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IMPROVING SHOULDER FUNCTION IN BRACHIAL PLEXUS BIRTH INJURY

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DOCTORAL DISSERTATION

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To everyone who made this possible

TABLE OF CONTENTS

ABSTRACT

The reported incidence of brachial plexus birth injury (BPBI) is 0.2-3 per 1000 live births. Most (70-80%) BPBI are temporary resolving within the first months of life. The extent and type of root injury in permanent BPBI can be evaluated with serial clinical examinations and with electroneuromyography (EMG), computer tomography (CT), or magnetic resonance imaging (MRI). Children with permanent BPBI may benefit from non-invasive therapy, Botulinum toxin A (BTX) injection and surgery. Permanent BPBI injury causes structural changes in the affected muscles, and dysplastic changes especially to the shoulder joint. These changes can lead to limited upper limb range of motion (ROM).

The aims of this study are: to calculate the annual incidence of permanent BPBI in the hospital district of Helsinki and Uusimaa in 1995-2019, to analyze whether cervical MRI is reliable in detecting root avulsions, to assess if shoulder dysplasia can be prevented by a protocol including early ROM exercises, ultrasound (US) screening, and BTX injections in combination with spica bracing, and to develop a new neurotization technique to restore active shoulder external rotation (ER) in adduction.

HUS, New Children's Hospital is the only treatment center for permanent BPBI for the 1.7 million residents of the region of Uusimaa, Finland. The hospital serves as a tertiary treatment center for a population of 2.2 million. 431 children with BPBI were referred to our brachial plexus clinic between 1995 and 2019. The injury was temporary in 173 and permanent in 258 children. Of children with permanent injury, 179 were born in our primary catchment area, with 437454 births during the 25-year-long study period. Cervical MRI was done to all 34 children born between 2007 and 2013 who were clinically potential candidates for plexus surgery. Root avulsion in MRI served as one indication to recommend plexus repair.

Our shoulder protocol to prevent shoulder dysplasia, including ROM exercises, US screening, BTX injections, and shoulder ER spica bracing, was developed between 2000 and 2009. The time of shoulder dysplasia detection and the type and rate of shoulder surgery were registered and shoulder outcome was assessed in 237 of the 285 children with permanent BPBI. A new surgical technique to restore active shoulder ER in patients with congruent shoulders and active abduction above horizontal was developed in 2014. The midterm outcome of our new technique to neurotize the infraspinatus muscle with the spinal accessory nerve (SAN) was clinically assessed in 14 children.

The risk for permanent BPBI in the hospital district of Helsinki and Uusimaa from vaginal births varied annually between 0.1 and 0.9 per 1000, with a decreasing tendency from 1995 to 2019. MRI was a reliable imaging modality with both high sensitivity (0.88) and specificity (1.00) for avulsion injuries. Posterior shoulder subluxation, as a result of advancing shoulder dysplasia, was verified by imaging in 48% (114/237) of children with permanent injury. Mean age at detection dropped from 5 years (range 0.3-8.6) in children born before 2000 to 4.9 months (range 1.1-12) in children born 2010 or later. The rate of shoulder relocation declined from 28% (15/55) to 7% (5/76) respectively. Active shoulder ER in adduction had improved by mean 57° (range 40-95°) in 12/14 children, active ER in abduction by mean 56° (range 30-85) and active abduction mean 27° (range 10-60°) in all 14 patients 4 years (range 2-5) after specific neurotization of the infraspinatus muscle with SAN.

The annual incidence of permanent BPBI shows marked variation with a decreasing trend in the region of Uusimaa, Finland. MRI has both high sensitivity and specificity for detecting root avulsion injuries. Half of all children with permanent BPBI develop shoulder dysplasia during the first year, which can be reliably detected with US. ROM exercises, BTX injections and spica bracing seem beneficial in preventing and treating shoulder dysplasia in children 6-12 months old. Active ER in adduction can be reliably restored and maintained by neurotizing the infraspinatus muscle with SAN.

ABSTRAKT

Obstetrisk brachialplexus skada (OPB) uppkommer i 0.2-3 av 1000 födslar och associeras oftast med vaginal förlossning. Till riskfaktorer för OBP räknas makrosomi (födselvikt >4.5kg), övervikt hos den gravida, Typ II diabetes samt avvikande foster presentation vid förlossningen. Skadans svårighetsgrad definieras av hur många av nerverna som drabbats, samt till vilken grad. En fjärdedel av skadorna är permanenta. De mildare, icke permanenta skadorna, läks helt under det första levnadsåret. Diagnosen är klinisk, och skadans svårighetsgrad kan vidare undersökas med hjälp av elektroneuromyografi, datortomografi med intratekalt kontrastmedel, eller magnet resonanstomografi (MRT). Under de senaste åren har MRT blivit allt mer populär som förstahands undersökning, då den är betydligt mindre invasiv.

Vården av bestående OBP i Helsingfors och Nylands sjukvårdsdistrikt (HUS) är centrerad till HUS barnkirurgiska enhet, Nya barnsjukhuset. Enheten ansvar även för vården av barn med bestående OBP födda i HUS tertiärvårds område. Vården avgörs beroende på skadans svårighetsgrad. I de mest alvarliga fallen rekommenderas kirurgisk rekonstruktion av brachialplexus under det första levnadsåret. Barn med bestående OBP utvecklar ofta muskulär obalans då musklernas normala utveckling störs av nervskadan. Som följd uppkommer rörelsebegränsningar i leder, främst axel- och armbågsleden. I axelleden leder dessa ofta till försämrad, eller obefintlig utåtrotation (UR). Även strukturellas förändringar, främst i axelleden, förekommer. Med hjälp av dagliga rörelseträningar kan man eventuellt minska uppkomsten av de förenämnda rörelsebegränsningarna och strukturella förändringarna, samt upprätthålla ledens passiva rörelse tills de egna musklerna återhämtat sig, eller funktionsstörningen kirurgiskt korrigerats. Under de senaste åren har det satsats mera på metoder som ämnar förebygga uppkomsten av bestående förändringar i axelleden.

Studiens huvudsyften är att reda ut incidensen för bestående OBP i Helsingfors och Nylands sjukvårdsdistrikt (HUS), reda ut om MRT är en pålitlig modalitet för påvisning av nervrots avulsion, reda ut om dysplastiska förändringar i axelleden kan reduceras med hjälp av daglig rörelseträning, ultraljuds (UL) screening, i kombination med Botulinum toxin A (BTX) injektioner och immobilisation i skena, samt utveckla en ny operationsteknik för att förbättra aktiv UR i axelleden. Studien omfattar barn födda mellan 1995 och 2019 med permanent OBP som vårdats på HUS barnkirurgiska enhet, Nya Barnsjukhuset. Under studiens gång vårdades 431 barn på enheten, 258 hade permanent skada. Under samma period föddes 437 454

barn i Helsingfors och Nylands sjukvårdsdistrikt, 179 av dem fick bestående OBP. Innan år 2000 fanns ingen regelbunden uppföljning av axelleden. Vårt nuvarande protokoll utvecklades mellan 2000-2010, och har varit i regelbundet bruk sedan 2010. Protokollet består av daglig rörelseträning, regelbunden UL screening under det första levnadsåret, och om dysplastiska förändringar, eller ledkontrakturer uppstår, behandling med BTX samt immobilisation av axelleden i UR-skena.

Incidensen för permanent skada för barn födda i Helsingfors och Nylands sjukvårdsdistrikt var över hela studieförloppet 0.5 per 1000 levandefödda, under de senaste fem åren (2015-2019) sjönk den till 0.3. Vi fann MRT att vara en pålitlig undersökning modalitet vid påvisning av avulsionsskador (sensitivitet 0.9, specificitet 1). Axelleds subluxation påvisades hos 48% (114/327) av barn med permanent OBP. Åldern då förändringen upptäcktes sjönk från 5 år (barn födda 1995-2000) till 5 månader (barn födda 2010-2019). Mängden kirurgiska relokationer av axelleden sjönk i förenämnda grupper från 28% (15/55) till 7% (5/76). Med hjälp av specifik neurotisation av infraspinatus muskeln med accessorius nerven (AN) förbättrades den aktiva UR i adduktion i medeltal 57° (40–95) hos 12/14 patienter. Alla 14 fick förbättrad aktiv UR i abduktion 56° (30-85) samt aktiv abduktion 27° (10 to 60) i axelleden under uppföljningstiden på 4 år (2-5).

Förekomsten av bestående OBP har under de senaste åren minskat i Helsingfors och Nylands sjukvårdsdistrikt. MRT har både hög sensitivitet och specificitet för detektion av avulsionsskador hos barn med OBP. Ca hälften av barnen med en permanent skada utvecklar dysplastiska förändringar i axelleden under det första året. Dessa kan upptäckas mha regelbunden UL screening, och deras svårighetsgrad möjligen minskas genom regelbunden rörelseträning samt BTX i kombination med immobilisation i UR-skena. Aktiv UR kan återfås och bibehållas genom neurotisation av infraspinatus muskeln med AN.

