From the Department of clinical science and education,
Södersjukhuset
Karolinska Institutet, Stockholm, Sweden

ROTATION AND DEVELOPMENT OF THE GLENOHUMERAL JOINT IN BRACHIAL PLEXUS BIRTH PALSY

Krister Jönsson

Stockholm 2022

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2022

ISBN 978-91-8016-442-9

ROTATION AND DEVELOPMENT OF THE GLENOHUMERAL JOINT IN BPBP
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Krister Jönsson

The thesis will be defended in public at sal Halldin Södersjukhuset, 220311 09:00

Principal Supervisor:
Tomas Hultgren MD, PhD
Karolinska Institutet
Department of clinical science and education, Södersjukhuset

Co-supervisor(s):
Mattias Sköld MD, PhD
Karolinska Institutet
Department of Neuroscience
Experimental traumatology unit

Mårten Risling MD, PhD Professor
Karolinska Institutet
Department of Neuroscience
Experimental traumatology unit

Henrik Hammarberg MD, PhD
Karolinska Institutet
Department of clinical science and education, Södersjukhuset

Opponent:
Yrjänä Nietosvaara MD, PhD
Helsinki University
Department HUS children and adolescents

Examination Board:

Thomas Hansson MD, PhD associate Professor
Linköping university
Department of Clinical and Experimental medicine

Sari Ponzer MD, PhD Professor
Karolinska Institutet
Department of clinical science and education, Södersjukhuset

Richard Wallensten MD, PhD associate Professor
Karolinska Institutet
Department of molecular medicine and surgery

TO: Ebbe, Assar and Louise

POPULAR SCIENCE SUMMARY OF THE THESIS

Brachial plexus birth palsy is a birth injury to the nerves that supplies the arm and one reason for weakened arm function. Among those afflicted, a majority heal without interventions from a physician. It starts as a traction injury to the nerves that gives motor signals to the shoulder and arm during delivery. The most common cause is the so-called shoulder dystocia, where the shoulder of a child gets lodged behind the symphysis, the front of the bony pelvis of the mother during delivery. Shoulder dystocia is an acute situation, and the child needs to be delivered without delay.

In delivering a child with shoulder dystocia the child's head often needs to be manipulated away from the symphysis. In doing so the distance between the nerves emergence from the spine and their entrance into the arm is widened and the nerves are stretched. This can cause everything from a mild irritation of the nerves that reverses within hours to rupture of the nerve substance and avulsion of the nerves from the spinal cord.

The patients with birth injuries to the arm plexus that does not heal most commonly suffer from an internal rotation contracture. In all probability because mainly one muscle in front of the shoulder, the subscapularis doesn't grow properly and becomes stiff because it is deprived of nerve signals during important development stages. The internal rotation contracture makes work on a keyboard or on a table difficult. Since reaching the head and neck also requires external rotation in the shoulder these patients often need to lift the elbow far out and up in order to reach the head and neck in what is called a trumpet sign. Some of those who suffer from internal rotation contracture also have a shoulder joint that is partly or even totally dislocated.

Both problems, the internally rotated shoulder and the dislocated joint can be addressed using an open operation which simultaneously repositions the joint and lengthen a tight tendon on the frontal side of the shoulder.

In the first two papers in this thesis, we have examined the long-term results (mean 10.2 years) of such operations regarding the range of motion and the joints further development after repositioning. It has been done by examining the joints range of motion and comparing preoperative and postoperative ranges. Radiological (MRI or magnet resonance imaging) examinations of the shoulders have been obtained preoperatively and in conjunction with the follow-up and compared. These studies are unique in the number of patients and the lengthy follow up time. The investigation shows excellent results in increasing the external rotation by a mean of 66° and a difference in congruence between the operated and unoperated of only 6.7 percentage points

The third study investigates what structure in front of the shoulder is the tight one hindering external rotation. We examined this by dividing suspect structures one by one until a relevant increase in external rotation occurred. There were only small changes in external rotation until we divided the tendon to the subscapularis muscle. Then a substantial increase occurred, external rotation sufficient for daily activities and to reverse the trumpet sign was achieved.

The fourth study looks at phenomenon called co-contractions, it makes it difficult to control the arm and limits the usage even after surgical release of the contracture, because the muscles that rotates the arm outward and inward are activated simultaneously. It has been hypothesized that this is due to nerves taking a different path through the nerve scar that form after a nerve injury. We created an animal model with juvenile rats trying to test this by pinching the nerves with forceps. A substance that is transported inwards from the muscles towards the spinal cord (fluorogold) was injected in the same muscle on both the injured and the untreated side a few weeks later.

We saw that the substance could be detected in a much larger area of the spinal cord on the injured side indicating a mismatch between proximal and distal paths through the scar tissue on the nerve. A bit like a train changing tracks on a marshalling yard the nerve ends up on a different location. This could be part of the explanation for the faulty contractions, but as the misguidance of nerves occur in other injuries without resulting co-contractions, we do not consider it to be a complete explanation.

ABSTRACT

Birth injuries to the brachial plexus occur in 2.2-2.9 livebirths in Sweden. This traction injury to the nerves can cause anything form a transient weakness in the shoulder to a flail limb that does not recuperate on its own. Of those affected 70-80% recover excellent function. The remaining patients most commonly develops an internal rotation contracture in the shoulder joint. The contracture limits the usability of the hand as it becomes more difficult to reach in front of the body and to reach the head, neck, and mouth. Many strategies to handle the contracture and the incongruity of the glenohumeral joint that sometimes coexists.

Some of the patients albeit with a good range of motion has difficulty utilizing it because of co-contractions in the muscles used to rotate the shoulder internally and externally.

The aims of this thesis are to present evidence-based treatment for rotational problems including glenohumeral joint incongruity, increase the knowledge on the biomechanics in the brachial plexus birth palsy shoulder joint, and to present a method of studying co-contractions about the shoulder in an animal model.

In Paper I 118 patients who had surgery with open subscapularis lengthening and repair a minimum of 7 years (mean 10.4 years) earlier were thoroughly re-examined for range of motion in the shoulder. Functional scores were also recorded. Comparisons were made with the preoperative values. The mean gain in external rotation was 66.5°, the mean loss of internal rotation was 22°, the mean mallet score increased by 3.1 points. The loss of internal rotation turned out to have very small effects on the midline and cross-midline function.

In paper II 61 of the 63 patients with a repositioned shoulder joint from paper I were re-examined using MRI regarding the glenohumeral joint development as measured with the percentage of humeral head in front of the scapular midline (PHHA), glenoid angle and size of the humeral head. All examined patients had a relevant and significant improvement. PHHA increased 27.6% (percentage points), and the glenoid retroversion decreased by 14.8°. at mean 10.2 years follow up. All measurements approached those on the unaffected side at follow up.

Paper III is a biomechanical study into what it is that resists external rotation in the BPBP afflicted shoulder joint as several anatomical structures has been suggested. We recorded the gain in external rotation for each surgical step of our standard operation in 24 consecutive patients and found only small changes in external rotation for most steps. Only when entirety of the subscapularis tenon was divided a substantial gain in external rotation (mean 43°) occurred. We also found that the lengthening of the subscapularis required to achieve a relevant gain in external rotation (mean 12mm) exceeded the mean passive excursion of the subscapularis muscle (mean 3mm).

Paper IV investigates how fluorogold is transported through a neuroma in continuity. By inflicting a crush injury to the superior trunk on one side on 14 juvenile rats. After 4 weeks fluorogold was injected into the infraspinatus and one week after that the spinal cord was

harvested and sectioned. We found significantly fewer fluorogold positive cells on the injured side (0.7073) compared to the injured side (1.0663). The fluorogold positive cells on the injured side were dispersed over a larger area indicating some kind of change in direction inside the neuroma. This may be a feasible model to study co-contractions in brachial plexus birth palsy.

LIST OF SCIENTIFIC PAPERS

I. Hultgren T, Jonsson K, Roos F, Jarnbert-Pettersson H, Hammarberg H. Surgical correction of shoulder rotation deformity in brachial plexus birth palsy: long-term results in 118 patients. Bone Joint J. 2014

II. Jonsson K, Werner M, Roos F, Hultgren T. Development of the glenohumeral joint after subscapular release and open relocation in children with brachial plexus birth palsy: long-term results in 61 patients. J Shoulder Elbow Surg. 2019

III. Jönsson K, Roos F, Hultgren T. Structures contributing to the shoulder contracture in brachial plexus birth palsy. An intraoperative biomechanical study. J Hand Surg Eur Vol. 2021

IV. Jönsson K, Hultgren T, Risling M, Sköld MK
On the origins of co-contractions in Brachial plexus birth palsy.
-Changes in number and distribution of spinal cord motoneurons after injuries to cervical nerve roots in fetal rats. (manuscript)

Scientific papers not included in the thesis

Hultgren T, Jonsson K, Pettersson H, Hammarberg H. Surgical correction of a rotational deformity of the shoulder in patients with obstetric brachial plexus palsy: Short-term results in 270 patients. Bone Joint J. Oct 2013

CONTENTS

LIST OF ABBREVIATIONS

BPBP	Brachial plexus birth palsy
SS	Subscapularis
CNS	Central nervous system
FG	Fluorogold
NeuN	Neuronal nuclei antibody
ROM	Range of motion
PHHA	Percentage of humeral head anterior to midscapular line
SPARC-procedure	Subscapularis-preserving arthroscopic release of capsule-procedure

1 INTRODUCTION

Brachial plexus birth palsy (BPBP) is by most accounts a traction injury to the cervical nerves that form the brachial plexus of the arm. It affects around 2.2/1000 livebirths in Sweden. Of children who sustain this type of injury most (70-80%) heal without subjective weaknesses or limitations in range of movement. For those who demonstrate weakness in elbow flexion still after 3 months, neurosurgical intervention is sometimes required and some sequel to the injury is to be expected. Many of the patients with persistent problems suffer from some degree of co-contractions.

A limitation in external rotation of the glenohumeral joint is the most common sequel, limiting the ability to position the hand in front of the body and to reach the head without elevating the elbow in what is called a trumpet sign.

There are numerous suggestions for the cause of the internal rotation contracture, the reasons for tightness, which structures are tight and how to treat it. This thesis investigates which structures are tight in the glenohumeral joint after brachial plexus birth palsy. The results of treatment of the rotational problems of the glenohumeral joint and the radiological development after subscapularis elongation and repositioning of incongruent joints. A model for studying co-contractions and their possible origin is investigated.

2 LITERATURE REVIEW

2.1 HISTORIC PERSPECTIVE

The earliest account of a brachial plexus injury is said to be the story of Hector striking Teucer "where the collarbone divides the chest from the neck" in Homers the Illiad[1]. After the blow Teucer's wrist stops functioning indicating nerve injury. This is a case of an adult traumatic injury to the brachial plexus. The first account I have found of a birth injury to the brachial plexus is from Smellie who in a publication 1784 discussed the paralyzed arms of a girl he delivered using forceps[2]. The paralysis of the arm in infancy and the internal rotational contracture that may follow the injury are overt and easy to discover and by the early 1900s the injury was readily recognized. Case series and treatment suggestions were being published. Different authors addressed the primary nerve lesion[3] and the internal rotation contracture and posterior subluxation of the affected shoulder[4].

2.2 EPIDEMIOLOGY

There is a wealth of studies into the epidemiology of brachial plexus birth injuries. The literature shows greatly varying numbers from 0.4-4.6/1000 livebirths[5]. Variance may be attributed to external socioeconomic factors, access to free healthcare and the quality thereof. Other effects of socioeconomic factors such as regional obesity and the increased risk of macrosomia that follows may influence the incidence[6]. Different definitions between centers or obstetricians, child neurologists and surgeons may also have an effect. In a Swedish setting the incidence is 2.2/1000 livebirths[6].

Factors that increase the risk of brachial plexus birth palsy (BPBP) are: high birthweight, instrumental delivery or vacuum extraction, gestational diabetes, earlier deliveries resulting in BPBP and shoulder dystocia. Children born vaginally in breech presentation have a higher risk of BPBP while caesarian section decreases the risk of BPBP regardless of presentation[6, 7]. The incidence of BPBP seems to be declining in countries comparable to Sweden[8] despite increasing obesity and macrosomia. Increased use of caesarian section in high-risk pregnancies may contribute to the decline.

