performing bimanual tasks (**Table 13**).

Objective improvement

Four patients had obvious improvement in their shoulder position on the 1st postoperative day and this improvement was maintained and confirmed for a minimum of 6 months after surgery on video recordings.

In one patient with minor motor impairment (GMFCS III, MACS II) it was possible to use AHA as an outcome measurement. AHA result improved from 41 to 50 logit-based AHA units 6 months after surgery.

Outcome	Task	Patient No.					
		1	2	3	4	5	6
Questionnaire	Very satisfied	+	+	+	+	+	
	Neither satisfied nor dissatisfied						+
	Better reaching to the mouth	+	+	+			
	Relaxed arm at rest	+	+		+	+	+
	Easier dressing		+		+	+	
	Improved sitting balance		+		+		
	Improved passage through doors	+	+		+	+	
	Bimanual task improvement	+	+	+			
Video records	Improvement of shoulders position	+	+	+	+		

Table 13. Results of patient's satisfaction and video records

PAPER IV

The use of descriptive part of the CP-thumb score

It was easy to answer for the first three questions based on the available videos footages. The sign of thumb-in-palm was observed in 26 thumbs, hyperextension of MCP joint was observed in 3 and hyperextension of IP joint was observed in 19 thumbs. For the last, fourth question concerning the active movement skills of the IP joint, in 11 cases, feature was not captured in the available videos. In 15 thumbs this function was confirmed and in 4 it was absent.

The assessment of radial abduction score

It was easy to assess both the active and passive abduction of the thumb in the CMC joint in almost all patients, based on the available videos. Only in one case, the passive radial abduction was not possible to assess.

Comments

All noted comments were related to the occurrence of wrist tenodesis (wrist flexion) during activity. In all 8 cases where this was observed, the investigator noted that by flexing the wrist, the patient augments the thumb volar abduction at the CMC joint while grasping the objects. All patients who used wrist tenodesis had reduced active radial abduction of the thumb in the CMC joint.

Comparison of the two thumbs assessments: House's Thumb-in-palm classification (H-TIP) versus CP-thumb score.

The results of assessment of 30 thumbs in 19 patients with CP are presented in **Table 14**. All thumbs were assessed twice. Once with H-TIP and second with CP-thumb score. The thumbs assessments were grouped according to the H-TIP type 0-3.

H-TIP	CP-thumb score	<i>sign of thumb-in-palm</i>	<i>MCP joint hyper-extension</i>	<i>IP joint hyper-extension</i>	<i>IP joint active movement</i>	<i>HOUSE</i>	<i>Age (y)</i>	<i>N Side L or R</i>
0	1A	-	-	-	+	7	11	15L
0	1A	-	-	-	+	6	11	15R
0	1A	-	-	-	+	2	7	13L
0	2A	+	+	-	+	5	5	3L
0	3A	-	-	-	?	5	8	10R
1	2A	+	-	+	+	5	9	6R
1	2A	+	-	+	+	5	13	18R
1	3A	+	-	+	+	5	5	8R
1	3A	+	-	-	+	7	19	7L
1	4A	+	-	-	?	3	1	1R
1	4A	+	-	+	?	1	7	13R
1	2B	+	-	-	+	4	9	5R
1	3B	+	-	+	+	5	7	9R
1	4B	+	-	+	-	2	7	9L
1	4B	+	-	-	?	0	13	11R
1	4B	+	-	-	?	1	13	11L
1	4C	+	-	+	+	3	17	19R
2	3A	+	-	+	+	6	7	4R
2	3A	+	-	+	?	4	8	10L
2	4A	+	-	-	?	2	2	2L
2	2B	+	-	+	+	4	24	17L
3	3A	+	-	+	+	3	9	14R
3	4A	+	-	+	-	2	5	8L
3	4A	+	-	+	+	4	13	18L
3	4A	+	-	+	?	2	9	14L
3	4B	+	-	+	?	2	18	16R
3	4B	+	-	+	?	2	18	16L
3	4C	+	+	+	-	2	45	12R
3	4C	+	+	+	-	2	45	12L
3	4?	+	-	+	?	3	24	17R

Table 14. Results of thumb assessment with H-TIP and CP-thumb score.