LIST OF ORIGINAL PUBLICATIONS

I Grahn P, Pöyhiä T, Sommarhem A, Nietosvaara Y. Clinical significance of cervical MRI in brachial plexus birth injury. Acta Orthop. 2019 Apr; 90(2): 111–118.

II Grahn P, Sommarhem A, Nietosvaara Y. Improving shoulder function in children with brachial plexus birth injury. Provisionally accepted for publication in J Hand Surg Eur July 2021.

III Sommarhem A, Grahn P, Nietosvaara Y. Selective neurotization of the infraspinatus muscle in brachial plexus birth injury patients using the accessory nerve. Plast Reconstr Surg. 2015 Dec;136(6):1235-1238.

IV Grahn P, Sommarhem A, Lauronen L, Nietosvaara Y. Mid-term outcome after selective neurotization of the infraspinatus muscle in patients with brachial plexus birth injury. Plast Reconstr Surg Glob Open. 2020 Jan 24;8(1):e2605.

The publications are referred to in the study by their roman numerals and reprinted with the permission of their copyright holders. Some previously unpublished data are also presented.

ABBREVATIONS

AMS	Active movement scale
bFFE	Balanced fast field echo
BPBI	Brachial plexus birth injury
BTX	Botulin toxin-A
CT	Computer tomography
CP	Complete plexus involvement
EMG	Electromyography
ER	External rotation
FU	Follow-up
FUE	Flail upper extremity
GHJ	Glenohumeral joint
GSA	Glenoscapular angle
HUS	Helsinki university hospital
IR	Internal rotation
IS	Infraspinatus muscle
IU	International units
LD	Latissimus dorsi muscle
MRI	Magnetic resonance imaging
MUP	Motor unit potential
PM	Pectoralis major muscle
PMC	Pseudomeningocele
SS	Subscapularis muscle
ROM	Range of motion
SAN	Spinal accessory nerve
SSN	Suprascapular nerve
SSNI	Suprascapular nerve to infraspinatus
TM	Teres major muscle
UP	Upper plexus injury
US	Ultrasound
3MTS	3-month Toronto test score

1 INTRODUCTION

William Smellie first described brachial plexus birth injury (BPBI) in 1764[1] when he reported on an infant with postpartum bilateral diminished motion of the upper limbs. The changes resolved within weeks. Nearly 100 years later the injury was further characterized by others, mainly Guillaume Duchenne, Wilhelm Erb and Augusta Klumpke,[2–7] to upper, lower, and whole arm injuries, either with or without concomitant injury to the humerus or clavicle. Erb, in his study of adults published in 1874, documented a typical point of injury where the fifth and sixth roots connect to form the upper trunk.[7] Hence, the name Erb´s palsy is commonly used in injuries concerning the upper plexus. In 1885, Klumpke[6] described 16 patients with complete paralysis, showing the now-pathognomonic signs for lower root avulsions; ptosis and miosis (partial drooping of the upper eyelid and constricted pupil). She was also the first to link the ptosis and miosis to T1 avulsion (C8-Th1). The rare injury of isolated lower root involvement thus bears her name. A few years before Klumpke made her discovery, the ptosis sign had been published by an ophthalmologist, Johann Horner. Although he failed to link the sign to its cause, it still bears his name today. Horner´s syndrom is considered predictive of an extended injury involving lower root avulsions.

BPBI is associated with shoulder dystocia, and it occurs when the nerves of the plexus are stretched during complications of childbirth (Figure 1). When the injury occurs, the nerves are damaged by either traction, tear, or complete avulsion from the spinal cord (Figure 2). A BPBI is often classified as permanent if it has not resolved completely during the first year of life. Over the years, the term “permanent” has been interpreted in various ways, leading to inconsistency in the recovery rate. Due to this difference, the recovery rate from BPBI varies between 66 and 92%.[8–10] Many today choose to define neurologic recovery as either complete or incomplete. Incomplete neurological recovery is defined as the long-term loss of strength in any muscle group, even when the function of the upper limb is satisfactory. Most children who recover fully do so during the first 3 months.[8,9,11]

Most authors divide the injuries into, upper-, complete plexus involvement, and flail-type injuries as described by Algimantas Narakas in 1987[12]. The more roots involved, the more severe the injury. Upper plexus injuries are the most common (~80%) and involve the two upper roots, C5-C6, with or without C7 involvement. Most of the upper plexus injuries heal well and do not require any interventions. In total plexus injury, all roots (C5-Th1) are injured, and there is no function of the upper limb at birth due to either avulsions from the spinal cord or complete rupture of the roots. Clark and Curtis developed the Active Movement Scale (AMS)

as a diagnostic and prognostic tool[13] for BPBI patients. The 3-month Toronto Test Score (3MTS),[14] which is a subset of the AMS, classifies children with BPBI as those who can benefit from early reconstructive surgery and those who might not. A score under 3.5 strongly suggests that early plexus reconstruction could be beneficial. In addition to the Narakas classification the AMS and especially the 3MTS are routinely used by many centers treating BPBI.

Severity of the injury can be further assessed by either electroneuromyography (EMG), computer tomography (CT) with intrathecal thecal contrast or magnetic resonance imaging (MRI). With high sensitivity for nerve root avulsion, CT has been the gold standard for imaging thus far. Children with a permanent BPBI injury are prone to develop muscle imbalance due to disruption of normal muscle development. This leads to a restriction of active and passive ROM, mainly in the shoulder and elbow joints. Structural changes to the glenohumeral joint also appear often, leading to a dysplastic joint. In combination with the disturbed muscle development, shoulder dysplasia tends to worsen if left untreated, eventually leading to permanent changes with limited motion.

The objectives of this study are to calculate the annual incidence of permanent BPBI in the region of Southern Finland in 1995-2019, to analyze, whether cervical MRI is reliable in detecting root avulsions, to assess if shoulder dysplasia can be prevented by a protocol including early ROM exercises, ultrasound (US) screening, Botulinum-toxin A (BTX) injections in combination with spica bracing, and to develop a new neurotization technique to restore active shoulder external rotation (ER) in adduction.

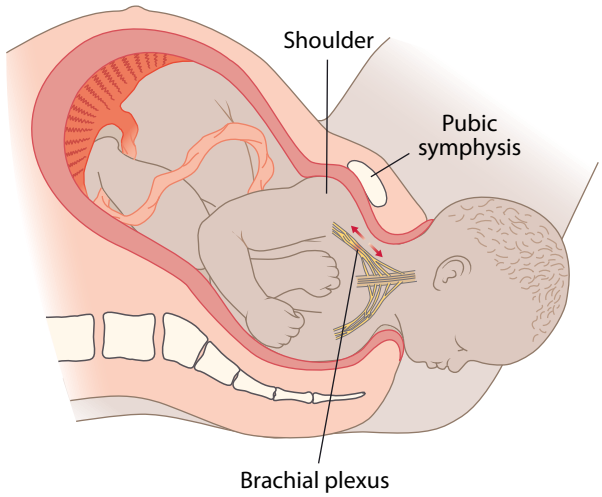


Figure 1 Shoulder dystocia during birth

Shoulder trapped under the pubic symphysis causes stretch and possible injury to the brachial plexus.

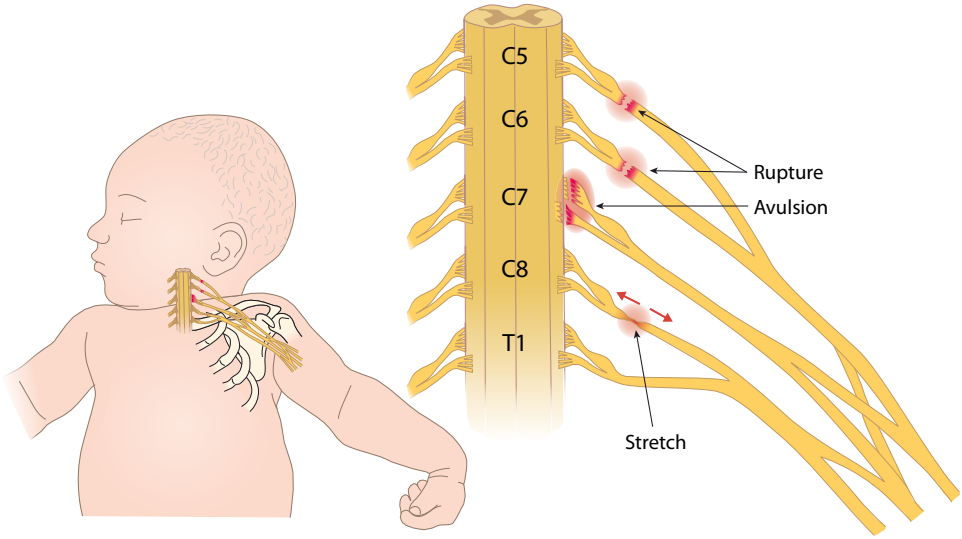


Figure 2 Child with complete plexus injury

Child showing typical "waiters tip" position with extended elbow, and internally rotated flexed wrist. C5-C6 roots ruptured, C7 avulsed from the spinal cord, C8 stretched.