2.3 PERTINENT ANATOMY AND PHYSIOLOGY

Five spinal nerves (C5-Th1) leave the cervical spine and goes on to form the brachial plexus via the formation of trunks, divisions, and chords. C5-6 forms the upper trunk, C7 forms the middle and C8-Th1 forms the lower trunk. This is also represented in the different injury patterns in BPBP. The nerves forming the upper trunk are more firmly attached to their vertebral foramina than the lower nerves of the brachial plexus[9].

The brachial plexus enters the neck between the anterior and middle scalene muscles before it passes between the clavicle and first rib to enter the arm.

The upper plexus or upper trunk originating in C5-6 supplies motor function to the shoulder for abduction, flexion (supraspinatus and deltoid) and external rotation (teres minor and infraspinatus), and to the elbow/forearm for flexion and supination (biceps, brachialis, and supinator).

The middle plexus (C7) supplies motor function to the elbow, wrist, and fingers for extension (triceps, extensor carpi and extensor digitorum).

The lower part or lower trunk (C8-Th1) supplies motor function to finger flexion (flexor digitorum) and the intrinsic muscles of the hand.

These three main groups correspond to the muscle groups that are possible to examine in infants in order to determine the severity of the injury, whether it is an upper (C5-6), upper-middle (C5-7) or total (C5-Th1) injury. Total injuries display a flail limb often with Horner's syndrome: ipsilateral miosis and ptosis Horner's syndrome indicates that the sympathetic nerves to the face are damaged, which in turn happens when there is an avulsion of C8-Th1 because the sympathetic ganglia are located very close to the roots.

Nerve injuries occur in different degrees of severity, several classifications have been proposed, the most widely spread is Seddon's classification from 1942:

- Neurapraxia where the axons are intact and survive but their ability to transmit electrical excitation is temporarily impaired. The macro and micro architecture of the nerve is intact. Full recovery can be expected after such an injury.
- Axonotmesis where the axons are severed, and Wallerian degeneration will occur, but the macro and micro architecture is still intact. If the distance to the target organ in short enough full recovery is likely.
- Neurotmesis where the axons are severed along with the macro and micro architecture i.e., the endo and epineurium are severed as well. No regeneration will occur unless the proximal and distal ends are connected again.

In Sunderland's and MacKinnon's classifications there are additional levels of severity, e.g. the Axonotmesis group is subdivided based on whether the support tissue inside the nerve is intact or not, Seddon's classification is sufficient for most clinical purposes.

2.4 THE NERVE INJURY

Smellie[2] believed the flail arm was due to compression during the time in the birth canal but did not specify what was compressed. Duchenne identified the neurological origin of the observed weakness after BPBP 1872. Five years later Erb described a common place of injury in birth lesions to the brachial plexus where C5-6 meet (Erb´s point). Stimulation here cause contraction of the same muscles that are affected in C5-6 lesions[1].

Kennedy described surgical repair of the brachial plexus injuries without knowing if the injury was the result of a compression or a traction[3]. Sever during "numerous" dissections of infantile cadavers performed traction tests. He saw that especially the two upper roots tensioned hard during widening of the angle between the head and shoulder and that only then the upper plexus tensioned at all. He concluded the forceful increase of the distance between head and shoulder to be the cause of the C5-6 lesion at Erbs point and that more violent traction could perpetuate the injury to the middle and lower parts of the plexus. He also noted that the nerves did not rupture sharply but frayed out over a distance [10].

During labor the shoulder presenting anteriorly or upward can get lodged behind the symphysis of the mother and slow the progress of labor down. This is called shoulder dystocia. Shoulder dystocia is an acute condition of threatening hypoxia which must be resolved[11]. In releasing the anterior shoulder, the head of the baby is manipulated downward or posteriorly which widens the angle between shoulder and neck. This causes the upper plexus to stretch, causing the typical paralysis for C5-6 lesions (shoulder motion and elbow flexion) and if the force increases the injury can perpetuate to the middle and lower plexus.

The spectrum of injury ranges from a very mild stretch causing neurapraxia which resolves promptly via rupture of nerves or trunks to avulsion of nerve roots from the CNS. These injuries can thus contain different levels of severity in different nerves and as mentioned within the same nerve or trunk.

2.5 SURGERY FOR THE NERVE INJURY

The majority 70-80% of BPBP lesions are of the milder stretch type which resolves without surgical intervention and without sequel[12]. Of the remaining 20-30% the majority have mixed injuries with neuromas in continuity which transmit some signals and have excellent potential to heal and therefore don't benefit from exploration and surgical intervention.

In a series of 274 consecutive patients operated at our unit for sequels of BPBP only 29 or 10% had undergone nerve reconstruction surgery[13]

After Kennedys report in 1903 of success in removing neuromas and suturing the remaining proximal stump to the distal[3] the technique spread to a number of centers in the following years. In 1920 however, Sever published a larger case series claiming that suture of the plexus was unnecessary in BPBP of the upper plexus injuries, and useless in the more severe injuries involving the middle and lower plexus[10]. This report led to a rapid decline in primary surgery of the brachial plexus in BPBP.

Interest in primary nerve repair of BPBP was rekindled in the 1980s when microsurgical techniques had improved, anesthesiology of small children was safe, and the use of nerve grafts had been tested and shown to have benefit in more distal large nerves.

In the newborn child it is not possible to distinguish a severe paralysis with neurotmesis or avulsion injuries from a milder type that can and will resolve without intervention. There are signs such as the severity of the trauma and the Horner's syndrome, that can lead to an early decision to operate, but in most cases the only way to determine whether an injury will resolve is by serial examination and evaluation of the development of muscle strength and contractures[12]. Infants are observed and their limb motions are evaluated, the range of motion against gravity and with gravity cancelled out is assessed. Reflexes can be used to examine differences between the sides[14].

There is no international consensus regarding the indications for surgical intervention with nerve repair. Many centers consider nerve reconstruction or transfers if there is no active biceps flexion at 3 months of age[8, 15, 16]. Others have advocated a longer wait until the child can voluntarily try to bring something to the mouth, the "cookie-test" usually performed at nine months[17].

The surgery consists of excision of the neuromas and reconstruction with nerve grafts. The sural nerves and sensory nerves of the forearm are most commonly used to bridge the gap once the neuroma is excised. This traditional technique is often combined with nerve transfers, or indeed replaced by it.
In nerve transfer fascicles of a healthy nerve, for example the spinal accessory nerve is directly connected to the distal stump of a suprascapular nerve in order to reanimate the supraspinatus and infraspinatus muscles.
Fascicles of the median, ulnar, or radial nerves can all be utilized to reinnervate selected parts of the injured plexus. Even intercostal nerves can be used as donors. The benefit of grafting is that it can restore the original anatomy to some extent and the technique is well proven. The benefit of using transfers is that the donor nerve is uninjured and the distance to the target muscle is short[7].

2.6 THE INTERNAL ROTATION CONTRACTURE

Of the around 2.2/1000 births that sustain BPBP we have now seen that 70-80% heal well and some 10% of the remaining 20-30% may need primary surgery. However, most or all the remaining 20-30% need monitoring for contractures and weakness. Even cases with full strength in all muscles a few months after birth may develop contractures[18]. Especially the C5-6 injuries often regain good function and strength in most dimensions but are then limited by an inability to externally rotate the shoulder. This severely limits the ability to position the hand in space and forces the elbow outward and upward when reaching the mouth - the so-called trumpet sign. It also affects the possibility to work on a keyboard or table with the arm in front of the body[4, 19-25]. The elbow often have some degree of contracture[16] albeit not as limiting as the shoulder internal rotation contracture.

The contracture is preferably measured using a goniometer standing behind and above the examined subject. Thoroughness patience and re-measuring are keystones in recording accurate and precise measurements. Care must be taken to account for the naturally occurring "cheating" in trying any difficult movement for example by twisting the torso in external rotation or extending the spine in flexion of the shoulder. Serial measurements in relevant dimensions should be performed in follow-up of these children. For the global function cruder scales can be used to categorize the range of motion or (ROM). The most widely used is the Mallet score which scores five motions: abduction, external rotation, (which are "pure" movements measuring one angle) hand to neck, hand to back, and hand to mouth (which are compriced of abduction/flexion and external rotation). The hand to mouth reveals the trumpet sign which is part of our surgical decision-making scheme.

2.7 THE NERVE INJURY'S CONNECTION TO INTERNAL ROTATION CONTRACTURE

The structure resisting lateral rotation is by most believed to be the subscapularis[4, 19-25]. Some claim it is rather the ligaments attaching the coracoid and glenoid to the humerus[26]. The mechanism linking the nerve injury of the brachial plexus to the contracture of the muscle is subject to more debate.

For a long time, the dominating theory was that the muscle contracted and became stiff because the externa rotators were weak and the subscapularis during recovery could contract unopposed; the muscle imbalance theory[19, 20, 27, 28].

Kambhampati stated that the SS muscle is fibrotic to a degree similar to what can be seen after compartment syndrome when ocularly inspected during surgery[24]. Our own group found normal histological appearance in 12/13 patients when examining biopsies from the SS muscle obtained during surgery[29].

Animal studies contend the muscle imbalance theory. Nikolaou et al found that denervated SS muscle in mice grow to a shorter length and smaller cross section than the uninjured side. In a control group with the external rotators cut through there was no contracture formation, showing that lack of antagonists is not enough to produce contractures[30]. Weekly et al found that the severity of a contracture in a BPBP mice model was proportionate to the severity of nerve damage[31].

2.8 TREATMENT FOR THE INTERNAL ROTATION CONTRACTURE

Fairbank in 1913 found the SS muscle to be the strongest resisting force to external rotation and that tenotomy of the subscapularis yielded free external rotation. Fairbank considered the anterior capsule to be contracted and part of the problem[19]. Sever added to this the division of the pectoralis major tendon as well, he did not consider the capsule to be part of the problem and warned that incising the capsule would cause adhesions[20].

Carlioz and Brahimi released the SS to achieve external rotation by disinsertion of its origin in place of a tenotomy[21]. Birch and Chen Refined the tenotomy of the subscapularis into a controlled lengthening and repair[22], the method used in our unit.

Pearl introduced an arthroscopic procedure with a tenotomy of the SS tendon and the underlying capsule[23]. Abid and Kany has since published an arthroscopic procedure (the SPARC-procedure) sparing the entire SS tendon and instead dividing the coracohumeral ligament and the joint capsule[26]. Tendon transfers about the shoulder with or without release of tight structures have been described in a large number of publications[25, 27, 32, 33].

Some authors have advocated external rotational osteotomy in cases of severe incongruence[28], this may move the hand, but it does not improve the ROM and does not treat the problem at its origin, an unstable joint will unlikely be more stable after an osteotomy. At Södersjukhuset we have had positive results from releasing the tight structures and repositioning the joint in dislocation and in the small number of patients that were over 5 years of age at operation [34, 35].

2.9 TENDON TRANSFERS FOR EXTERNAL ROTATION

It was believed that it was the lack of external rotational power that caused the contractures and thus L'Episcopo added to Severs contracture release by moving the insertion of the teres major in under the short head of the triceps for external rotational power[27]. The release by L'Episcopo was very extensive, sometimes the tendons from SS, pectoralis major, teres major and latissimus dorsi were all transected.

In 1978 Hoffer presented series of eleven patients, they had undergone serial casting preoperatively and the pectoralis tendon was divided to improve passive external rotation intraoperatively. To augment the active external rotation the teres major and latissimus dorsi tendons were sutured to the rotator cuff as external rotators. The authors reported improvements in external rotation and abduction two to six years postoperatively[36].

Transfers of tendons, the latissimus dorsi tendon or the teres major and latissimus dorsi with or without simultaneous release of structures in front of the shoulder is widely used also today with good results reported[15, 33].