Comparison of thumb assessment with H-TIP and with CP-thumb score shows the variety of obtained results. In all H-TIP groups there are different result of thumb assessment using CP-thumb score.

In type 0 according to H-TIP which means normal, healthy thumb, there are 3 healthy thumbs assessed similar by both tools (1A according to CP-thumb score), however, there are two thumbs in which assessment with CP thumb score indicated the reduction of active radial abduction in the thumbs CMC joint (2A, 3A). At the same time in one of these thumbs the sign of thumb-in-palm and MCP joint hyperextension were observed.

In the group 1 and 2 according to H-TIP all thumbs had reduction of active radial abduction in different degree (2-4) and in almost half of them the reduction of passive radial abduction (B-C) was observed according to CP-thumb score.

In type 3 according to H-TIP the active radial abduction was major limited (3-4), however, the passive radial abduction varies from normal (A) to major limited (C). Notably, all thumbs classified in this group showed hyperextension in the IP joint and only in two of them the presence of hyperextension in the MCP joint was seen. It is worth recalling that in type 3, according to H-TIP, hyperextension in the MCP joint is assumed.

The assessed group is too small for statistical analysis however some correlations seems to be observed. Reduction of active radial abduction is more impaired in the type 2-3 of H-TIP. It seems that reduction of passive radial abduction is more impaired (B-C) in the older patients with more limited hand function (under 5 according to the House functional classification).

DISCUSSION

PAPER I

Paper I presents results of repeated BoNT-A treatments over a long-lasting time period in the muscles of ULs combined with training and orthosis used in a group of patients, which is rarely the subject of research, namely children with severe CP (GMFCS IV-V, MACS IV-V) and very limited or absent hand function.

Contracture prevention

The main goal of the treatment was to preserve passive movement in the joints of the ULs. However, the results of treatments are present based on the results of preserved movement in the wrist and fingers expressed as PWE-EF. Our choice of this measurement for evaluation of treatment outcome was mainly due to availability in medical records. This does not mean that other muscles of the ULs were not treated at the same time, but the lack of a sufficient number of mobility values of other joints made it impossible to analyze them.

For the wrist, the aim of the treatment was to preserve the PWE-FE value within the “green” limits in the CPUP guidelines. Its deterioration indicates the development of flexion contracture of the wrist and/or fingers which may lead to pain, nerve compression, joint deformation and damage. Flexion contracture in the wrist and fingers may cause difficulties in performing hygienic procedures and negatively affect self-esteem for aesthetic reasons.

We compared the result of PWE-FE at the individual level and between groups. The study population was divided according to the age at which they received their first BoNT-A treatment. In patients from group 2 and 3 this possibility appeared after reaching the age of 7 or later. Group 3 includes children who were born at a time when BoNT-A therapy was not yet available before reaching the age of 7. Group 2 included children who, for other reasons also did not receive BoNT-A therapy before reaching the age of 7, even though it was available. Group 1 included children who received the first BoNT-A therapy before they reached the age of 7. Obtained results and their comparison between the groups suggest that the treatment used help to preserve PWE-EF value. Especially the

comparison of PWE-FE values, at same age of 14 years, between group 1 and 3 suggest a positive effect of starting the therapy in early age.

Surgical treatment

In most patients in Group 3, treatment with BoNT-A did not improve joint mobility, although in some cases it may have slightly slowed contracture development. In 5 cases we decided to go for surgical treatment. The aim of surgery was primarily to facilitate hygiene. In group 2, decision was made to surgically treat flexion contracture in the elbow in two patients. In group 1, surgical treatment was performed in two patients, in one case due to side effects after BoNT-A, and in one due to the inability to use the optimal dose of toxin in all muscles that required its use. However, the results of surgical treatment are not the subject of this paper since the small number and the variety of used surgical procedures do not allow for this to be analysed.