2 REVIEW OF THE LITERATURE

2.1 Epidemiology of brachial plexus birth injury

The reported incidence for BPBI is 0.4-3.8 per 1000 live births,[11,15–19] while the incidence for permanent injury is between 0.1 and 1.6.[9,11,19,20] There have been some reports of a decrease in incidence, thought to be at least partly due to the simultaneous increase in cesarean deliveries and better training of midwives.[15,16]

Shoulder dystocia is the number one risk factor; others include instrumented forceps birth, breech delivery, and gestational diabetes (Figure 1). Ethnicity has been reported as a risk factor in recent studies, where Black, Asian and Hispanic infants were more likely to sustain BPBI in comparison to Caucasians.[16,21] Socioeconomic factors were also suspected to play a role.[16] In about 50% of BPBI there is no known risk factor.[17,22]

2.2 Anatomy of the brachial plexus

The brachial plexus provides innervation to the skin, subcutaneous tissues, and muscles of the entire upper limb from the shoulder to the fingers, as well as articular innervation to the joints. The anatomy of the brachial plexus has been extensively studied over the years. The plexus consists of five nerve roots exiting the spinal cord above the transverse process of the corresponding vertebrae. The nerve roots are formed from the spinal nerves connected to the spinal cord. The spinal nerve consists of nerve fibers exiting the ventral horn of the spinal cord (ventral root) as well as fibers entering the dorsal horn of the spinal cord (dorsal root) through the dorsal root ganglia. At the lever of the intervertebral foramen, the spinal nerve divides into two parts, forming the anterior and posterior rami. The anterior ramus of the spinal nerves C5 to T1 then becomes the peripheral nerve roots of the brachial plexus (Figure 3).

At the level of the scalene muscles, the roots form trunks. Trunks are divided to divisions at the level of the clavicle, and divisions still further divided into cords at the axillary level. The five main terminal peripheral nerves of the upper extremity (musculocutaneous, axillary, radial, median, and ulnar) are formed from the cords at the level of the glenohumeral joint (GHJ) (Figure 3). Smaller peripheral nerves exit from the brachial plexus already at the root level, with the long thoracic nerve and the dorsal scapular nerve being the first. The phrenic nerve that supplies the diaphragm, the main muscle for respiration, receives a contribution from C5 and

also exits at this level.[23,24] In more severe injuries (Narakas III-IV, see Table 1), the phrenic nerv can be injured.

The majority of the nerve fibers (axons) in the brachial plexus are afferent, bringing sensory and proprioceptive feedback to the brain. Only 4-12 % of the axons are efferent motor fibers supplying the musculature of the upper limb. The C5 nerve root has the highest proportion of motor fibers (12%) in the brachial plexus, while T1 has the lowest (4%).[25] The root size directly correlates with the total axon count per root, with C8 having the highest number at ~90,000, and C5 the lowest at ~38,000.[25] The root size increases with age. In children under 1 year of age the diameter is between 1.5 and 2.5 mm while in adults 2.3 to 4.3 mm. The order of the largest root in diameter to the smallest is; C8, C7, C6, T1, and C5.[23,25–27]

The brachial plexus may receive a contribution from the anterior rami of C4 or T2. Depending on the size of the branch, it can be classified as either a communication branch (often from T2), or a pre- (C4) or post-fixed (T2) plexus (Figure 3).[28] With a prefixed plexus, the C5 root is usually the same size or larger than the C6, with the T1 root being smaller or absent, whereas in a post-fixed plexus the C5 root is much smaller or may be absent.[26,28,29] This in accordance with Herringham's law from 1887 that "any given fiber may alter its position relative to the vertebral column, but will maintain its position relative to other fibers".[29]

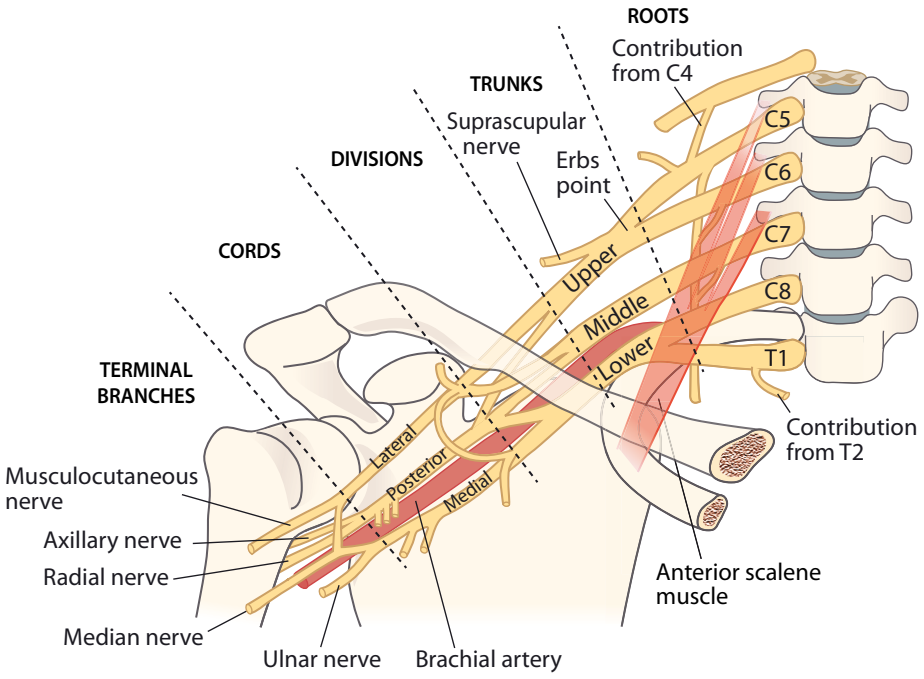


Figure 3 Anatomy of brachial plexus

2.2.1 Structure of nerves

A nerve is a bundle of axonal extensions of neurons (cell body). The neurons of the nerves from the brachial plexus lie in the dorsal root ganglia or the spinal cord. The nerve is surrounded by connective tissue, epineurium, that gives protection. Inside this outer layer of connective tissue lies the axons arranged in bundles surrounded by loose connective tissue and blood vessels. Each axonal bundle (fascicle) is surrounded by a layer of stronger connective tissue, the perineurium (Figure 4). The axon itself is further protected by a layer of myelin, produced by cells surrounding the individual axons. The thickness of the myelin sheath varies between different types of axons, with efferent motor axons having a thicker layer.

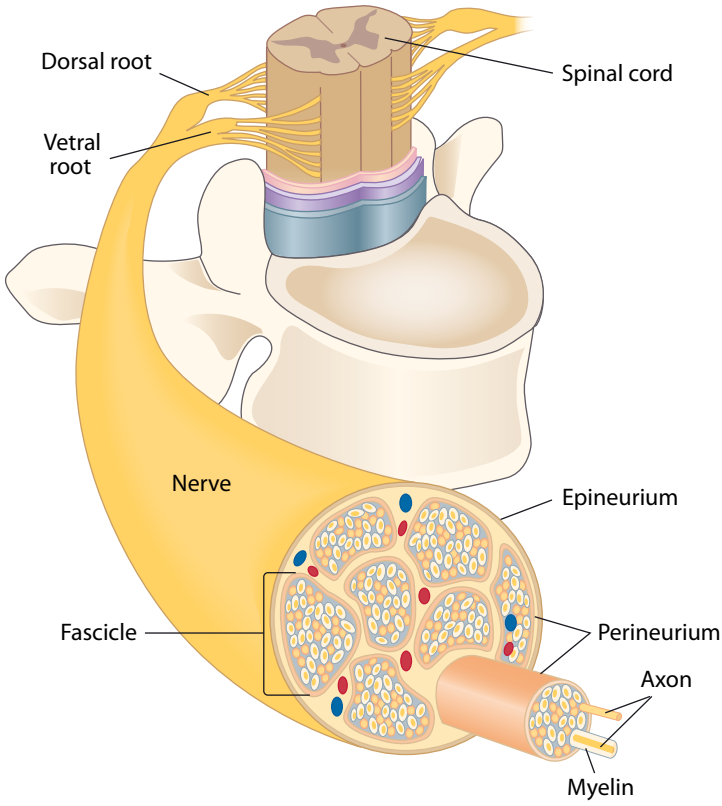


Figure 4 Structure of the terminal nerves

2.2.2 Main terminal nerves of the brachial plexus

The five main terminal nerves from the brachial plexus supply the upper extremity. Any disruption of the path of the axons of these nerves affect the end organs supplied by the nerve. This leads to a loss of sensory and, in most cases motor function. This function deficit can be reversible or permanent depending on the severity of the injury.