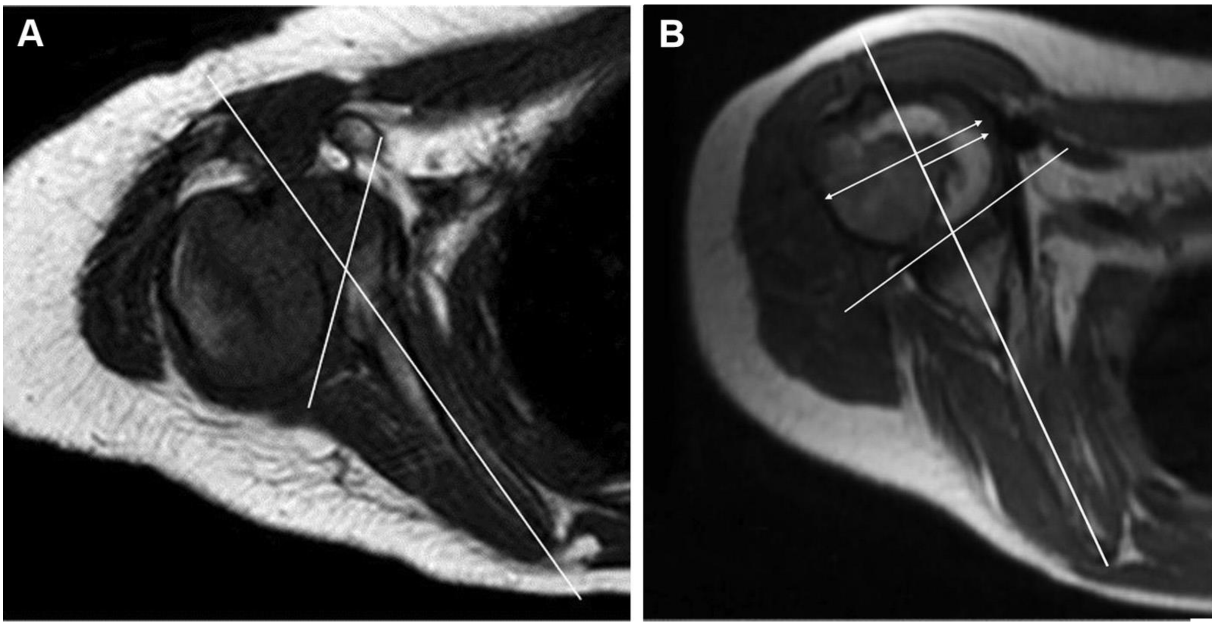
2.10 JOINT INCONGRUENCE IN BPBP AND ITS TREATMENT

At our center about 45% of the patients with a rotational contracture also have some degree of glenohumeral incongruity[13, 34].

General skeletal deformities are seen in BPBP. Often a curved acromion and enlarged coracoid co-exists with the deformities that comprise the incongruence.

The measurable incongruity consists of

- A posteriorly subluxed or dislocated humeral head as measured in percentage of the humeral head diameter anterior to a line drawn through the body of the scapula (PHHA).
- A posterior glenoid version, the glenoid joint surface faces more posteriorly relative to the long axis of the scapula.
- A smaller humeral head diameter.



An incongruent (dislocated) shoulder joint, A preoperatively, B 7 years postoperatively

The joint deformity has historically been described as a consequence of muscular imbalance, with the humeral head exerting its pressure not in the centre of but posteriorly on the joint surface causing a weakening of the posterior support and retroversion of the glenoid progressing to a posterior subluxation of the humeral head[19, 24, 28], similar to the development of the hip joint in children with congenital hip dysplasia. More recent investigations show that the glenohumeral incongruence can occur as early as at three months of age[37] and we have treated children with complete dislocation at six months of age. We have found that in our series of patients there is no clear correlation between age and the severity of the incongruence. In fact, most cases requiring relocation surgery are young. The mechanisms are not well understood.

Pearl[38] and Waters[28] described and classified the radiologic changes of BPBP-affected joints, building on radiological work describing similar changes in other shoulder pathologies[39]. Our classification is based in the findings during surgery[35].

The release of the internal rotation contracture, and the treatment of the deformed or incongruent glenohumeral joint are central in the management of BPBP, and as can be seen here the two has mostly been treated in conjunction.

Whitman in 1905 performed a forceful closed reduction and casting to try and destroy or diminish the old articulation[4]. Fairbank described the incongruity as the only thing standing in the way of recovery in cases with rapid return of strength in the affected muscles[19].

Sever recommended shortening the acromion to help with reduction but advocated against opening the shoulder joint capsule something that he felt should have made reduction difficult[13].

Birch and Chen described a technique with controlled lengthening of the subscapularis tendon and when needed (in cases of incongruence) combined with open and precise relocation. This is possible because of the excellent access to the joint after division of the subscapularis tendon [22].
Pearl described an arthroscopic procedure where the SS tendon and glenohumeral joint capsule are divided to relocate incongruent joints[23].
The above-mentioned SPARC-procedure which divides glenohumeral and coracohumeral ligaments but spares the SS tendon has however shown unsatisfactory results in treating incongruent joints[26]. Similarly, Kozin and Waters separately evaluated tendon transfers without relocation and found only a small effect on PHHA and glenoid version[32, 40].

Several authors have considered derotational osteotomies as the treatment of choice in older patients[15, 33]

.

2.11 UTILIZATION OF THE AVAILABLE RANGE OF MOTION

Children affected by internal rotation contracture have a limited arc of motion, practical use of an arc of motion inside of -70-80° is very limited. When the subscapularis musculotendinous unit is lengthened the arc of motion expands and is placed in a more favorable position, where more of the range of motion may be utilized. In cases where the glenohumeral joint needs to be externally rotated to a large degree to achieve glenohumeral joint congruence the arc may end up to laterally and a secondary rotational osteotomy may be required to get the arm in the useful arc from 20-30° and inwards[13, 35, 41].

A derotational osteotomy does nor expand the available rotational arc but may improve the position of the hand[42].

2.12 CO-CONTRACTIONS IN BPBP

In our clinical practice we have encountered patients who suffer various degrees of co-contractions about the shoulder. Patients with co-contractions may have excellent passive and well-placed ROM, often after lengthening of the SS. But as they activate their agonists (external rotators) and antagonists (internal rotators) simultaneously they either can’t utilize their good range of motion or the antagonist weakens the strength in external rotation. This occurs in the elbow aside from the shoulder. The phenomenon has been known clinically for a long time and has drawn the attention of neurophysiologists and those who treat BPBP sequalae with Botulinum toxin[43, 44].

The pathophysiology of these co-contractions is unknown[44] albeit there are in some articles general sweeping statements of “misled” axons or nerves that seem to have perpetuated through the literature with little supporting evidence[43, 45]. Co-contractions has also been studied in adult subacromial pain where coactivation of adductors and abductors seem to give a more favorable outcome[46].

Longitudinally transected neuromas when examined under microscope show that only a small number of axons will cross a suture line even if masterfully coapted. A great number will simply wither and die, and some will turn and grow outwards or backwards. This supports the thought of misguided axons. However, the injury in BPBP differs in many ways from a type injury of a transected nerve stem in an adult.

- The injury is a traction injury of mixed severity
- The nerves of an infant cannot be expected to behave as those of an adult
- The plasticity of the brain is very different in children.

Children have greater plasticity in the brain and coapted nerve stem injuries in children have superior results to adults with the same injuries[47]. Extrapolating from this the potential function should be even greater in the BPBP affected infants, but this is not the case in many patients.

2.13 THE COMMON RAT AS A MODEL FOR BRACHIAL PLEXUS BIRTH PALSY

Rats have a brachial plexus anatomy that is similar to that of humans[48]. Juvenile rats exposed to an experimental nerve injury to the brachial plexus develop the same characteristic contracture and glenohumeral deformities as humans do. Rats then can be used as a model to understand the link between nerve injury and contracture[30, 49].

2.14 FLUOROGOLD AND NEU N

Fluorogold is a commercially available neural tracer used for over 30 years. It is stable for up to two months and can be either injected into muscle for motor-end plate uptake or taken up directly into an exposed proximal ending of a transected nerve. In both cases it undergoes retrograde axonal transport to the central nervous system. It can without further fixation or treatment be identified within neuron cell bodies using ultraviolet emitting fluorescence-microscopy. It has proven effective and reliable in tracing from muscle to cervical spine[50]. Antibodies for neuronal nuclei or Neu N has been used in a variety of applications to detect neurons[51]. Unlike FG it requires treatment with a secondary antibody to emit light under a fluorescence microscope.

2.15 RATIONALE

The problem of the internal rotational contracture has been known for a long time[19]. Despite this there has been surprisingly little consensus surrounding this phenomenon.

There is debate on what causes the contracture, there is debate on what structures are the tight (or weak) ones, and there is debate on how to treat them.

The lack of consensus reflects the state of evidence on the treatment of brachial plexus birth palsy. This thesis will by no means end the debate, but it will hopefully add a piece of the puzzle large enough to confidently claim our standpoint in treatment of sequels of BPBP.

There is something to be said about the study designs we have chosen. As I have been encouraged countless times to change focus from cohort studies to controlled studies, preferably randomized ones. The idea is excellent per se but as patients are few a randomization between treatments would take a long time (longer than is practically possible within the scope of a thesis). Also, as we at Södersjukhuset provide a treatment that has better results, documented over a longer time than any other treatment that I am aware of, it raises serious ethical questions, is it ethical to withhold the treatment we believe work well in order to investigate the efficacy of other less well documented ones?

3 RESEARCH AIMS

The overall aim of the thesis is to provide solid evidence for treatment of range of motion limitations and glenohumeral joint incongruity in brachial plexus birth palsy. To increase the knowledge on what causes the limitations in glenohumeral rotation in BPBP and to start systematic investigations of co-contractions in brachial plexus birth palsy.

The specific aims for respective study were:

I. To Evaluate the long-term changes in shoulder mobility and shoulder function for patients that have undergone open subscapularis lengthening and repair, with or without tendon transfers and open joint relocation. Secondarily the need for additional surgery during the follow-up (minimum seven years) was recorded.
II. To evaluate the potential for remodeling towards normal of the incongruent glenohumeral joint in brachial plexus birth palsy after open subscapularis lengthening and repair with open relocation.
III. To provide a thorough account of, and a biomechanical scientific basis for, the surgical treatment used to treat internal rotation contracture in brachial plexus birth palsy in our unit by investigating the contribution of different structures to the contracture.
IV. To investigate whether the phenomenon of co-contractions in brachial plexus birth palsy originates in the peripheral neve neuromas caused by a non-disrupting nerve injury.

4 MATERIALS AND METHODS

4.1 PATIENTS (PAPER I-II)

The patients that make up the populations for paper I, II and III were all treated for their brachial plexus birth palsy at Södersjukhuset. The patients in study I and II were operated between 1997 and 2009 and are drawn from a previously published consecutive series of almost 300 patients all operated by the same surgeon using the same criteria for surgery. Of these 207 were eligible, 118 (64 female, 54 male) responded and were available for clinical examination. 63 of these had had some type of incongruence that was rectified at the time of surgery and all but 2 of these (who were too young to accept unsedated MRI) were included in paper II.

The patients in paper I and II were on average 3 years old at the time of surgery and the mean follow up time was 10.2 years with a minimum of 7 years passing between surgery and follow up.

For paper II the patients were divided into subgroups depending on age (under 2 years, 2 to 5 years, and over 5 years) and joint category (type 1 with a flattened glenoid where the humeral smoothly transitions anteriorly in outward rotation, type 2 with a bifaceted glenoid where the humeral head snap or click into place anteriorly in outward rotation, and type 3 where the humeral head rolls up from behind the glenoid in outward rotation).

4.2 PATIENTS (PAPER III)

For paper III participation was offered to any and all patients scheduled to undergo surgery for internal rotation contracture between May 2015 and April of 2019. Inclusion criteria was the same as the surgery, both congruent and incongruent shoulders being eligible, exclusion criterion was to deny participation, and as none declined 24 consecutive patients were enrolled. The mean age were 3.9 years. There were 16 female and eight male patients.