Hand function

At the time of first UL assessment, all patients had no observable hand function and only some patients had preserved hand function at level 1 according to House functional classification. It is believed that the position and mobility of the wrist play a key role in the effectiveness and ability of the hand to perform a grip (Eliasson 1998). Hand function has never been the primary subject of treatment in the presented population. Nevertheless, a pleasant surprise was that some of the children in group 1 showed improvement in hand function. Of course, when the appearance of the function was observed, the treatment goals were modified and activities improving the function were intensified to further support its development. Even if the statistical analysis did not show significance, it should be remembered that at the level of the individual, the difference between not using the hand at all and using it at the level of 1 or 2 according to House functional classification is of great importance and makes a big difference in everyday life. For example, in some cases, this meant gaining the ability to press a button and thus being able to communicate or be able to steer specially designed, easy-to-navigate devices such as the versatile mobility platform (Akka Smart). This ability developed in two children in group 1, aged 11 and 13. Two other children from group 1 developed the ability to move around with a powered wheelchair.

For comparison, in group 3, five out of eight participants had no hand function, and in group 1, only two of seven. In addition to improving the functions, caregivers paid attention to signs of reduced pain, facilitating hygienic activities, improving the aesthetic appearance and reducing the burden on caregivers.

Problems with the use of long-term therapy

The use of complex and long-term therapy in children with major motor impairment of CP often encountered many difficulties in its proper course and performance. These difficulties could have a significant impact on the final effects of the treatment. For example, delays in BoNT-A injection, and periodic cessation of the use of orthoses or training during the period when the patient was undergoing other difficult treatments such as scoliosis surgery or hip surgery. Other are the limitations resulting from the maximum recommended dose of toxin by treatment, which in some cases could mean the abandonment of treatment of some muscle groups or the use of too low dose, so the expected treatment result could not be sufficient.

Another important aspect is the need for systematic control of the mobility of the joints in the UL in patients with CP. Registration and analysis of regular measurements provides a chance to intervene in time. Good long-term communication and cooperation between the habilitation team and caregivers are crucial for the success of treatment.

Limitation

The main drawback of the work is the rather small and non-homogeneous population despite the strictly established criteria, which were GMFCS MACS and the primary lack or very low (max 1 according to House) level of hand function. The small size of the group is due to the small number of patients with this type of injury in our region. The non-homogeneity results, among others, from the inclusion of patients with two types of CP, BSCP and DCP. This has great consequences, considering that these two groups differ significantly in terms of the mechanism and time of the formation of contractures. In patients with DCP, limitation of joint mobility is observed at an older age (Hedberg-Graff 2019). This fact, previously reported by other researchers, is confirmed in this work.

Also, impairment of hand function in patients with DCP result from different mechanisms than in patients with BSCP.

In BSCP, the dominant symptom is hyper-resistance, increased muscle tone responding to stretching while in DCP the dominant symptom is dyskinesia, variability of muscle tone in different muscle groups, independent of stretching observed as involuntary movements. Another problem is the correct diagnosis of the CP type. The criteria for diagnosis are strictly defined, however, in practice, we cannot exclude that some patients may experience a compilation of both types, i.e., a mixture of hyper-resistance and dyskinesia.

Treatment with orthoses was used at a later age in patients with DCP than in patients with BSCP. There are several reasons for this. First, in early childhood, limitations in joint mobility are not observed, and second, the use of orthoses in people with involuntary movements is associated with a significant risk of complications in the form of abrasions and skin damage due to frequent rubbing.

An additional problem is the different goals of treatment in the patients with DCP than in patients with BSCP. In the case of BSCP, the aim of treatment is to reduce the tone of muscles and thus to facilitate the implementation of stretching and the use of orthosis. Under favorable circumstances, reducing muscle tone in treated muscles may favor the development of function in weak antagonistic muscles. In the case of DCP, the goal of BoNT-A treatment is to reduce the force of the involuntary movements, making them less expressive and less strenuous. The muscles of DCP patients are often well developed as they are in constant motion. The most common wish of DCP patients is that their ULs stop moving and lay still.