Axillary nerve

The axillary nerve, which arises from the posterior cord of the brachial plexus is together with the musculocutaneous nerve, the smallest main terminal branch. The axillary nerve has a motor neuron proportion of 9.5 % with approximately 22,500 axons. The axillary nerve supplies motor branches to the deltoid, teres minor and the long head of the triceps muscles, and sensory feedback from the shoulder.[25,30,31]

Radial nerve

The radial nerve, which also rises from the posterior cord, is the largest terminal nerve from the brachial plexus with ~65,700 axons. It has a motor neuron proportion of 6.7 % and supplies the extensor muscles of the upper limb as well as the anconeus, supinator, and brachioradialis muscles. The radial nerve provides sensory innervation to the back of the arm, dorsum of the hand, and first web. In about 80% of cases, the radial nerve also innervates part of the brachialis muscle.[24,25]

Musculocutaneous nerve

The musculocutaneous nerve originates from the lateral cord and is roughly the same size as the axillary nerve with roughly the same amount of motor neurons as the radial nerve. It gives motor supply to the coracobrachialis muscle and the elbow flexors (biceps and brachialis muscles). After giving off its motor branches, the musculocutaneous nerve ends as a sensory nerve, providing sensation to the lateral aspect of the forearm.[24,25]

Median nerve

The median nerve is formed from the lateral and medial cords of the plexus. It is the second biggest terminal nerve, comprising approximately 60,500 axons having the highest number of sensory fibers (94%) of all the main terminal nerves from the brachial plexus. The median nerve provides sensory innervation to the radial side of the wrist and hand as well as the volar aspect of digits I-IV. The nerve provides motor neurons to the pronators of the forearm and part of the flexors of the fingers and wrist (flexor digitorum superficialis, flexor digitrum profundus to digits II-III, palmaris longus, flexor pollicis longus, opponens pollicis, flexor pollicis brevis and first to second or third lumbrical muscles).[25,30]

Ulnar nerve

The ulnar nerve originates from the lateral cord. It is comprised of roughly 6.7% motor neurons with a total axon count of about 40 400. It provides motor neurons to the finger and wrist flexors and muscles providing hand dexterity (flexor carpi ulnaris, flexor digitorum profundus to digits IV-V, third and fourth lumbrical muscles, opponens-, flexor-, and abductor digiti minimi, interossei, adductor pollicis and flexor pollicis brevis).[25,30]

2.3 Nerve injury

In 1943 Seddon classified nerve injuries into three categories: neurapraxia, axonotmesis, and neurotmesis.[32] In neurapraxia, transient functional loss is observed without affecting loss of nerve continuity. A complete disruption of the nerve axon and surrounding myelin along with preservation of the perineurium and epineurium is observed in axonotmesis. Neurotmesis causes complete functional loss because of nerve discontinuity. Sunderland further classified nerve injury into five categories by dividing Seddon's axonotmesis into three subcategories (Table 1). Mackinnon has suggested a sixth category for the classification, which is a combination of various degrees of nerve injury.[34] The degree of injury directs the treatment (Table 1). Mild injuries (Seddon neurapraxia, Sunderland I) heal well while severe cases do not recover spontaneously and require surgical repair to heal (Seddon neurotmesis, Sunderland V).

When the axons are injured, a degeneration pathway is activated that causes changes within the nerve both proximal and distal from the injury. Proximal changes lead to cell death (apoptosis) in some of the neurons providing the nerve. Distal from the injury disintegration of the axons within the myelin sheath occur.[35] This injury induced Wallerian degeneration was first proposed by Augustus Waller in 1850.[36,37] After a period of disintegration, the regeneration of the nerve starts; axons sprout from the proximal stump toward the distal stump. When the distal stump is reached, the recovery advances at a speed of ~1 mm/day.[35,38] The muscle endplate through which the motor nerve communicates with its end organ remains viable for up to 3 years from injury, limiting the time frame for spontaneous or surgical nerve repair.[39]

Table 1

Seddon and Sunderland Classification of Nerve Injury				
Seddon	**Sunderland**	**Injury**	**Treatmnet**	**Prognosis**
Neuropraxia (Compression)	I	Local myelin damage with nerve still intact	Good spontaneous recovery (days-weeks)	excellent
Axonotmesis (crush)	II	Continuity of the axon is lost. Endo-, peri- and epineurium intact. Wallerian degeneration.	Full recovery possible wihout surgery (regeneraton 2-3mm/ day)	
	III	Same as above with endoneurial injury	Slower regeneration as scar hinders axonal growth (regeneration 1mm/day)	
	IV	Same as above with endo- and perineurial injury	Surgical reconstruction. Scar build up block nerve regeneration.	
Neurotmesis (transection)	V	Complete disruption of the nerve	Surgical reconstruction	worst

Adapted from Sunderland (1990)

2.4 Diagnosis, clinical presentation, and natural history of brachial plexus birth injury and its sequelae

Diagnosis of BPBI is usually made at the birth hospital and is clearly evident in the more severe types (Narakas II-IV). A newborn with a more extensive injury typically has the affected limb in inward rotation, wrist flexed and elbow extended without clear movement in the shoulder joint (Figure 2). Typically the child fails the Moro test.[40] The milder type (Narakas I) can initially be over looked, and thus, the diagnosis is delayed or missed.

Most patients (>80%) with BPBI will experience spontaneous recovery. A strong prognostic marker for full recovery is the activation of full ROM elbow flexion against gravity by 2 months of age.[8,10,41] On the other hand, it has been shown that complete recovery is highly unlikely if there is no biceps activation by 3 months of age[42,43] or a failed cookie test at 9 months of age.[44] Other factors associated with worse recovery are concomitant phrenic nerve injury and Horner's syndrome, both of which strongly associate with nerve root avulsions.[45,46]

In addition to impaired active muscle function due to the nerve damage, children with permanent BPBI develop secondary changes to the affected limb. Internal rotation contracture and glenohumeral dysplasia is the most common, affecting 60-80% of children with permanent palsy.[11] Its early stages can be detected by 1 month of age.[11,47] Without intervention, the dysplasia may lead to the development of a pseudoglenoid communicating in a hinge-type joint with a flattened humeral head. In this setting the humerus is typically rotated inward,

with shoulder abduction and flexion movement restricted under horizontal, with an abducted resting position.[48] Flexion contracture of the elbow develops in the more severe cases as early as the first year but can appear throughout growth.[49] Other notable features are the pathognomonic waiters tip position of the limb (Figure 2) and, later, diminished limb length.[50] Especially in Narakas type III and IV injuries, even after attempted repair, many patients have diminished sensation in the distal part of the limb and hand, and some experience pain.[51]

2.4.1 Diagnostic tools

Horner's syndrome

Horner's syndrome includes a triad of miosis, ptosis and anhidrosis (reduced sweating of the face) on the same side as the brachial plexus lesion. Horner's syndrome is a sign of severe injury and is often present in avulsion type injuries, most often involving roots T1 and/or C8. The presence of Horner's syndrome is predictive of permanent injury and is a reliable indicator for operative management.[52] Injury accompanied by the syndrome has the worst prognosis. The triad is caused by injury to the sympathetic chain of nerves (T2-4) and often involves injury to the phrenic nerve which innervates the main breathing muscle, the diaphragm.

Horner's syndrome can occur in other clinical settings (idiopathic, tumor, carotid artery dissection, i.a.) and is thus not a sign of BPBI in itself.

Elbow flexion

Recovery of active elbow flexion by 3 months correlates well with spontaneous recovery by 12 months.[10,42,53] If solely used it is suspected to incorrectly predict recovery in 13% of infants with BPBI.[14] Gilbert and Tassin found that children with lack of elbow flexion at 3 months showed poor shoulder function in older age.[43,53] In his study of the natural recovery of BPBI, Tassin's main conclusion was that if there was no sign of recovery of the biceps muscle within 3 months, shoulder function would not reach abduction above 90° or external rotation above 20° at the final FU.[53] Both suggested that one indication for brachial plexus reconstruction should therefore be lack of biceps function at 3 months.

Active Movement Scale (AMS)

This 15-point scale was developed and validated to assess upper extremity movement in infants and children with BPBI.[44,57,58] The AMS is easy to use as it requires no cooperation other than the child being awake during the assessment. The movements are graded on an ordinal scale from 0 to 7 and utilize gravity and the ROM of the uninjured limb in the scoring. The AMS can be used to follow

recovery. A subset of the AMS is used to determine potential need for plexus reconstruction at 3 months of age.