4.3 ANIMALS (PAPER IV)

For paper IV two pregnant Sprague Dawley rats were purchased though the animal handling system at Komparativ medicin biomedicum, Karolinska institutet.

The animals were kept together with their respective mothers in temterature controlled ventilated cages. Food and water were provided ad libitum. The day-to-day handling regarding food, water, and hygiene was managed by animal handling staff at Komparativ medicin biomedicum. All according to institution guidelines.

4.4 INDICATIONS AND SURGERY (PAPER I-III)

Our indication and technique to operate on children with brachial plexus birth palsy has not changes since the 1990s. Patients with a passive external rotation of less than 0° or less than 20° of passive external rotation if the patients demonstrate a trumpet sign when trying to reach the mouth.

The technique used was first published Birch and Chen[22]. If there is any suspicion of incongruence to the glenohumeral joint and the patient is too young to endure MRI unsedated, anesthesia starts at the radiological department where the patient goes through preoperative MRI. The patient is then transferred to the OR in the anesthetized state. Patient is positioned supine with the arm placed on a small maneuverable table. Local anesthetic and adrenaline are instilled in the deltopectoral groove, at the place of the incision. Using knife, scissors and diathermy dissection is directed towards the joint, passed the cephalic vein, the conjoined tendon is identified and split along its fibers to provide access to the subscapularis tendon. The commonly enlarged coracoid is diminished, and for paper III it was also carefully denuded of tendinous insertions. The subscapularis tendon is then exposed, dissected from underlying tissue, and split along the fibers. The step cut is made cranially/laterally and caudally/medially. After dividing the last fibers of subscapularis tendon, the contracture is usually released. If the joint is incongruent the head of the humerus will come forward during external rotation, sometimes a cut has to be made into the capsule as well in order to allow the full reposition of the humeral head. For paper II the passive excursion of the tendon was tested before repairing the SS tendon in elongation with the arm in 30-35° of external rotation and closing the wound in layers. Before the anesthesia ends the arm is placed in a bespoke splint fabricated beforehand. The splint is maintained five to seven weeks postoperatively.

4.5 SURGERY FOR ANIMAL SUBJECTS (PAPER IV)

A first trial on adult animals was performed to ensure the method was working and determine a reasonable waiting time between injection and harvest. The acromiodeltoid muscle was first used for injection as it is larger and can receive more fluorogold (Fluorogold™ Fluorochrome LLC, Colorado, USA) without overflow. These specimens were harvested between 1 and 7 days in the same manner as described below. When a timeframe of seven days was set injection was moved to the infraspinatus muscle as it is easier to define anatomically in smaller animals and has a good bony corner to place an injection needle in.

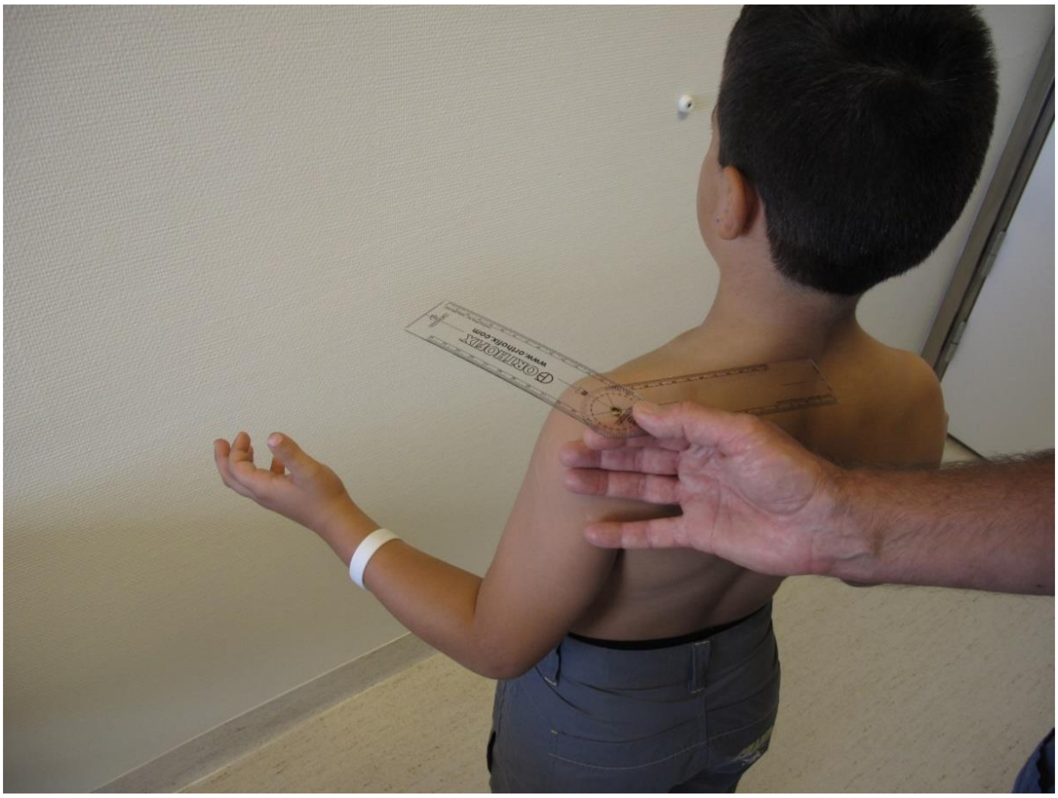
The specimens were anesthetized on a thermostat-controlled heat pad using isoflurane gas and pure oxygen, gas flow, saturation and temperature were controlled using specialized rodent specific apparatus (Agnthos®, Lidingö Sweden). Through the magnification of a microscope an incision was made right above the clavicle. Using blunt dissection through the muscles on the neck the brachial plexus was freed. The suprascapular nerve is easily identified here but a nerve stimulator (Bovie Neuro-pulse, Bovie Medical Corporation, Florida USA) was used for verification. After a 10 second crush with forceps the wound was closed. The rat pups were hydrated and provided analgesia using intraperitoneal injections of saline, NSAID (Rimadyl® Bovis vet, Zoetis, Finland) and opioids (Temgesic®, Reckitt Benckiser Healthcare, UK). All subjects limped after surgery but regained some function during the five following weeks.

The second surgery four weeks later was performed using the same anesthesia, small incisions were made over the spina scapulae, a microinjector needle was seated in the infraspinatus muscle and a slow injection of 10µl Fluorogold™ 4% (Fluorochrome LLC, USA) was injected, before wiping the fascia and closing the wounds.

One week after that the rats were heavily sedated using isoflurane and air, the ribcage cut, and a perfusion pump needle was introduced into the left ventricle of the heart. Perfusion began with saline and continued with 4% formaldehyde (Histolab, Sweden). The spinal cord was harvested through a midline incision followed by laminectomy. One group were carefully dissected from the medulla oblongata and as far caudally as it was technically possible. The other group were marked using a surgical marker at C5-6 and this segment was carefully dissected out. The specimens were postfixed in formaldehyde and cryoprotected in ascending concentrations of sucrose.

4.6 MEASUREMENTS (PAPER I-III)

Papers I-III report thoraco-humeral, gleno-humeral movement and joint angles and distances measurements for the results. In paper I and III using goniometer and functional scores. Using a goniometer is the recommended tool for measurement of joint mobility in for example the national manual of measuring movement in the hand elbow and forearm, it gives precise measurements provided the goniometer used is large enough. Accuracy of measuring angles of motion in children requires more from the examiner. There is need to compensate for thoracic “cheating” movement as the subjects twists and reaches to perform the requested motions. Use of proper sightlines such as the spine for flexion and abduction or an imaginary line between the shoulder joints (pictured) for external rotation are essential. Repeated measurements are essential to improve accuracy. In paper I the measurements are the total achieved motion that is the combination of glenohumeral and thoraco-scapular movement.



Measurement of external rotation in adduction

Measuring pure glenohumeral passive motion in children as in paper III requires relaxed patients and care not to exert too much lateral rotational force, whilst movements in the scapula are monitored both by the surgeon holding the arm and the assistant measuring the angle. The patient needs to be placed perfectly flat. In clinical follow up of these patients range of motion measurements are recorded together with Mallet functional score. The Mallet score is the most widespread functional test for sequels of BPBP, it has shown to be reliable and reproducible[52]. For paper I questions on how midline and across midline activities functions was also recorded to be compared to the internal rotation.

The angular and distance measurements in paper II, (picture seen in chapter 2.10) were;

- PHHA which is the percentage of humeral head diameter anterior to the midscapular line
- Glenoid version which is the angle between the midscapular line and a line drawn between the cartilaginous labra of the glenoid
- Humeral head diameter

Measurements for paper II were recorded using the tools in IDS7 (Sectra, Linköping Sweden) the tools are very precise and the measurements have shown to be reliable both between examiners and at re-examination by the same investigator[53].

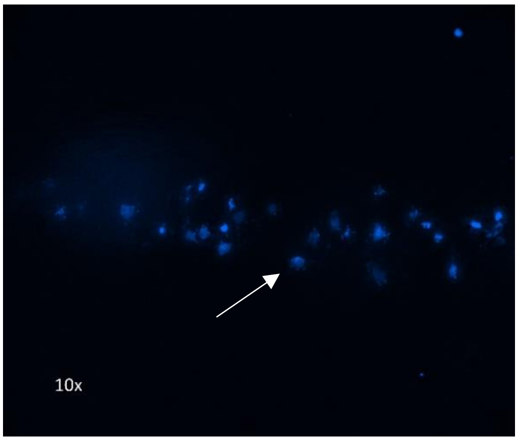
The measurements in paper III were recorded with the arm abducted and adducted after each of the following steps:

1. Before surgery
2. After excicion of the coracoid and division of the coracohumeral ligament
3. After division of the upper part of the subscapularis tendon
4. After division of the subscapularis tendon in its entirety
5. After tendon repair

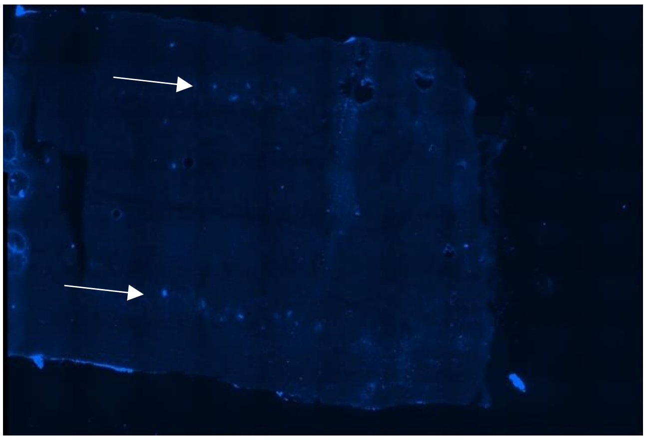
In addition, the passive excursion of both the cranial and the caudal part of the tendon and the length of the step-cut elongation was measured in millimeters.

4.7 ANIMAL SPECIMENS (PAPER IV)

The cryoprotected spinal cords were frozen on dry ice. Mounted in Cryostat embedding media (Thermo Scientific Richard-Allan Scientific [sic!] Neg 50 Kalamazoo, MI, USA) on a 30mm chuck and cut 14µm thick using a Leica cryotome, the specimens were mounted on gelatin-coated microscope slides and thawed to adhere to the slides. The specimens from the trial run were transected longitudinally in the coronal plane, at first to maximize the chance of finding FG positive cells and when cells were found to determine the central area of interest, that is, where to focus the transverse cuts for the main run of animal experiments.



Flourogold positive cells in coronal cut



Large image compounded from several micro-photographs showing one coronal cut of spinal cord with bilateral uptake of flourogold

We split the specimens used for counting into two groups, one consisting of five animals that was transversally cut from the most cranial part preserved and as caudally as the cord was intact. Around 1250 separate specimens came out, faulty cuts and losses gave about 21mm of spinal cord to examine. The second group of nine animals' spinal cords were marked using a surgical marker at level C5-6 and this particular segment was dissected out, mounted, and transversely cut, around 200 separate specimens representing 5.5mm of spinal cord came out.