Another limitation of paper I is the division into groups according to the age of starting BoNT-A treatment. Despite this, there are significant differences between and within groups in term of age, training program, BoNT-A injections sites, amount, dose and intervals, the presence of co-interventions such as baclofen therapy or surgery of other body part. Therefore, the presented results should be approached with great caution. We cannot be sure that the used treatment was the only and most significant factor influencing the achieved results.

Paper I is primarily descriptive, presenting the way of working and efforts to maintain the mobility of the joints of the hand, although I emphasize that other joints were also treated simultaneously. Due to the lack of sufficient data in medical records, it was impossible to analyze changes in whole ULs. More complete data would help to create a wider picture and thus a better paper. However, I consider the work to be important given the presentation of many years of experience in working with patients with most severe CP and multiple disabilities.

PAPER II

Questionnaire

The use of the questionnaire we created to capture incidence of AEs and side effects after BoNT-A treatment turned out to be effective. A large percentage (85%) of responses as well as the lack of resignation from the proposed treatment after providing information about possible side effects is a confirmation of its usefulness. In 21 (20%) of the questionnaires 53 questions were not answered, 50% of missing answers concerned two questions. This was mainly due to the caregivers' uncertainty about how to answer the question concerning symptoms that already existed in the patients before treatment. This proves that the questionnaire is not optimal and need to be validated.

Sides effect and AEs

The reported number of AEs and side effects turned out to be greater than assumed (Bakheit 2001, Naidu 2010). We believe that it is due to the method of collecting data using prospective, active surveillance of harm, therefore it is difficult to compare our results with other studies. All noted AEs were discussed during follow-up visit 1-3 months after treatment. A total of 61% of patients reported one or more AEs or side effects after BoNT-A treatment. In only 8 (11%) of them the AEs or side effects caused changes in future therapy. For 3 patents (4%), the treatment was discontinued and for 5 (7%) it was modified. The question is whether all the reporting of side effects took place and whether they were all reported. Unfortunately, it is not possible to measure this objectively. For instance, it is difficult to measure fatigue or to determine whether pneumonia was the result of BoNT-A treatment or the effect of endemicity in the patient's environment. Some of the side effects may have been ignored due to the

lack of evaluation, e.g., worsening of urinary incontinence in patients using diapers or deterioration of swallowing in a patient who is fed through gastrostomy. All reported side effects and AEs were divided into two main groups. The first group, systemic and focal distant, are those that may indicate the spread of BoNT-A toxin to the whole body. The second group consisted of focal local and procedural side effects and AEs. The spread of BoNT-A beyond the treatment area is generally not desired and therefore we specifically focused on the analyses of AEs and side effect from the first group. Generalized weakness and/or fatigue (tiredness) were frequently reported side effect. caused by systemic spread of the toxin. In previous studies weakness was only assessed as a result of either fatigue in the treated muscles or toxin leakage to the adjacent muscles of the lower extremities (Bakheit 2001, Desloovere 2001). Only 2 out of 19 our patients experiencing these symptoms were ambulant and treated in the lower limb at the same time as the ULs.

We found almost 2 times higher incidence of generalized and focal distant AEs in female. This difference when compared to the male was significant (relative risk F/M 1.9, $p=0.029$). Only one previous study suggested similar correlation (Jankovic 1991). The reasons are unknown. We do not know if metabolism of BoNT-A is similar or not in female and male or if the quantitative differences in muscle mass or in number of nerve ends (targets for BoNT-A action) play a role. The study population addressed was small, and this may be the reason why we did not find any other associations which could explain our findings. The side effects and AEs that occur after the BoNT-A treatment have different health consequences for each patient therefore individual assessment is important. It seems that the exact number of complications is of less importance than their assessment and influence on further treatment. We have demonstrated that the use of a questionnaire about side effects and AEs increase the safety of the BoNT-A treatment in patients with CP.