3-month Test Score (3MTS)

Michelow et al. found that lack of elbow flexion at 3 months incorrectly predicted poor recovery in about 13% of patients, but when added to elbow, wrist, thumb and finger extension from the AMS at the same age, incorrect prediction was reduced to 5%.[14] The 3MTS is determined by first converting the scores from the AMS and adding up the total converted scores for elbow flexion, elbow extension, and wrist, finger, and thumb extension. A 3MTS less than 3.5 is strongly predictive of poor recovery without surgical intervention. Together with the Narakas classification, the 3MTS score is one of the most widely used in determining the need for early surgical reconstruction.[59]

Cookie test

The cookie test is performed at 9 months by placing a cookie in the child's hand, holding the upper arm by the child's side, and allowing the child to attempt elbow flexion sufficient to bring the cookie into the mouth without flexing the neck beyond 45°. If the child successfully reaches the mouth with the cookie, he or she passes the cookie test, and non-operative management is usually recommended. If the child does not reach the mouth with the cookie, operative management should be considered.[60,61]

Narakas classification

According to the Narakas classification, newborns with BPBI are classified into four groups with the severity of the injury advancing with group number (Table 2).[12] Birch recommended that the classification should be applied after 2 weeks of birth, by which time lesions due to simple conduction block have begun to recover.[62] He also recommends that the classification should not be used to indicate need for surgery, although he found that as one goes down from Group 1 to 4, the overall prognosis for spontaneous recovery gets worse and, hence, the likelihood for benefits for primary surgery gets higher.[63] The Narakas classification is widely used in clinical practice as it provides an overall view of the expected prognosis of the new born.[64]

Table 2 Narakas classification of BPBI

Narakas classification of brachial plexus birth injury			
Group	**Type**	**Involved roots**	**Affected area**
1	Upper	C5 to C6	Shoulder abduction/external rotation, elbow flexion
2	Extended upper	C5 to C7	As above with drop wrist
3	Total palsy without Horner´s syndrome	C5 to T1	Complete flaccid paralysis
4	Total palsy with Horner´s syndrome	C5 to T1	Complete flaccid paralysis with Horner syndrome

C= Cervical root, T= Thoracal root
Adapted from Narakas (1987)

Modified Mallet Score

The Mallet classification from 1972 was initially described to classify the performance of upper extremity movements, which reflect those used in activities of daily living (abduction, hand-to-mouth, etc.) among children with BPBI.[65] It has since been further modified adding a sixth position (hand-to-belly).[66] Administering the modified Mallet classification involves observing the child positioning his/her upper extremity in standard positions unaided by compensation and scoring the observed movement on a scale between I (no function) and V (full function) (Figure 5). The Mallet classification is validated for use in children with BPBI and has demonstrated good intra- and inter-observer reliability, as well as internal consistency.[44,58,67,68] It is one of the most frequently cited methods used to evaluate the upper extremity of children with BPBI in the literature.[68] As accurate scoring depends on reproducibility, requiring communication and cooperation between the child and examiner, the scoring system cannot be reliably used in infants or very young children. Another of its down-sides is that a change of only 1° can move a child from one grade to the next, even if the function itself is not significantly better.

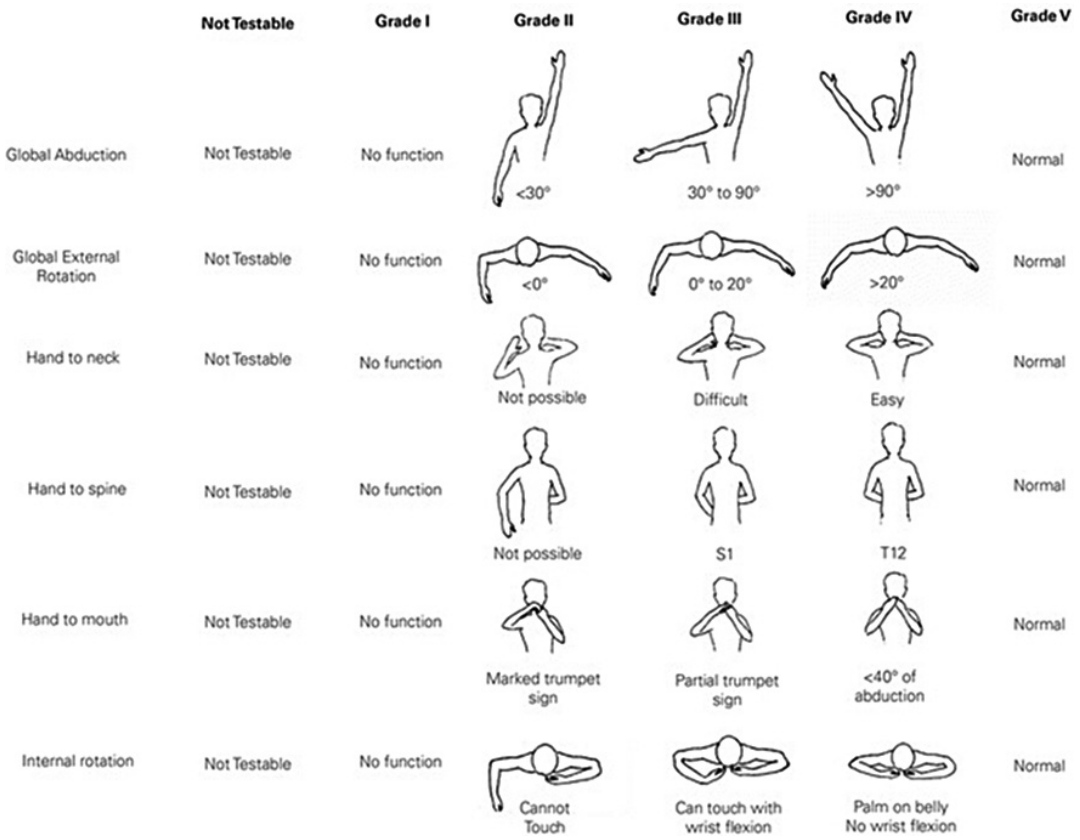


Figure 5 Modified Mallet classification. Adapted from Abzug et al. (2010)

Glenohumeral deformity classification

The scale was developed to classify the spectrum of glenohumeral deformities in BPBI patients as seen on MRI (Table 3).[69]

The score can be used as a tool to guide treatment as patients with milder type-I or II changes can be managed with a tendon or nerve transfer, and those with type-V changes may be managed with a humeral osteotomy. Intermediate types of deformity pose a more difficult problem as the age of the patient affects the choice of treatment. Especially younger children have remodeling potential of the glenoid and the humeral head if congruency is restored in time.[69–71]

Table 3 Glenohumeral deformity score

Glenohumeral deformity score		
Classification	**Severity**	**Description**
Type I	Normal glenoid	Less than 5 degree difference in retroversion compared with that on the normal, contralateral side
Type II	Minimun deformity	More than 5 degree difference in retroversion compared with that on the normal side, with no posterior subluxation of the humeral head
Type III	Moderate deformity	Posterior subluxation of the humeral head, defined as less than 35 percent of the head anterior to the scapular line
Type IV	Severe deformity	Presence of a false glenoid
TypeV	Severe deformity	Severe humeral head and glenoid flattening, with progressive or complete posterior dislocation of the humeral head
Type VI	Severe deformity	Posterior dislocation of the glenohumeral joint in infancy
Type VII	Severe deformity	Growth arrest of the proximal humeral physis

Adapted from Waters et al. (1998)

The score can be calculated from either axillary MRI or CT images. On MRI scans, the cartilaginous margins are used while on CT scans the osseous margins are used.

2.4.2 Imaging modalities

Magnetic resonance imaging (MRI)

MRI can be used in children with more severe injuries to exclude root avulsions and help in clinical decision-making. MRI has been shown to have the same sensitivity (75%) and specificity (83%) as computer tomography (CT) myelography (sensitivity 72%) in diagnosing root avulsion injuries.[72,73] MRI often requires sedation. MRI is also useful in evaluating secondary changes to the GHJ as well as results of possible interventions.[69]

Ultrasound (US)

US screening has been shown to be reliable in detecting early dysplastic changes in the GHJ,[11,74] thus enabling treating physicians to try to further prevent and reverse early changes with different interventions. Many institutions routinely screen the shoulder joints of BPBI children during the first year.[74] US can also be used to diagnose radial head dislocation.

Other imaging modalities

Computer tomography (CT) myelography is still used in many places despite MRI having the same sensitivity and specificity for diagnosing avulsion injuries. CT myelography is more invasive and, due to the need for intrathecal contrast injection, can thus be seen as inferior to MRI in diagnosing infants. CT myelography also requires sedation.

Standard radiographs (X-ray) are sometimes used to diagnose humeral or clavicular fractures after birth. Chest X-ray is a good way to diagnose a phrenic nerve injury in a new born with a completely flail upper limb.