60 sections (20 sections from three different animals) were subjected to treatment with NeuN NeuN antibody 1:1000 (Millipore Coorporation USA) by marking the edges with PAP PEN®, re-moisturizing the specimens and treating with NeuN antibody 1:1000, phosphate buffer and normal serum. The specimens were incubated for 18 hours, rinsed, and treated with donkey anti mouse 1:400 before final rinse and covering.

For the first group one in five microscope slides each containing six sections were thawed and counted for fluorogold positive cells. For the second group every microscope slide was thawed and counted for fluorogold positive cells.

The sections were examined under fluorescence microscope (Nikon Eclipse Ni-E, Nikon, Japan) and photo-micrographed using the camera fitted to the microscope (Andor Zyla sCMOS, Oxford instruments, UK). For fluorogold detection the built in DAPI filter cube (Nikon) (extitation 340-380nm, emission 435-485nm) was used for NeuN detection FITC filter cube (Nikon) (excitation 465-495nm, emission 515-555nm) was used.

The pictures were captured using NIS Elements 5.02, (Nikon, Japan) and the photographs were processed in Photoshop (CS5 Adobe, USA) Neurolucida 360®, (Neurolucida, MBF bioscience, USA) was used to create a 3D rendition of the transverse images. See chapter 5.4.

4.8 STATISTICS

Apart from paper I the statistical methods represented in this thesis are quite simple. For papers II-IV the statistics are common tests for paired/unpaired data, with or without normal distribution. For paper III repeated ANOVA was performed to avoid aggregate risk of type I error when performing a series of dependent t-tests. $p \leq 0.05$ were considered significant.

All data was processed in SPSS Statistics software (IBM, Armonk, NY, USA).

Paper I

A mixed models test was used to test association between; examination (pre-post-surgery) gender, age, joint subgroup and use of muscle transfer. Tests was also run between examination and gender/age/joint for two-way analysis. Tests were run prior to main calculations to evaluate the need for random intercepts.

Paper II

The normality assumption was tested using the Shapiro-Wilk test and being normally distributed the differences before and after surgery was tested using the dependent t-test for paired data. Differences in results and changes between different ages and joint types was tested with analysis of variation (ANOVA). The unpaired data compiling the differences between sexes, and the groups who had been preoperatively examined radiologically and those who hadn't were tested using the independent t-test.

Paper III

The differences between actions were tested for normal distribution using the Shapiro-Wilk test and found to not differentiate significantly from normal distribution. When testing a series of measurements one after the other the risk of a type I error and chance significance increases. Therefore, the whole series of measurements with the arm adducted and abducted respectively was tested at once using the repeated ANOVA test and found to have significant differences. Thereafter the dependent t-test was used for each pair of actions.

Paper IV

The normality distribution of the differences found between sides was tested using the Shapiro-Wilk test. As they differed significantly from normality the Wilcoxon sign test was used to evaluate the differences between sides.

4.9 ETHICAL CONSIDERATIONS

There is no way around the fact that all papers compiling this thesis are mostly done on subjects without a voice of their own. The only adults are a smaller number of the patients found in papers I-II. Apart from those there are only children and juvenile animals, subjects with little or no autonomy. The animal subjects are even forced to rely on me for alimentation and shelter, the children likewise for their guardians.

To defend themselves the rats can bite (at least by the time their time has come), whilst the pediatric group can merely scream and protest to get their will. All of the subjects have their very closest personal space invaded as their own skin is incised.

All oral and written information concerning participation in the human studies emphasize voluntary participation and that it is possible to opt out at any time. But it is given by us, the healthcare providers, and there aren't many to choose from for these surgeries. The information is to be processed by families who may have traveled far, whose children are cranky because they are susceptible to the tension and who have just learned that their child needs surgery. It is an information gap that needs to be thoroughly considered in every single contact with the study subjects.

However, the ethical rules of the studies not being possible to perform on a less vulnerable group and being the most beneficial to the group studied without anyone else needing to stand back are fulfilled in all human studies.

For the animal studies other ways of investigating was considered and rejected (replacement). The studies were conducted as pain free as possible and in communication with animal handlers and veterinarians (refinement), lastly no more animals than was necessary for the study were used (reduction).

Ethical permit for paper I, II and III was granted by the regional ethical review board of Stockholm under number 2011/790-31/4 (paper I and II) and 2015/2146-31/1 (paper III).

Ethical permit for paper IV was granted by the Stockholm board for ethics in animal experiments under number 9876-2018.

Furthermore, I consider the idea that one can plagiarize one-self to be preposterous and it needs to be combated by all writers.

5 RESULTS

5.1 PAPER I

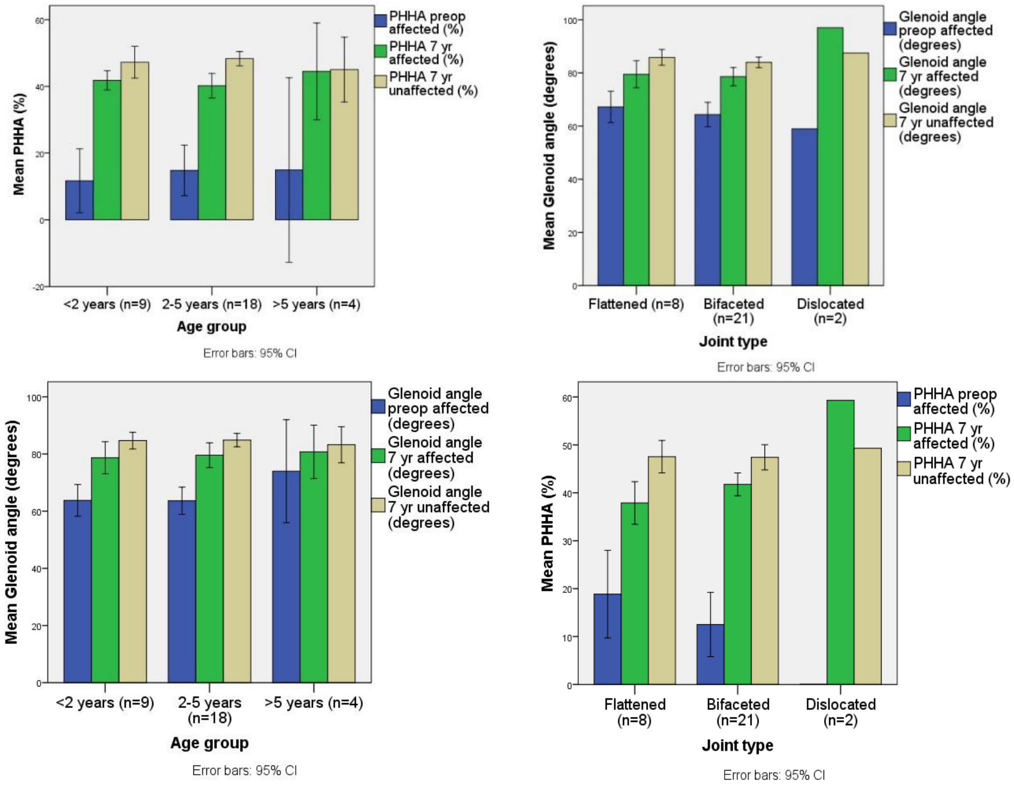
The primary outcome of mean external rotation was significantly improved at 7-year (mean 10.2 years) follow up with a mean change of 66.5° (95% CI 61.5° to 71.6° $p< 0.001$) The improvement can appear slightly less in numbers when looking at repositioned joints who had gone through a derotational osteotomy (after relocation) during the follow up time. This is deliberate as they have had the rotational sector placement optimized for functional use. They had a mean of 45.0° (95 % CI, 35.0° to 55.0°$p< 0.001$). On average these patients lost -7.4° (95% CI -2.0° to -12.7°; $p = 0.007$) of abduction during the follow-up time. The average Mallet score increased 3.1 (95% CI: 2.7 to 3.4; $p < 0.001$) There was as expected a small loss of internal rotation, the mean loss of internal rotation was 22° (95% CI 18.7° to 26.5°). This loss had very little effect on the functional tests (hand to back from the mallet score did not change significantly; (95% CI: -0.2 to 0.1; $p = 0.56$)), and the questionnaire on midline activity, where all (100%) could button a shirt, 97% could put their hand in their pocket and 93% could wash their contralateral armpit.

5.2 PAPER II

The primary outcome of paper II was the Percentage of humeral head anterior to midscapular line (PHHA), the angle of the glenoid in relation to the midline of the scapula and the humeral head diameter. (picture in chapter 2.9) Secondarily the differences between the affected and unaffected shoulder joints were measured. PHHA changes are presented as percentage points meaning an increase in PHHA from 25-50% is equal to a 100% increase.

The patients were on average 3.2 years and included eight patients over five years of age. The mean follow-up time was 10.2 years; 40 female and 21 male patients were included. 59 patients had Erbs palsy and two the more severe C5-Th1 type.

All patients in this cohort of 61 had a beneficial change in the chosen measurements at follow-up from surgery. The average change in PHHA was 27.6% (95% CI, 22.4%-32.7% $p < 0.01$). The average change in Glenohumeral angle was 14.8° (95% CI, 11.1°-18.4°; $p < 0.01$). The average increase in glenohumeral diameter was 16.5 mm (95% CI, 14.0-19.1 mm; $p < 0.01$).



PHHA and Glenoid angle pre/postop for affected and postop for unaffected in age and joint categories.

Age group	n	PHHA (percentage points)	Glenoid angle (degrees)	Diameter (mm)
< 2 y/o	20	6.5 (95% 3.9-9.3 p<0,0001)	5.1 (95% 1.3-8.9 p=0.010)	1.2 (95% -0.5-2.9 p=0.151)
2-5 y/o	29	7.1 (95% 4.7-9.5 p<0,0001)	4.7° (95% 2.4-7.1 p<0.0001)	-0.1mm (95% -1.6-1.5 p=0.946)
> 5 y/o	8	5.9 (95% -1.7-13.5 p=0.109)	7.9° (95% 0.7-15.0 p=0.035)	3.06 (95% 0.3-5.8 p=0.032)
Joint type				
Flattened	14	8.4 (95% 5.6-11.3 p<0.0001)	5.9° (95% 2.7-9.0 p=0.002)	0.4mm (95% -3.0-2.3 p=0.777)
Bifaceted	39	6.6 (95% 4,7-8,9 p<0,0001)	5.9° (95% 3,5-8,3 p<0,0001)	1.3mm (95% 0.2-2.4 p=0.018)
Dislocated	4	0.5 (95% -13.4-14.3 p=0.923)	-2.4 (95% -14.2-9.5 p=0.570)	0.2 (95% -10.1-10.6 p=0.944)

Table showing the differences between affected and unaffected sides at 7 year follow up

When divided into subgroups depending on age and joint classification (see chapter 4.1) all but the dislocated group (n=2) had a significant and relevant increase in PHHA. For the latter group the difference was still positive and large enough to be relevant but as there were few patients the differences were not significant 49.0% (95% CI, 81.5% to 179.6%; p = .132).

We found good results regarding PHHA 29.5% (95% CI, 9.1%-49.9%; p=0.019) and good but no significant changes in glenoid angle 6.7° (95% CI, 13.5°to 27.0°; p = 0.367). in the group of patients that were older than 5 years at the time of surgery.

No significant differences were present when examining male/female affected shoulder in PHHA (95% CI, -4.8% to 1.7%; p= .340), glenoid angle (95% CI, -5.4° to 3.0°; p= 0.558), or diameter (95% CI, -0.6 to 3.5 mm; p=0.171) no difference was seen between the groups with or without preoperative radiology in PHHA (95% CI, -2.8% to 3.3%; p=0.885), glenoid angle (95% CI, -2.3°to 5.4° p=0.431), or diameter (95% CI, -2.6 to 1.3 mm; p=0.531).