PAPER III

There are not many treatment options of involuntary movements for the patients with DCP, which is evident by the fact that their physiopathology has not been fully explored. Pharmacological therapy acting on central nervous system such as levodopa, benzodiazepines or baclofen can be helpful. Intrathecal administration of Baclofen (ITB therapy) is assessed as helpful (Eek 2018). Neuromodulation with deep brain stimulation (DBS) is an option for treating dystonia, but patients with DCP can rarely be the beneficiaries. Different reasons make this treatment less effective than in other types of dystonia (Monbaliu 2017). Many patients with DCP have movement disorders other than dystonia alone or structural changes in the brain (basal ganglia). In addition, axial growth may cause displacement of implant in the brain. All these reasons significantly affect the effects of using DBS in them (Sanger 2019).

Treatment of involuntary movements by using BoNT-A is widely used. BoNT-A acts on the peripheral nervous system by causing a temporary chemodenervation in the treated muscle. Surgical cutting of the selected nerve causes permanent denervation of the selected muscle. Reports on the use of this method in patients with CP are sparse, and very few reports concern patients with DCP type (Maarrawi 2006, Sitthinamsuwan 2010, Puligopu 2011). The reduction of the effects of BoNT-A treatment or the occurrence of side effects after its use concerned, among others, patients whose goal of treatment was to weaken the strength of the external rotators of the shoulder. We decided to use surgical treatment that could cause a similar effect to the BoNT-A treatment. Surgical treatment consisted in reducing the external rotation of the shoulder through denervation of the infraspinatus muscle and release of the posterior deltoideus muscle. Both are powerful external rotators of the shoulder. The third muscle producing external rotation, the teres minor muscle, was left untouched. The procedure was performed in 6 patients, in one of them on both sides.

One of the most important challenges was the evaluation of the treatment effect. Unfortunately, there was no reliable assessment for involuntary movements in selected parts of the upper limb in the patients with very limited hand function, so we had to assess the effect of surgical treatment based on postoperative satisfaction questionnaire and video records.

However, in one of the patients with preserved bimanual task ability it was possible to use AHA.

Evaluation of video recordings showed improvement in the shoulder position in 4 out of 6 patients. The observed changes were described as dramatic. They were noticeable already on the first postoperative day and persisted in all patients during the entire follow-up period (6-36 months). Five of the 6 patients were very satisfied with the result. Five noted the UL was relaxed at rest and 4 saw improvement on passage through doors. Three felt it easier to get dressed. Three noted easier to reach the mouth with hand and perform bimanual task. Only one patient did not notice significant changes (see Table 11). In one case, there was a complication in the form of overcorrection and the tendency of the shoulder to position in internal rotation. This condition was successfully treated with BoNT-A injections in the pectoralis muscle and the latissimus dorsi muscle which both internally rotate the shoulder. The same patient had multiple incidents of shoulder dislocation prior the surgical treatment and often reported shoulder pain. Earlier intensively BoNT-A injections and two attempts of DBS treatment had been unsuccessful. The neurotomy created an opportunity to perform an open stabilization and at the same time, the pectoralis muscle was released to correct internal rotation pattern observed after the first surgery. Unfortunately, earlier frequent incidents of shoulder dislocation led to the development of degenerative changes in the humeral head, which were the cause of recurring significant pain complaints despite the good stabilization of the shoulder. For this reason, a few years after the shoulder stabilization surgery, it was necessary to remove the damaged head of the humerus. After this treatment, the pain disappeared. It is possible that earlier denervation and release of the muscles rotating the shoulder performed before the incidents of shoulder dislocation, could have prevented the destruction of the articular surface of the humeral head, and all subsequent complications could thus have been avoided.