Electromyography (EMG) has been used to evaluate the extent of injury in BPBI and to follow up recovery. It is invasive and has low prognostic value, so it has been discontinued in many institutions.[75] EMG can be used when planning neurotizations or muscle transfers in order to make sure the donor nerve or muscle is working accordingly.[76]

2.5 Patomechanics of shoulder dysplasia

The development of glenohumeral dysplasia in patients with BPBI is poorly understood, although it is extensively studied. What most agree on is the major role the subscapularis muscle has in the development of the internal rotation contracture, and that shoulder external rotation is one of the last movements to recover.[9,53] What is not agreed upon is how the contracture develops. One thought is that muscle imbalance due to the injury leads to the pathognomonic internal rotation contracture of the shoulder due to weak external rotators and functioning strong internal rotators.[77,78] Support for this theory was found in an MRI study where the ratio of the cross section area of the internal rotators (PM and SS) to external rotators (IS and teres minor) correlated with the degree of shoulder contracture.[79] Others have shown that the degree of contracture correlates only with the atrophy of the SS and is not in relation to the external rotators.[80,81] More recently, the focus has moved to the structure of the muscle itself; in mice and rat models, impaired growth of the SS and internal rotation contracture formation was noticed after creating a BPBI-like injury.[82,83]

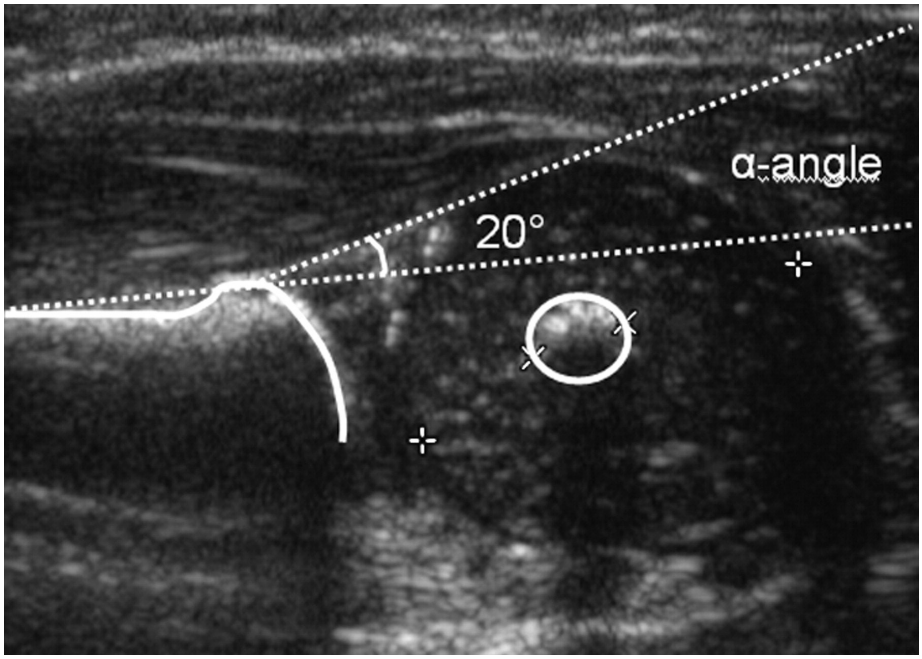
Structural changes to the GHJ itself has been both reported and disputed in rat models after creating a BPBI-like injury with structural changes to the SS appearing.[83–85] What is clear is that changes to the glenoid and the humeral head appear early in the injury and are already detectable at 1 month of age.[11] Typically, a smaller ossification center of the humerus is seen, with or without posterior rounding of the glenoid.[11] These early structural changes to the bones cannot be

fully explained by the impaired muscle growth or imbalance theories, and are possibly an entity by themselves. Further support for this has been found in animal models where rats who underwent SS tendon transection with an intact brachial plexus did not develop changes to the glenoid or humeral head.[82,83]

2.5.1 US for detecting shoulder dysplasia

US for detecting shoulder dysplasia has been available for some time and is gaining popularity. It was first introduced in 1998[86] and has since been shown to be a reliable method in evaluating shoulder subluxation in relation to BPBI.[11,74,87–89] The benefit of the US in comparison to MRI is that is requires no sedation, and a dynamic evaluation of the shoulder joint can be performed. In a dynamic US scan of the shoulders, the patient's arm is kept in adduction with the elbow in 90° flexion. The arm is then rotated in this adducted position to full external and internal rotation, while the radiologist evaluates a possible change in the humeral head position. Normal position is defined as an α angle less than 30° (Figure 6 a and b).[88]

a



b

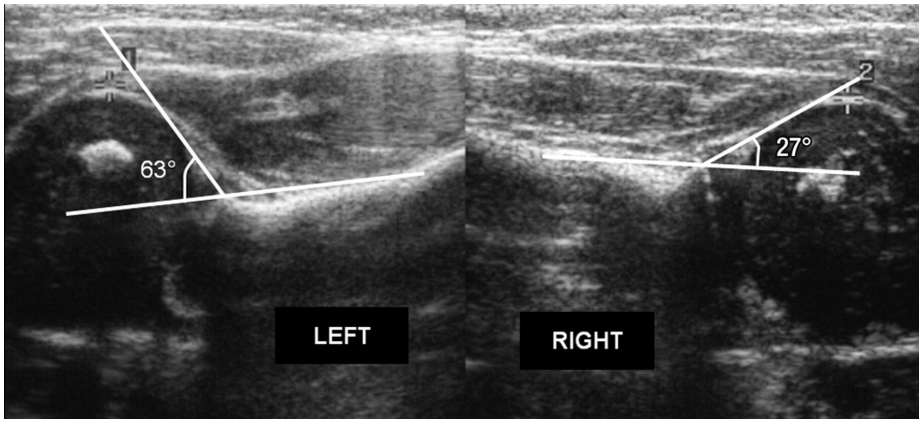


Figure 6 Calculation of the α angle from shoulder US images

A) The α angle is the angle between the posterior margin of the scapula and the line drawn tangentially to the humeral head and posterior edge of the glenoid. The normal value of the α angle is ≤30° or less as described by Vathana et al.[88] The humeral ossification center is normally located anterior to the posterior margin of the scapula. Shoulder subluxation is defined as α angle >30° measured in IR of the adducted shoulder which if reducible, returns to a value corresponding the uninjured side in full ER. Posterior subluxation of the humeral head is also assessed during the dynamic phase of the study where the shoulder is scanned throughout full range of IR and ER in adduction with elbow flexed at 90°. Image from a 3 month old child. B) US images of a 3 month old child with left sided BPBI and subluxed shoulder. Increased α angle (63°) on the left, with the ossification center dorsal to the posterior margin of the scapula. Uninjured right side shows normal findings.

Figures reprinted with permission from the Radiological Society of North Amreica. Figure source: Pöyhiä et al. 2010.[11]

2.6 Treatment of BPBI

Choice of treatment should be carefully considered and based on the available evidence.[90] Regardless of the extent of injury at birth, all children should start with passive ROM exercises. Depending on the extent of the injury, different treatment options are available. In patients with good hand function and recovery of active elbow flexion against gravity by 6 months, plexus reconstruction is rarely needed. In the more severe cases plexus reconstruction using autologous nerve grafts is performed during the first year. BPBI Patients can benefit from tendon-, or nerve transfers aimed at strengthening weakened muscles.

2.6.1 Non-operative treatment

Range of Motion (ROM) exercises

ROM exercises are commenced as soon as possible after birth, and should be carefully instructed to the parents by either a physiotherapist, an occupational therapist or treating physician with knowledge of BPBI treatment. It is recommended that the limb is exercised daily. Passive ROM exercises are usually instructed to be continued, with regular checkups until full active motion is restored.[91,92] Adverse effects from early passive ROM exercises have not been reported.[93]

Botulinum toxin-A (BTX) injections to shoulder internal rotators

BTX injections to the internal rotators of the shoulder have gained popularity, with very few reported complications.[94,95] The main aim of the BTX treatment is to maintain GHJ congruency and ROM, while giving time for the IS to recover. BTX should be administered early, preferably during the first year, and in combination with splinting or passive ROM exercises.[94–96] There is no consensus about the optimal dosage, target muscles, timing and efficacy of BTX injections,[94] with a mean dosage reported as 10IU/kg.[96–98] The reported injection sites are either all four internal rotators (SS, PM, TM and LD) or SS without or in combination with one or more of the others.[95,96]

Shoulder splinting

At the beginning of the 1900s shoulder bracing was in regular use in many centers. Bracing came to an end around 1970, when it was noted that bracing not followed by physiotherapy induced external rotation and abduction contractures.[99–101] Since then, splinting has found its way back and is now again part of the standard treatment in many centers.[96,102–104]

As with BTX, no clear recommendation exists regarding timing and duration of shoulder ER splinting. Different splints have been developed to maintain

shoulder position, with or without the use of BTX.[96,104] The aim of the splinting is to maintain shoulder congruency while waiting for active external rotation to recover. Some centers use continuous splinting (Sup-ER protocol), while others splint only in combination with BTX, shoulder relocation or muscle/nerve transfer. According to the Sup-ER protocol, an elbow extension, forearm supination, and shoulder external rotation splint is used from 6 weeks of age for a duration of 8-12 months. During the first 4 weeks, it is used 22 hours per day, after which usage is reduced to bed and naptime.s[104] The shoulder spica brace (Figure 7) is often used in combination with BTX and is worn continuously for 4-6 weeks, after which passive ROM exercises commence.[95,96,98]