5.3 PAPER III

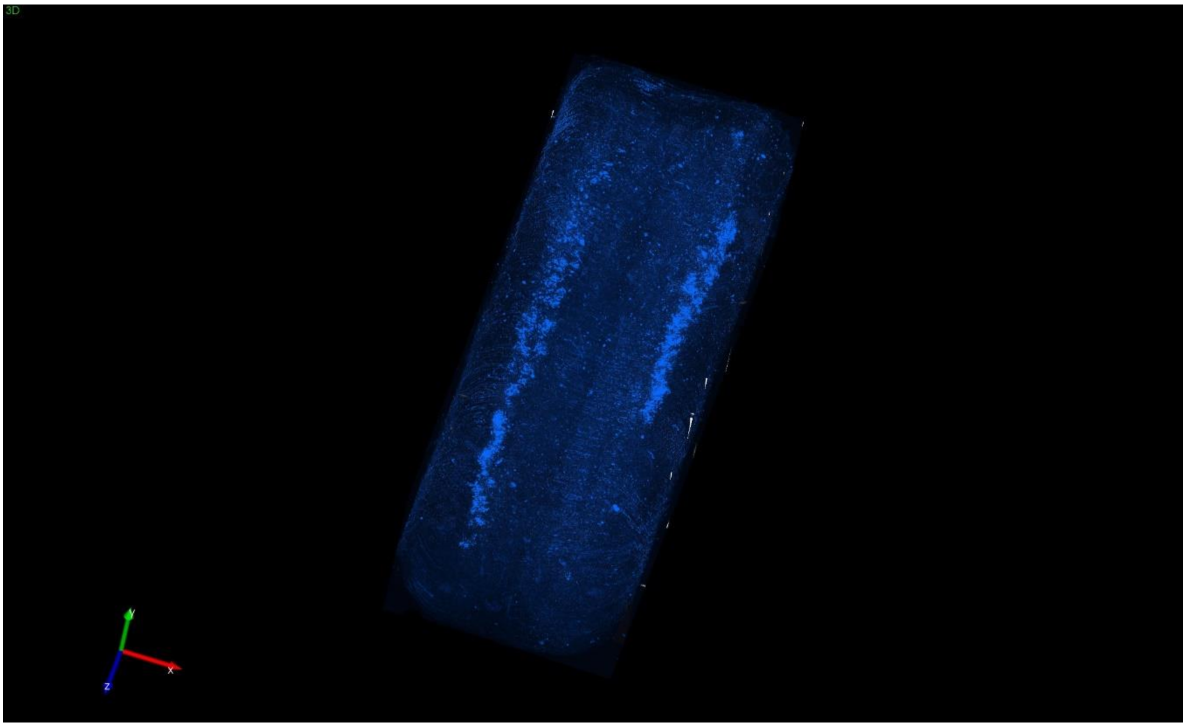
Measurements with the arm in adducted and abducted position differed substantially the mean external rotation before surgery was -8° (95% CI, -15° to -2°) in adduction. With shoulder joint abducted the preoperative external rotation was substantially larger 30° (95% CI, 21°-39°) and the gains during each step of the surgery were less dramatic. The respective values in external rotation after each surgical action can be followed in the table below. The mean excursion of the cranial and caudal part of the subscapularis tendon when pulled with a hemostat was 3mm (95% CI, 2mm to 4mm) and 2.5mm (95% CI, 2mm to 3 mm), respectively. The amount of lengthening required to achieve our desired external rotation was on average 12mm (95% CI, 10mm to 14 mm). Some patients had no passive excursion in the subscapularis tendon at all.

	Adducted	Abducted
Preoperatively	-8° (95% CI, -15°--2°)	30° (95% CI, 21°-39°)
After coracoidectomy	-5° (95% CI, -11°-2°)	37° (95% CI, 27°-47°)
After division of upper SS tendon	1° (95% CI, -6°-8°)	
After division of entire tendon	43° (95% CI, 40°-47°)	64° (95% CI, 56°-72°)
After repair	35° (95% CI, 33°-38°)	60° (95% CI, 53°-66°)

Table showing the average change in external rotation per surgical action with adducted and abducted shoulder

5.4 PAPER IV

Small differences in total fluorogold positive cells were seen in total between the side with a crush injury and the unaffected side. The injured side demonstrated less dense clustering of the fluorogold positive cells. This illustrated in the picture below a stack of transverse images lined up in a computer.



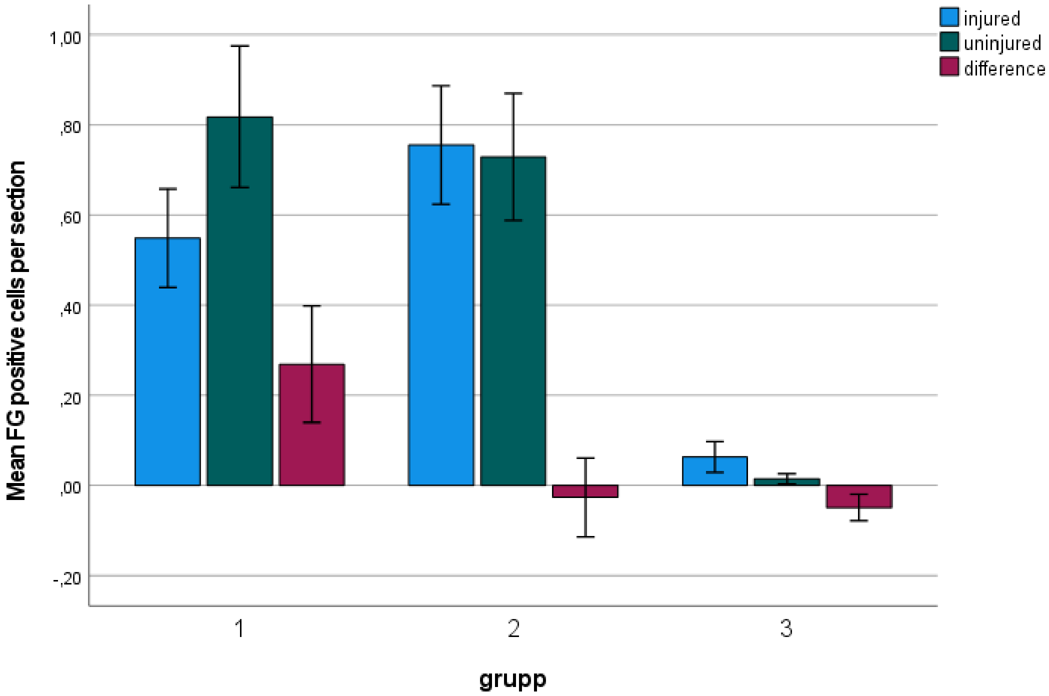
Compound image of ca 700 transverse cuts from one specimen. injured side to the left

When we examined the second group, which was transversally sectioned in the central area of interest (C5-6) and counted in full. We saw an average of 0.7073 (SD=0.71961) fluorogold positive cells per section. For the unaffected we saw an average of 1.0663 (SD=1.0663) fluorogold positive cells per section. The differences in FG positivity between sides departure significantly from normality W(89)=0.909, p<0.001). The difference in FG positive cells per section 0.3590 (SD=0.77790) was statistically significant (Z=-3.912, p<0.001).

When the longer part of spinal cord was examined (1/5 transverse sections examined) we saw similar differences in the cranial part (group 1) containing the C5-6 segments. 0.5542 (SD=0.49588) fluorogold positive cells per sedtion on the uninjured side while the uninjured side had an average of 0.8177 (SD=0.71199). The differences in FG positivity between sides departure significantly from normality W(83)=0.874, p<0.001). The difference in FG positive cells per section 0.2635 (SD=0.58679) was statistically significant (Z=-3.738, p<0.001).

In the following segments (group 2-3) the wider spread of fluorogold positive cells on the injured side levelled out and reversed the differences as illustrated in the below bar chart.

We found fewer NeuN positive cells on the injured side, the average was 6.3123 (SD=1.48605) NeuN positive cells and 7.0276 (SD=2.16876) Neu N positive cells for the uninjured and injured sides respectively. The difference in Neu N positive cells per section was not statistically significant (Z=-1.069, p=0.285).



Bar chart showing the average fluorogold positive cells per section for different areas of the spinal cord

6 DISCUSSION

The idea behind this work was as a wish to present solid evidence-based rational treatment for sequels of brachial plexus birth palsy. As it grew into a thesis, other aspects of the shoulder rotation needed to be addressed, for a complete presentation of the surgery and rotational problems but also to achieve a broader educational value of the work.

As we set off, having read thousands of charts regarding preoperative visits, surgical notes, and postoperative follow-up, I anticipated the compilation and statistical examination of the numbers would yield a fairly good outcome.

In surgical treatment and research achieved differences need to be substantial. Especially so if the surgery is not lifesaving. The risks involved when anesthetizing and breaking the skin barrier on someone does not allow for differences that need advanced statistics to show. Presentation of significant results without relevance should be avoided. In non- lifesaving surgery the number needed to treat should not exceed one. In the three clinical papers presented here we have achieved both statistically significant and clinically relevant results for our patients.

Study I and II are unusual in the literature on brachial plexus birth palsy in that they are prospectively gathered cohorts with a very long follow-up time and an adequate number of patients. That the patients were systematically examined by others than the surgeon is a strength the lack of controls are a weakness, albeit one that is hard to overcome. A smaller loss of follow up between one and seven years would perhaps be achieved by following the patients even if they demonstrate a stable level of function postoperatively more regularly (this has been implemented since the publication).

When a large group of patients are contacted years after the last visit the risk of inclusion or sample bias needs to be addressed. In this study we examined differences at one and seven years between the group that wished to participate with the group that did not respond. The group that responded and were examined had a higher degree of incongruence to the shoulder and slightly worse range of motion. This may explain their higher tendency to show up for examination. Although not recorded for this study it is reasonable to believe they have had more visits due to their status and thus may have a lower threshold to show up. On the other hand, the total nerve injuries which also often have more pronounced restrictions in movement and more frequent visits are underrepresented in paper I-II.

Since the group examined appear to have slightly worse status at one year postoperatively this investigation runs very little risk of overestimating the results of subscapular lengthening and repair with or without shoulder relocation and tendon transfers about the shoulder.

In paper I a large number of observations and variables were recorded for many patients over a long period of time. There are patients and measurements lost to follow up. In these cases, like in paper III, repetition of t-tests would aggregate the risk of false positive or type I error. It would also not take into account the short time follow-up values taken between preoperative investigation and at 7-year follow-up. Repeated ANOVA would be able to test all timepoints if taken simultaneously (the same time gaps) but is sensitive to missing values and always calculate with the base level as a mean. Mixed models is not sensitive to differences in time between measurements on different patients and can handle randomly missing data without omitting subjects[54]. A statistician (H Pettersson) was invaluable in setting up the statistical calculations and the carefully selected and executed statistics are a strength in this study.

The main finding is that the results from the one year follow up stands well over time. The gain in external rotation and its effect on the protruding elbow in the trumpet sign are good from the subscapularis release whilst the tendon transfers have less impact. The mallet score was also improved at long term follow-up. There was a slight loss of internal rotation.

Secondarily this study showed that the loss of internal rotation had only minute effect on the midline and across midline activities such as buttoning a shirt, and the results were very similar for the older age groups especially those with congruent joints.

This means in practicality that open subscapularis lengthening and repair with reposition of incongruent shoulder joints is a good treatment alternative for internal rotation contracture and that the results stand also for the older patients in these studies, something that may affect the decision to use derotational osteotomies as primary treatment for older children[15, 33].

In paper II the main finding was the consistent positive remodeling of repositioned joints over time, and that this applies to all examined patients regardless of age, and joint subcategory, sex or presence of preoperative radiology benefitted equally from the surgery.

All pre-postop measurements improved, albeit the diameter of the humeral head increases naturally as the shoulders grow and it is preferable to compare the affected and unaffected joint for this measurement (see table in chapter 5.3).