The presented surgical denervation of the infraspinatus muscle combined with release of the posterior deltoid muscle can solve the local problem of shoulder external rotation pattern in a very special group of patients with DCP. Its use should be preceded by a carefully analysis and, in our opinion, only in a situation where other treatment methods do not give the expected results. Preoperatively, we could not determine to what

extent each of the 3 external rotators affected the external rotation pattern for each patient. This is one of the limitations with this technique. An option is to start the surgical treatment with posterior deltoid release, and only in the case of insufficient effect perform complementary infraspinatus muscle denervation as a second procedure. Although one could argue that the study population was small and there are big differences between patients, we consider the effects as robust. In some cases, the intensity of involuntary movements was asymmetrical and mainly related to one UL, in others the changes affected symmetrically both ULs. In one patient, a transient positive effect was observed in the untreated UL. However, after a few years, results of repeated assessments changed, and a significantly better control and position of the surgically treated UL was noticed. Therefore, a decision was made to perform the same procedure on the other side and a significant improvement was achieved. We can speculate that after surgery, reduction of involuntary movements in the treated limb, released some of the potential for better control of the non-operated limb. In turn, this patient opened the possibility of better use of the hand in the treated limb, which in turn contributed to a change of priority where to direct the effort and therefore our and patient's assessment that the previously noticeable effect of improvement disappeared. There is also a possibility that the treated side improved so much that over time the difference between the treated and untreated side turned out to be significant.

Another difference is the number and distribution of the muscle groups responsible for involuntary movements. In some patients there were significant involuntary movements of the fingers and wrist beyond the shoulder girdle, in others they were more pronounced in the elbow joints and pronation-supination movement of the forearm. One of the patients had choreoathetosis whereas the others had dystonia.

The improvement in UL position and improved quality of life, encourage the use of the presented surgical treatment in selected cases where other treatment methods do not bring the expected improvement.

A better method of assessing involuntary movements, specific for individual segments of the UL, would help in better assessing the effects of surgical treatment. Currently available assessment methods, such as dyskinesia impairment scale (DIS), require the patient to be able to grasp

and manipulate the object in the hand. Unfortunately, this function was absent in majority of patients in our group.

PAPER IV

Lack of reliable thumb assessment was an impulse to create the CP-thumb score. The shape and form have been designed to be suitable to be used by medical staff who do not have detailed knowledge about the action of all muscles responsible for moving the thumb's joints. The thumb assessment using CP-thumb score is cheap, not time-consuming, does not require any apparatus, and it can even be performed based on video recording of the hand grip function.

We performed the pilot study to test if it is easy and possible to assess the thumb in all people with different type and level of CP impairment using CP-thumb score. In addition, we assessed all thumbs with the previously used H-TIP classification for comparison. We judged that it was easy to use the CP-thumb score in all cases. It seems that compared to the H-TIP, the CP-thumb score can capture small changes in the active and passive movement of the thumb's joints at an early stage. In a few cases we had difficulties in correctly assessing the thumb's MCP joint hyperextension using the H-TIP classification. This is in line with earlier reports of unreliability and difficulties in its application even by people with extensive experience in assessing patients with CP (Smeulders 2005, Glaas 2017).

The central part of the CP-thumb score is the assessment of impaired radial abduction of the thumb's CMC joint. Reduction of radial abduction in the CMC joint lead to the development of severe thumb deformity characterized by CMC adduction contracture, MCP joint hyperextension or MCP flexion contracture. The early detection of changes may initiate interventions to promote radial thumb abduction. The aim of almost all used interventions for CP thumb treatment is to augment the thumbs radial abduction such as thumb splints, botulinum toxin in the adductor and thumb flexor muscles or surgical release and different muscle transfers. Therefore, the surveil of radial abduction of the thumb seems most justified.

One of the interesting observations seen in some of the patients was the use of wrist flexion tenodesis and the use of volar abduction in the thumb when gripping objects. In other words, some patients flex the wrist probably to diminish the muscle tone in the thumb and fingers flexors. At the same time, this increases action of the often-weak thumb and fingers extensors, including thumb abductor. This increases the distance between thumb and other fingers thus enabling gripping of the object. Abductor pollicis longus which often inserts on the volar aspect of the thumb basis act as volar abductor and wrist flexor. We think that this type of grasping of objects can favor the development of reduction in radial abduction of the thumb in CMC joint and consequently lead to further deformation of the other joints of the thumb and the wrist. It is not known whether the primary disorder is the inability to actively radially abduct the thumb, and therefore the patient uses volar abduction, or if it resulting from the need to increase the strength of the weakened finger and wrist extensors muscles in order to increase the hand grip. Suddenly observing this phenomenon in patient should be the subject of the analysis. When assessing the function and condition of the thumb, it should be remembered that it is only part of a very complicated organ, which is the hand. The assessment of the observed changes in its condition and function must always be combined with the assessments of other parts of the hand and whole UL. CP-thumb score is not yet validated, and its validation must be done before wide use.