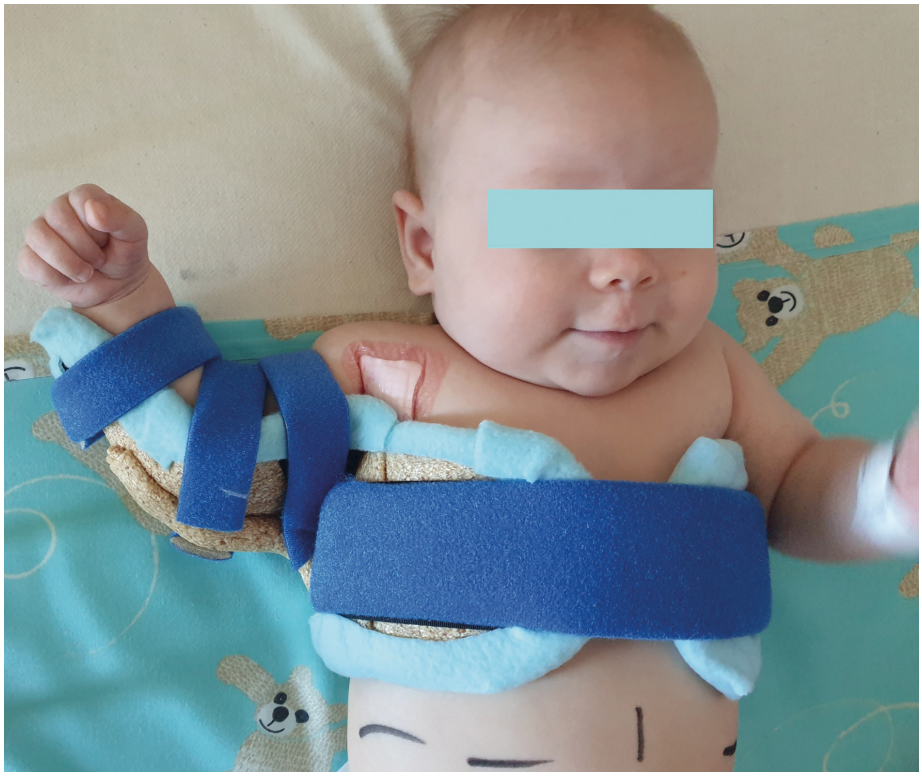


Figure 7 Spica brace

To children less than 1 year old with an US verified posterior shoulder subluxation, or limited passive ER in adduction (≤70°) we apply a thorachobrachial ER brace after administering 100IU of BTX to the shoulder internal rotators (SS, PM, TM/LD). The spica brace is worn continuously for 6 weeks.

2.6.2 Operative treatment

Operative treatment for patients with BPBI can be divided into primary, and secondary surgery. Primary surgery aims to restore function of the brachial plexus either by reconstructing it or through extraplexal neurotizations. Secondary surgery is done at a later age and aims to improve specific functions. Typical secondary procedures are shoulder relocation, tendon transfers, neurotizations and rotational osteotomies to enhance shoulder function.

Primary surgery

Brachial plexus reconstruction

Plexus surgery in BPBI was first described by Kennedy in 1903.[105] He published a series on three patients using direct repair at the C5-6 level. At the time the paper was published, only one of the patients had had sufficient time for recovery (9 months), with improvement of active abduction, elbow flexion, and shoulder ER. Although Kennedy and others advocated for early surgery and reconstruction of the brachial plexus, interest in the procedure declined, as the benefits of reconstruction were not seen in the long-term.[3] In the 1960s, with the emergence of microsurgical techniques in combination with increased understanding of peripheral nerve anatomy, physiology, and pathophysiology, brachial plexus reconstruction started to gain popularity again. Alain Gilbert emerged as one of the new pioneers and was a driving force for surgical reconstruction in BPBI.[48] In 1993 Lauren et al. published a paper comparing different treatment modalities (conservative, neurolysis, direct suture, or sural nerve grafts) and found superior results using sural nerve grafts.[8] Plexus reconstruction with sural nerve grafts has since become the gold standard of treatment for infants that demonstrate limited spontaneous neurological recovery during the first year.[8,43,57,61,77] Some consensus exists regarding patient selection for plexus reconstruction, as has been discussed earlier (see section 2.4.1; Narakas group III-IV, lack of elbow flexion at 3 months, 3MTS <3.5, and failed cookies test at 9 months).

Methods for plexus repair include nerve grafting after neuroma resection, nerve transfers in the case of avulsion type injuries, or a combination of both.[43,106–108] The current understanding is supported by prospective studies,[14,109,110] and although plexus repair is said to be superior in outcome compared to conservatively treated patients with identical lesions,[42,43,111,112] no randomized study has been performed as of today. Classic plexus reconstruction is done using autologous nerve grafts.[61,77,110] Nerve allografts have been used, but very few publications exists regarding outcome after use in BPBI.[113]

Nerve transfers

In segmental avulsions injuries, nerve transfers are used in combination with classic grafting. Common transfers are intercostal nerves to the musculocutaneous nerve[107,114] or the spinal accessory nerve (SAN) to either C5 or C6.[106,115] In the rare instance of complete brachial plexus avulsion, nerve transfers are the only reconstructive option available and may include the aforementioned options as well as the phrenic nerve, cervical plexus, contralateral C7 and hypoglossal nerve transfer.[116–119]

Triple nerve transfer

In upper plexus injuries that fill the criteria for plexus reconstruction, another option for primary reconstruction is the triple nerve transfer. Rather than upper plexus reconstruction using sural nerve grafts,[120] extraplexal neurotization is performed by SAN to the suprascapular nerve (SSN),[121] the long head of triceps radial nerve branch to the axillary nerve,[122] and a fascicle of the ulnar nerve to the musculocutaneous biceps nerve branch.[123]

Secondary surgery aimed at improving shoulder function

As previously described, shoulder function, especially ER and, to some extent, abduction, often remains affected even when recovery has otherwise progressed.[9,53] Diminished shoulder function has been reported in over 35% of children with BPBI.[9,124] Shoulder function can be augmented by nerve or tendon transfer, but to be susceptible to transfer, the GHJ needs to be congruent with good passive ROM. Several authors today advocate for early tendon or nerve transfers, preferably under 3 years of age, with the hope of decreasing the development of glenohumeral dysplasia.[71,125–12770] If detected early enough, the dysplastic changes of the GHJ can be lessened.[71,125,127–129]

Shoulder relocation

If unreducible shoulder dislocation occurs and is recognized before significant changes to the glenoid are observed, shoulder relocation can be successful. Relocation can be done either arthroscopically or through an open approach, and if done at a young enough age structural changes may be reversed.[71,125,127–129] An anterior release of the thickened capsule, middle, and inferior glenohumeral ligaments, a resection of the coracoid process and lengthening of the subscapularis are often needed. Even if there are some long-term results showing lasting joint congruency with relocation alone,[130,131] concomitant tendon transfer is advised.[70] Waters et al. showed improvement of glenoid retroversion in 83% of patients that underwent shoulder relocation with concomitant tendon balancing procedures.[71] Similar results have been reported by others using both open and arthroscopic techniques.[71,129,132]

Tendon transfers

The first tendon transfer in BPBI was described in 1934 by L'Episcopo, who transposed TM and LD to the rotator cuff in an attempt to restore shoulder ER.[133] Until then, restoration of ER had been attempted with tendon lengthening of mainly SS and PM, as described by Sever and others.[134] Tendon transfers to restore shoulder ER in combination with tendon lengthening have since become standard procedures in treating patients with BPBI.[47] Hui found that tendon lengthening combined with tendon transfer reduced glenoid retroversion in 30% of their patients.[127]

The most common transfers are LD, TM, or the lower trapezius to the IS insertion, all of which have been shown to increase active ER.[71,135,136] After congruence and active motion are achieved at a young enough age, it appears to remain; Vuillermin et al. found that the greatest improvement in ROM after tendon transfer came during the first year, after which there were no significant changes in the Mallet, AMS, or radiographic outcome. They reported no decline in outcome after a mean FU of 4.2 years (range 2 to 6 years) in their study of 20 children who underwent glenohumeral joint reduction with concomitant PM and/or SS lengthening in combination with TM transfer at mean 2.4 years of age.[70]

Nerve transfers

Promising results in improving ER have been achieved with neurotization of the IS using the SAN. SAN, which is a strong motor nerve with a motor axon proportion of 23 %,[25] can be transferred to either the SSN[121] or directly to the infraspinatus branch of the suprascapular nerve (SSNI).[137] Early results are promising and are similar to those achieved by the more traditional muscle transfers.

Somsak described neurotization of the axillary nerve in adult patients using the radial nerve branch to the long head of triceps.[122] This procedure has been used in brachial plexus patients in an attempt to restore shoulder abduction.[120]

Rotation osteotomy of the humerus

Rotation osteotomy of the humerus can be seen as a salvage procedure, as it is used only when no other viable options for improving shoulder function exist. When permanent irreversible deformity of the GHJ has developed, patients can benefit from rotational osteotomy of the humerus. The main aim of this procedure is to position the movement sector with regards to ER and IR of the upper arm in a more neutral and, thus, functional position.[138,139] Through rotation osteotomy of the humerus active ER rotation can be improved with the loss of a similar amount of IR or vise versa.