Unlike other examinations of shoulder incongruity in BPBP who categorize joints radiologically[28, 38] our classification is based in the findings at surgery for several reasons:

- Dynamic inspection allows to take into account the movement of the humeral head from internal to external rotation (wether it translates forward and clicks into place over a ridge)
- MRI with arms at the sides sometimes miscategorize joint congruity
- Via direct inspection we can verify that the joint really is positioned in the correct glenoid

Paper II presents strengths in the number of patients, prospective design, and number of patients. A drawback is the missing data preoperatively and that all measurements are performed by one radiologist. The groups who had and did not have preoperative data do not differ in achieved percentage of humeral head anterior to midscapular line, humeral head diameter or glenoid angle.

Regarding the measurement's usability, the glenoid angle is difficult to measure accurately and reliably repeatable. There are several problems with measurement of glenohumeral angle. It is in a convex glenoid difficult to accurately place the antero-posterior line. Most importantly, in an article by Pedowitz et al[55] MRI was performed during the immediate postoperative period (<5 weeks) on 22 children who underwent arthroscopic anterior capsular release, subscapularis tenotomy, and glenohumeral reduction. During those five weeks their glenoid angle is stated to have improved from a mean of -37° to mean -8°. This is of course far too fast for bony remodeling. This is presumably then an effect of the pliability or sponge-like properties of the glenoid cartilage which expands behind the glenoid to change the angle at this remarkable rate. Percentage of humeral head anterior to the midscapular line is a more reliable measurement but needs to be documented after any postoperative fixation cast, splint, or orthosis has been removed. A forced externally rotated position will keep the humeral head anteriorly positioned but unless that position is maintained after removal of the fixation it does not provide evidence of treatment success. We have seen the oldest patients in the cohort remodeling towards good results and this strengthens the argument from paper I that also older patients benefit from open subscapularis elongation and an externally rotating osteotomy should be considered only after a repositioning has been considered and deemed impossible or without chance of success.

The youngest patient in our material with an incongruent shoulder was around 6 months and as mentioned in the introduction there are reports of incongruence in children as young as 3 months[37]. This and the fact that we unlike others[24] find a poor correlation between age and type of incongruence has led to questioning of the theory that there is a clear chain of events with internal rotation contracture leading to unbalanced forces on the glenoid surface, leading to light then more pronounced incongruence followed by complete dislocation.

The results support open reposition of the glenohumeral joint together with subscapularis lengthening and repair as treatment for the rotation contracture with shoulder incongruence in brachial plexus birth palsy. Repositioning of the joint yields favorable results also in the few older children we have treated.

In paper III the main finding is the very large proportion of gain in external rotation that occurs when the entirety of the subscapularis tendon is divided. This is the biomechanical explanation for the results in paper I-II. Secondarily but very interesting and building on the senior authors previous work[29] we find that the subscapularis muscle does not provide enough passive excursion in either part to exert internal rotational force across the entire rotational sector. The lengthening in relation to the excursion is simply too great.

It is hard to extrapolate which surgical actions yield results when performing the surgery arthroscopically, which is a widely spread treatment of rotational contracture in brachial plexus birth palsy. A corresponding study from a center which treats these patients arthroscopically would be welcome. Given the large impact the subscapularis musclo-tendinous unit has in our material it is not likely that it is possible to achieve a controlled surgical lengthening without addressing the subscapularis tendon.

The smaller differences between surgical actions and greater external rotation at the beginning of surgery with the shoulder abducted may be attributed to the fact that the subscapular muscle transitions from a band in front of the shoulder to an oblique narrower structure in abduction[56]. Abducted rotational measurements are not used in our clinic as standard.

We try to achieve a consistent and precise way to evaluate external rotation with minimal force exerted and both examiners paying attention to the transition from glenohumeral to thoraco-scapular movement. But these measurements, while very precise will have some individuality and thus less accuracy between examiners. In this study we find such a dramatic increase in external rotation with the division of the subscapularis tendon that it is unlikely that differences in measuring technique would change the results.

It is likely not impossible to achieve congruence and external rotation without a controlled subscapularis lengthening, at least at the time of surgery. Closed manipulation of the joint was proposed as early as 1905[4]. However, in view of the quite substantial elongation that is required to achieve adequate external rotation it is doubtful it can be accomplished by manipulation without tearing the subscapularis musculotendinous unit to some extent. The short excursion of the muscle also raises the question of how Botox can aid in the treatment. When the muscle is passively stiff less activity at the motor endplates should not affect the resting length of the muscle.

In paper IV results of preclinical experiments on co-contractions in a rat model are presented. We found a slightly smaller number of cells with detectable fluorogold on the injured side. This is to be expected since some neurons go through cell death after injury, especially in juveniles[57].

The study is novel in the sense that the phenomenon of co-contractions in brachial plexus birth palsy has to our knowledge not been studied in an animal model before. More animals could have added strength to the study, in investigating and comparing other muscles and their innervation’s reaction to injury.

On the injured side the fluorogold positive cells were dispersed over a longer distance with less densely packed cells. This supports the theory of “misguided” nerves[45] as the fluorogold must have taken a different route through the neuroma to land in a new area of the spinal cord.

There are however problems with misguided nerves as the sole explanation. Misguided nerves can be compensated for by the plasticity in the brain even in adults[58]. Moreover, children have better functional outcome after nerve stem injuries[59]. The problems for the brachial plexus birth palsy patients with large amounts of co-contractions may then be central rather than peripheral. In investigations of eyesight in laboratory animals it has been found that research models that creates temporary blindness on one eye during some development stages causes irreversible changes to the visual cortex representation for that eye[60]. Analog to this the damage to input or feedback loops may be what cause a faulty pattern of activation in some BPBP patients.

.

7 CONCLUSIONS

The injury to the nerves in brachial plexus birth palsy causes an array of consequences for the affected limb. The structure that causes internal rotation contracture is a short and unpliable subscapularis musculotendinous unit. To controllably release the contracture without unnecessary trauma the entire subscapularis tendon needs to be surgically divided or lengthened.

When lengthening the subscapularis tendon, a loss of internal rotation is expected, and clinicians should strive to place the available rotation in the most useful sector.

Open subscapularis lengthening and repair with relocation of the joint if incongruent provides excellent results on internal rotation contracture and correction of the trumpet sign, the loss of internal rotation is small and has a small impact on daily function. In cases of incongruence the procedure also provides excellent remodeling of the glenohumeral joint towards normal. The procedure has had favorable results in the few patients we have treated in adolescence and should be considered as an option also in older patients.

A neuroma in continuity has potential to cause axons to take the wrong path as they grow to reach the periphery, but this alone is unlikely to be the sole cause of co-contractions.

8 POINTS OF PERSPECTIVE

The two first papers in this thesis presents what I believe to be, at present, the best available evidence for any treatment of the internal rotation contracture and incongruent shoulder joint in brachial plexus birth palsy. The patients that make up this cohort were operated between 1997 and 2009. The studies represent unique material in that they were prospectively included, were operated using consistent indication and method by one single surgeon. They have been thoroughly examined clinically and radiologically at one and 7 years. The oldest patient at the long-term follow-up was 34 years old and the bulk of patients were examined before adulthood.

This presents an immense opportunity for further research; hard clinical data should be presented on the results in range of motion and radiological development once all patients have stopped growing and reached adulthood. The implications of the injury and the treatment on life and function of these patients, things such as choice of occupation, pain, and hindrances in daily life should be recorded and preferably compared to a cohort that has not been surgically treated.

Further studies into the biomechanics of the open subscapularis release are at this point superfluous, but it would be interesting to engage a center who today has arthroscopy as standard treatment to perform the same measurements whilst performing subscapularis release via their approach. If the arthroscopic methods show similar results over time the methods could be directly compared to the open approach, maybe even randomized.

Regarding the origins of co-contractions there are numerous questions that need answering. Now that we have presented a model that seems to work in studying the behavior of axons through a neuroma in continuity the approach needs to broaden.

First the presence of co-contractions about the shoulder needs to be established in our animal model, this can be done via neurophysiology with surgically recording electrodes in the muscles affected by the afflicted nerve injury. Rats can´t tension their muscles on command and this needs to be addressed, continuous recording or transcranial stimulation could be used to overcome this. Transcranial stimulation can also be used to map the differences in the affected and unaffected limbs representation in the motor cortex.

The tracing should evolve to include at least two antagonistic muscles on each side each with different tracers. By using for example Fluororuby on the internal rotators and Fluorogold or Fastblue on the external rotators we should be able to detect differences and calculate the overlap of the representation of the different muscles in the motor neurons tracts. If the numbers representing overlapping areas in the motor horn, then could be related to the already recorded frequency of co-contractions we could come closer to a stand on whether this phenomenon has peripheral or central origin.

FMRI images of the motor cortex activity on patients with debilitating co-contractions and patients with little or no co-contractions should be collected and compared. The ultimate goal here must be to either create better training programs to allow the motor cortex to mature in the correct way, or change the surgical indications, like amblyopia in a 3-year-old is aggressively treated to avoid cerebral visual impairment, maybe we need to include those who run the risk of cerebral motor impairment in the indications for nerve reconstruction.

ACKNOWLEDGEMENTS

Marie Andersson, for your sharp mind and for your commitment and care for the patients and these studies

Jenny Gustavsson, for literally letting me through the gates and more at KI

Maria Angeria, for teaching me all I know about tissue handling, sectioning, and immunofluorescence

Anette Fransson, for teaching me animal perfusion and for running the animal lab like a swiss watch

Erik Lidin, for invaluable help in image handling and microscopy

Jenny Skogsberg, for teaching me how to handle, care for and like rats

Fredrik Wermeling, for advice and friendship above and beyond your role as mentor for this project but also for being in the top 0.8 ‰

9 REFERENCES

1. Mehlman CT. Neonatal Brachial Plexus Palsy: History and Epidemiology. In: Abzug JM, Kozin S, Zlotolow DA, eds. *The Pediatric Upper Extremity*. Springer New York; 2013:1-21.
2. Smellie W, Bell A. *A Treatise on the Theory and Practice of Midwifery*. C. Elliot; 1784.
3. Kennedy R. SUTURE of the BRACHIAL PLEXUS in BIRTH PARALYSIS of the UPPER EXTREMITY. *Br Med J*. Feb 7 1903;1(2197):298-301. doi:10.1136/bmj.1.2197.298
4. Whitman R. VIII. The Treatment of Congenital and Acquired Luxations at the Shoulder in Childhood. *Ann Surg*. Jul 1905;42(1):110-5.
5. Hoeksma AF, Wolf H, Oei SL. Obstetrical brachial plexus injuries: incidence, natural course and shoulder contracture. *Clin Rehabil*. Oct 2000;14(5):523-6.
6. Aberg K, Norman M, Pettersson K, Ekeus C. Vacuum extraction in fetal macrosomia and risk of neonatal complications: a population-based cohort study. *Acta Obstet Gynecol Scand*. Oct 2016;95(10):1089-96. doi:10.1111/aogs.12952
7. Abzug JM, Kozin SH. Evaluation and management of brachial plexus birth palsy. *Orthop Clin North Am*. Apr 2014;45(2):225-32. doi:10.1016/j.ocl.2013.12.004
8. Buterbaugh KL, Shah AS. The natural history and management of brachial plexus birth palsy. *Curr Rev Musculoskelet Med*. Sep 28 2016;doi:10.1007/s12178-016-9374-3
9. Pederson WC. In: Wolfe SW, Hotchkiss RN, Pederson WC, Kozin SH, Cohen MS, eds. *Green's operative hand surgery*. 7 ed. Elsevier; 2017:1237.
10. Sever JW. Obstetric Paralysis-Its Cause and Treatment. *Can Med Assoc J*. Feb 1920;10(2):141-61.
11. Christoffersson M, Rydhstroem H. Shoulder dystocia and brachial plexus injury: a population-based study. *Gynecol Obstet Invest*. 2002;53(1):42-7. doi:10.1159/000049410
12. Pondaag W, Malessy MJ, van Dijk JG, Thomeer RT. Natural history of obstetric brachial plexus palsy: a systematic review. *Dev Med Child Neurol*. Feb 2004;46(2):138-44.
13. Hultgren T, Jonsson K, Pettersson H, Hammarberg H. Surgical correction of a rotational deformity of the shoulder in patients with obstetric brachial plexus palsy: Short-term results in 270 patients. *Bone Joint J*. Oct 2013;95-b(10):1432-8. doi:10.1302/0301-620x.95b10.32049
14. Duff SV, DeMatteo C. Clinical assessment of the infant and child following perinatal brachial plexus injury. *J Hand Ther*. Apr-Jun 2015;28(2):126-33; quiz 134. doi:10.1016/j.jht.2015.01.001
15. Vuillermin C, Bauer AS. Boston Children's Hospital approach to brachial plexus birth palsy. *J Pediatr Orthop B*. Jul 2016;25(4):296-304. doi:10.1097/bpb.0000000000000330
16. Waters PM. Update on management of pediatric brachial plexus palsy. *J Pediatr Orthop B*. Jul 2005;14(4):233-44.
17. Clarke HM, Curtis CG. An approach to obstetrical brachial plexus injuries. *Hand clinics*. Nov 1995;11(4):563-80; discussion 580-1.
18. ter Steeg AM, Hoeksma AF, Dijkstra PF, Nelissen RG, De Jong BA. Orthopaedic sequelae in neurologically recovered obstetrical brachial plexus injury. Case study and literature review. *Disabil Rehabil*. Jan 7 2003;25(1):1-8.
19. Fairbank H. Birth palsy: subluxation of the shoulder-joint in infants and young children. *Lancet*. 1913;1(1217-1223):6.
20. Sever JW. THE RESULTS OF A NEW OPERATION FOR OBSTETRICAL PARALYSIS. *JBJS*. 1918;s2-16(4):248-257.
21. Carlioz H, Brahimi L. [Place of internal disinsertion of the subscapularis muscle in the treatment of obstetric paralysis of the upper limb in children]. *Ann Chir Infant*. Mar-Apr 1971;12(2):159-67. La place de la desinsertion interne du sous-scapulaire dans le traitement de la paralysie obstetricale du membre superieur chez l'enfant.
22. Birch R, Chen L. The medial rotation contracture of the shoulder in obstetric brachial plexus palsy. *J Bone Joint Surg Br*. 1996;78(suppl I):68.
23. Pearl ML. Arthroscopic release of shoulder contracture secondary to birth palsy: an early report on findings and surgical technique. *Arthroscopy*. Jul-Aug 2003;19(6):577-82.