We hope that the presented score will be helpful in tracking changes in the function and condition of the thumb. It will help to initiate the appropriate treatment early and it may even be used to assess the outcomes of applied treatments.

Summing up my scientific effort presented above, I can say that the main problem I encountered in my work was to create a homogeneous group according to type of CP and kind of applied treatment. Therefore, the groups are small, which limits interpretations of the results. However, I believe that even with small steps such as those presented in this thesis, we have the possibility to improve the quality of life for people with CP

CONCLUSIONS

Paper I

- spasticity-reducing treatment and movement training/orthoses applied from early age help prevent critical loss of passive range of motion of the wrist and fingers
- the presented treatment regime promotes hand function development in children with severe CP

Paper II

- consecutive collection of AEs incidence and side effects should be routine in daily care after BoNT-A treatment
- the presented questionnaire is a usable tool to capture AEs and side effects and is helpful in assessing whether further therapy is safe

Paper III

- the presented results of surgical denervation of infraspinatus muscle and posterior deltoid muscle release is a treatment option for patients with DCP and external rotation pattern in the shoulder when other treatment alternatives are insufficient
- the candidate for presented surgery treatment should be carefully selected

Paper IV

- the presented thumb assessment, CP-thumb score, is easy to perform in any patients with CP independent of CP type and level of impairment.
- CP-thumb score needs to be validated before widely use

IMPLICATION FOR FUTURE RESEARCH

Based on the experience I have gained from this thesis the following future research seems warranted.

Paper I

- Continued follow-up of the children in Group 1 will tell whether the age-related PWE-EF decline is inevitable or if positive effects might be maintained. There is a need for continued research regarding the effects of spasticity-reducing treatment in children with severe CP.
- There is a need for synchronization between the treatment applied and data collection to be reliable and reflect the actual effect of the treatment applied.
- There is a need to distinguish the study population according to CP diagnose type and not only on CP motor impairment level as the interventions type and goals differ between them.

Paper II

- Larger study population may give opportunity to explore the finding of more frequently reported AEs and sides effects in females compared to males, and possibly also find other correlations.
- Validation of questionnaire about AEs and sides effects will improve the quality of the questionnaire and thus-improve the quality of the collected data.

Paper III

- There is a need for a validated scale to assess all parts of the UL dyskinesia that can be used in all patients with DCP regardless of the degree of impairment in UL function.
- Very little is known about involuntary movements in the ULs in patients with DCP more studies concerning this group are justified.
- Long follow-up results of infraspinatus muscle denervation and posterior deltoid muscle release could further improve this knowledge.

Paper IV

- CP-thumb score needs to be validated. Validation and reliability study is already in progress.
- If CP-thumb score will be widely used by OTs during regular repeated CPUP UL assessments, very quickly a large amount of data will be possible to collect. Although the assessment alone without knowing about the therapy used at the time will not answer why eventually observed changes occurred. That is why it is so important to comprehensively collect all data that may affect each individual measurement.
- In addition to the CP-thumb score, an assessment of wrist movement together with wrist function could be developed to improve the assessment of the wrist and fingers condition and function in the patients with all CP type and level of impairment. Currently, the wrist assessment is based on the PROM flexion/extension/ulnar and radial deviation of the wrist and Zancolli. Zancolli is a measurement of ability to active extend the fingers and/or wrist. Combining several measurements in one score might facilitate the assessment of observed changes in wrists and fingers.

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