24. Kambhampati SB, Birch R, Cobiella C, Chen L. Posterior subluxation and dislocation of the shoulder in obstetric brachial plexus palsy. *J Bone Joint Surg Br*. Feb 2006;88(2):213-9. doi:10.1302/0301-620x.88b2.17185
25. Waters PM, Bae DS. The early effects of tendon transfers and open capsulorrhaphy on glenohumeral deformity in brachial plexus birth palsy. Surgical technique. *J Bone Joint Surg Am*. Oct 1 2009;91 Suppl 2:213-22. doi:10.2106/jbjs.i.00501
26. Kany J, Kumar HA, Amaravathi RS, et al. A subscapularis-preserving arthroscopic release of capsule in the treatment of internal rotation contracture of shoulder in Erb's palsy (SPARC procedure). *J Pediatr Orthop B*. Sep 2012;21(5):469-73. doi:10.1097/BPB.0b013e328353a19f
27. L'Episcopo JB. Tendon transplantation in obstetrical paralysis. *The American Journal of Surgery*. 1934/07/01/ 1934;25(1):122-125. doi:https://doi.org/10.1016/S0002-9610(34)90143-4
28. Waters PM, Smith GR, Jaramillo D. Glenohumeral deformity secondary to brachial plexus birth palsy. *J Bone Joint Surg Am*. May 1998;80(5):668-77.
29. Hultgren T, Einarsson F, Runesson E, Hemlin C, Friden J, Ljung BO. Structural characteristics of the subscapularis muscle in children with medial rotation contracture of the shoulder after obstetric brachial plexus injury. *J Hand Surg Eur Vol*. Jan 2010;35(1):23-8. doi:10.1177/1753193409349153
30. Nikolaou S, Peterson E, Kim A, Wylie C, Cornwall R. Impaired growth of denervated muscle contributes to contracture formation following neonatal brachial plexus injury. *J Bone Joint Surg Am*. Mar 2 2011;93(5):461-70. doi:10.2106/jbjs.j.00943
31. Weekley H, Nikolaou S, Hu L, Eismann E, Wylie C, Cornwall R. The effects of denervation, reinnervation, and muscle imbalance on functional muscle length and elbow flexion contracture following neonatal brachial plexus injury. *J Orthop Res*. Aug 2012;30(8):1335-42. doi:10.1002/jor.22061
32. Waters PM, Bae DS. Effect of tendon transfers and extra-articular soft-tissue balancing on glenohumeral development in brachial plexus birth palsy. *J Bone Joint Surg Am*. Feb 2005;87(2):320-5. doi:10.2106/jbjs.c.01614
33. Abzug JM, Kozin SH, Waters PM. Open Glenohumeral Joint Reduction and Latissimus Dorsi and Teres Major Tendon Transfers for Infants and Children Following Brachial Plexus Birth Palsy. *Tech Hand Up Extrem Surg*. Jun 2017;21(2):30-36. doi:10.1097/bth.0000000000000150
34. Hultgren T, Jonsson K, Roos F, Jarnbert-Pettersson H, Hammarberg H. Surgical correction of shoulder rotation deformity in brachial plexus birth palsy: long-term results in 118 patients. *Bone Joint J*. Oct 2014;96-b(10):1411-8. doi:10.1302/0301-620x.96b10.33813
35. Jonsson K, Werner M, Roos F, Hultgren T. Development of the glenohumeral joint after subscapular release and open relocation in children with brachial plexus birth palsy: long-term results in 61 patients. *J Shoulder Elbow Surg*. May 10 2019;doi:10.1016/j.jse.2019.02.025
36. Hoffer MM, Wickenden R, Roper B. Brachial plexus birth palsies. Results of tendon transfers to the rotator cuff. *J Bone Joint Surg Am*. Jul 1978;60(5):691-5.
37. Poyhia TH, Lamminen AE, Peltonen JI, Kirjavainen MO, Willamo PJ, Nietosvaara Y. Brachial plexus birth injury: US screening for glenohumeral joint instability. *Radiology*. Jan 2010;254(1):253-60. doi:10.1148/radiol.09090570
38. Pearl ML, Edgerton BW. Glenoid deformity secondary to brachial plexus birth palsy. *J Bone Joint Surg Am*. May 1998;80(5):659-67.
39. Friedman RJ, Hawthorne KB, Genez BM. The use of computerized tomography in the measurement of glenoid version. *J Bone Joint Surg Am*. Aug 1992;74(7):1032-7.
40. Kozin SH, Chafetz RS, Shaffer A, Soldado F, Filipone L. Magnetic resonance imaging and clinical findings before and after tendon transfers about the shoulder in children with residual brachial plexus birth palsy: a 3-year follow-up study. *J Pediatr Orthop*. Mar 2010;30(2):154-60. doi:10.1097/BPO.0b013e3181cfce09
41. Jönsson K, Roos F, Hultgren T. Structures contributing to the shoulder contracture in brachial plexus birth palsy. An intraoperative biomechanical study. *J Hand Surg Eur Vol*. Aug 3 2021:17531934211034968. doi:10.1177/17531934211034968

42. Waters PM, Bae DS. The effect of derotational humeral osteotomy on global shoulder function in brachial plexus birth palsy. *J Bone Joint Surg Am*. May 2006;88(5):1035-42. doi:10.2106/jbjs.e.00680
43. Rollnik JD, Hierner R, Schubert M, et al. Botulinum toxin treatment of cocontractions after birth-related brachial plexus lesions. *Neurology*. Jul 12 2000;55(1):112-4. doi:10.1212/wnl.55.1.112
44. Buchanan PJ, Grossman JAI, Price AE, Reddy C, Chopan M, Chim H. The Use of Botulinum Toxin Injection for Brachial Plexus Birth Injuries: A Systematic Review of the Literature. *Hand (N Y)*. Mar 2019;14(2):150-154. doi:10.1177/1558944718760038
45. Roth G. [Reinnervation in obstetrical brachial plexus paralysis]. *J Neurol Sci*. Jan 1983;58(1):103-15. Réinnervation dans la paralysie plexulaire brachiale obstétricale. doi:10.1016/0022-510x(83)90113-2
46. Overbeek CL, Kolk A, Nagels J, et al. Increased co-contraction of arm adductors is associated with a favorable course in subacromial pain syndrome. *J Shoulder Elbow Surg*. Nov 2018;27(11):1925-1931. doi:10.1016/j.jse.2018.06.015
47. Costales JR, Socolovsky M, Sánchez Lázaro JA, Álvarez García R. Peripheral nerve injuries in the pediatric population: a review of the literature. Part I: traumatic nerve injuries. *Childs Nerv Syst*. Jan 2019;35(1):29-35. doi:10.1007/s00381-018-3974-8
48. Bertelli JA, Mira JC, Gilbert A, Michot GA, Legagneux J. Anatomical basis of rat brachial plexus reconstruction. *Surg Radiol Anat*. 1992;14(1):85-6.
49. Li Z, Barnwell J, Tan J, Koman LA, Smith BP. Microcomputed tomography characterization of shoulder osseous deformity after brachial plexus birth palsy: a rat model study. *J Bone Joint Surg Am*. Nov 3 2010;92(15):2583-8. doi:10.2106/jbjs.i.01660
50. Schmued LC, Fallon JH. Fluoro-Gold: a new fluorescent retrograde axonal tracer with numerous unique properties. *Brain Res*. Jul 2 1986;377(1):147-54.
51. Mullen RJ, Buck CR, Smith AM. NeuN, a neuronal specific nuclear protein in vertebrates. *Development*. Sep 1992;116(1):201-11.
52. Bae DS, Waters PM, Zurakowski D. Reliability of three classification systems measuring active motion in brachial plexus birth palsy. *J Bone Joint Surg Am*. Sep 2003;85(9):1733-8. doi:10.2106/00004623-200309000-00012
53. Lippert WC, Mehlman CT, Cornwall R, et al. The intrarater and interrater reliability of glenoid version and glenohumeral subluxation measurements in neonatal brachial plexus palsy. *J Pediatr Orthop*. Jun 2012;32(4):378-84. doi:10.1097/BPO.0b013e31825611bd
54. Järnbert-Pettersson H, Vixner L. Labour Q1 pain – poorly analysed and reported: a systematic review. *BMC Pregnancy and Childbirth*. 2018/12/07 2018;18(1):483. doi:10.1186/s12884-018-2089-2
55. Pedowitz DI, Gibson B, Williams GR, Kozin SH. Arthroscopic treatment of posterior glenohumeral joint subluxation resulting from brachial plexus birth palsy. *J Shoulder Elbow Surg*. Jan-Feb 2007;16(1):6-13. doi:10.1016/j.jse.2006.04.008
56. Turkel SJ, Panio MW, Marshall JL, Girgis FG. Stabilizing mechanisms preventing anterior dislocation of the glenohumeral joint. *J Bone Joint Surg Am*. Oct 1981;63(8):1208-17.
57. Lowrie MB, Vrbová G. Repeated injury to the sciatic nerve in immature rats causes motoneuron death and impairs muscle recovery. *Exp Neurol*. Sep 2001;171(1):170-5. doi:10.1006/exnr.2001.7739
58. Dahlin LB, Wiberg M. Nerve injuries of the upper extremity and hand. *EFORT Open Rev*. May 2017;2(5):158-170. doi:10.1302/2058-5241.2.160071
59. Chemnitz A, Björkman A, Dahlin LB, Rosén B. Functional outcome thirty years after median and ulnar nerve repair in childhood and adolescence. *J Bone Joint Surg Am*. Feb 20 2013;95(4):329-37. doi:10.2106/jbjs.L.00074
60. Blakemore C, Garey LJ, Vital-Durand F. The physiological effects of monocular deprivation and their reversal in the monkey's visual cortex. *J Physiol*. Oct 1978;283:223-62. doi:10.1113/jphysiol.1978.sp012498