3 AIMS OF THE THESIS

1. To calculate the annual risk and changes in incidence of permanent BPBI in vaginal deliveries in the primary care district of Helsinki University Hospital (HUS), New Children's Hospital during the last 25 years.

2. The gold standard for root avulsion diagnostics has long been intrathecal contrast-enhanced CT myelography, which is an invasive imaging technique. We aimed to assess whether root avulsions can be reliably detected by MRI.

3. Treatment of patients with permanent BPBI has evolved over time. Recently more focus has been put on keeping the shoulder in place in an attempt to improve the overall functional outcome. Although different treatment modalities exist, their exact timing, use, and effects remain disputed. We aim to assess whether shoulder dysplasia can be prevented by a protocol including early ROM exercises, ultrasound (US) screening, BTX injections in combination with spica bracing, and specific surgery to restore active shoulder external rotation (ER) in adduction.

4. It has been suggested that shoulder congruence can be better retained if active ER is restored before 3 years of age. Our aim was to develop a new surgical technique that would reliably restore shoulder ER with better long-term outcome compared to previously published tendon transfers.

5. Our final goal was to introduce a guideline for early detection and treatment of shoulder dysplasia in BPBI.

3.1 Specific objectives of the thesis

Study I
To analyze if root avulsion injuries can be reliably detected with MRI in patients with permanent BPBI. We assumed that MRI is a sensitive and specific tool in root avulsion diagnosis.

Study II
Development of a protocol for prevention, early detection, and intervention of shoulder sequelae in patients with permanent BPBI. We hypothesized that we could decrease the risk of shoulder dysplasia in patients with permanent BPBI

utilizing a combination of passive shoulder ROM exercises, US screening, BTX injections, shoulder ER spica bracing, and specific surgery.

Study III
Development of a novel technique to restore active shoulder ER in adduction in patients with permanent BPBI, congruent shoulder joints and above 90° of active shoulder abduction. We hypothesized that IS function could be restored by selective neurotization of the SSNI with SAN.

Study IV
To analyze mid-term results of the technique developed in study III. Our hypothesis was that the restored IS function would not deteriorate over time.

4 PATIENTS AND METHODS

HUS, New Children's Hospital is a tertiary treatment center for patients with permanent BPBI; it serves a population of ~2.2 million people and is the primary care center for patients presenting with BPBI in the hospital district of Helsinki and Uusimaa, providing care to 1.7 million inhabitants.

All children born in our tertiary catchment area are examined by the referral center's pediatrician at 0-2 days of age. Children born with a flail upper extremity (FUE) are instructed to be referred to our BPBI clinic at discharge from the maternity hospital. Children with diminished upper limb motor functions are re-examined by a physiotherapist at 2 weeks of age. If full recovery has not occurred within 4 weeks, the child is referred to our BPBI clinic for further evaluation by a BPBI specialized team consisting of a hand surgeon, occupational therapist, and physiotherapist. Extent of the injury is graded as FUE; no movement at all, complete plexus involvement (CP); shoulder, elbow, wrist, and hand affected and upper plexus injury (UP); shoulder and elbow and, in some patients, wrist extension affected. Patients are scheduled to be seen on a regular basis by the same team at set time intervals from 1 month of age (at 3, 6, and 12-months, and 2, 4, 7, 10, 14, 16, and 18 years of age). Active and passive ROM of upper extremity joints are measured at each appointment using a goniometer.

The patients included in this study have been referred to our clinic between 1995 and 2019. Birth weight, type of delivery, sex, side of injury, and ethnicity have been recorded (Table 4). For most patients, the 3MTS has been calculated on time and, for others in retrospect (1995-2005). Permanent BPBI was defined as clinically evident limited active or passive ROM or decreased strength of the affected limb detected at 1 year of age.

Table 4

Patients and birth data			
Sex	**Birth weigh**	**Injury side**	**Type of delivery**
124 Girls 113 Boys	4.2 kg (range 2.7 to 5.6, SD 0.5)	136 right, 99 left, 2 bilateral	226 normal, 8 breech, 2 face, 1 C-section

All childern born fullterm, except 1 premature at gestation age 36+4

Birth data of patients included in the study. All patients born in HUS tertiary treatment district between 1995 and 2019.

4.1 Incidence of permanent BPBI in the hospital district of Helsinki and Uusimaa

Of the 237 children included in the study, 179 were born in the hospital district of Helsinki and Uusimaa, Finland. The number of live births and type of delivery during the study period (1995-2019) were collected from the national register.[142]

4.2 Root avulsion diagnosis with MRI (I)

Children that were considered for plexus surgery between 2007 and 2015 underwent MRI for detection of root avulsions. During this time 157 BPBI patients were referred to our brachial plexus clinic. Of these patients, 34 (1 bilateral) fit the inclusion criteria which were FUE or CP at one month of age or UP injury without antigravity biceps function by 3 months of age. Among the patients, 10 had FUE, 4 of which had a positive Horner's syndrome, 14 had CP, and 10 had UP.

All MRI studies were done under general anesthesia and analyzed by a pediatric radiologist with more than five years of experience in BPBI imaging. Type and number of root injuries (no avulsion, thinned roots, partial avulsion, and total avulsion) as well as location of pseudomeningoceles (PMC) were registered. Total root avulsion was defined as both anterior and posterior roots avulsed from the spinal cord. Partial avulsion was defined as either anterior or posterior root avulsed from the spinal cord. Thinned roots are seen on MRI when some of the rootlets emerging from the spinal cord, forming the anterior or posterior root, are ruptured.[140.141] From the shoulder images, the positions (normal, posteriorly subluxed, posteriorly dislocated) of both humeral heads, the shapes (normal, posteriorly rounded, pseudoglenoid) of both glenoids, and glenoscapular angles (GSA) were assessed.

Sensitivity and specificity for total avulsions and PMC on MRI were calculated in relation to the intra-operative findings. Brachial plexus reconstruction was recommended to all patients with total root avulsion(s) on MRI. If no total avulsion(s) were detected observation was continued for another three months. Surgery was recommended again if no improvement was clinically observed. Findings on MRI and surgery were compared to clinical outcome at a mean follow-up (FU) of 5 years (range 2 to 9 years) to assess results of treatment.

High-resolution MRI protocol (1.5T Philips Medical Systems, Achieva)

After running the localizer sequences, T1-weighted spin-echo images in the sagittal plane are obtained followed by T2-weighted spin-echo images in the axial, sagittal, and coronal planes. Slice thickness for coronal T2 is 2 mm and for all others 3 mm. MR myelography is performed using a balanced fast field echo (bFFE) sequence

in the coronal and axial planes with 0.5 mm slice thickness. The T2 weighted axial sequences covers both shoulders.

4.3 Shoulder protocol in BPBI (II)

We had no standardized prevention or treatment scheme for shoulder sequelae in BPBI patients before the year 2000. The development of our current protocol commenced in 2000 and finished in 2009. During this time, instructions for passive ROM exercises to the parents were updated, dynamic US of the shoulder screening was established, BTX injections for children with IR contracture or posterior shoulder subluxation was started, and a shoulder ER spica brace was designed (Figure 7). Since 2010, our protocol has been in routine use; a physiotherapist specialized in BPBI gives individual instructions of passive ROM exercises with special emphasis on shoulder ER in adduction to the parents in the maternity hospital. We recommend doing the exercises as often as possible (>5 time per day). The child is assessed again by a physiotherapist at 2 weeks and at 1 month. A hand surgeon examines children with CP or FUE at 1 month of age and children with UP at 3 months. We recommend brachial plexus reconstruction to children who have FUE at birth, avulsions on MRI, or a 3MTS below 3.5. Primary surgery is again considered if there is no progression of elbow flexion by 6 months or a failed cookies test at 9 months of age.

A pediatric radiologist performs a dynamic shoulder US on all children who have not recovered full shoulder function by 3 months of age. In children with permanent BPBI, US is repeated every three months until one year. In full-term, healthy, normally developing children with an alfa (α) angle exceeding 30° or less than 70° of passive ER in adduction,[11, 88] we inject 100 IU of BTX equally divided between the SS, PM, and TM/LD complex, and apply a shoulder spica brace for 6 weeks (Figures 6 and 7). Parents continue passive ROM exercises of all missing active movements of the affected upper extremity. We recommend neurotization of the SSNI with the SAN to children who can abduct their arm ≥ 90° against gravity but who have no active shoulder ER in adduction (≤0°) by 2 years of age. If irreducible shoulder posterior subluxation or dislocation due to advancing shoulder dysplasia is observed, we advocate open relocation in combination with SS tendon lengthening and resection of the coracoid process.

From 1995 to 2019, 431 children with BPBI were referred to our clinic. Of these, 173 underwent full recovery during the first year, 8 were lost to FU, and 13 moved to our area after 6 months of age. The remaining 237 children with permanent BPBI were included in the study. Among the sample, 2 children had a bilateral injury, 136 were right-sided, 124 of the patients were girls and the mean birth weight was

4.2 kg (range 2.7 to 5.6 kg SD 0.5). Age at detection of dysplastic posterior shoulder subluxation either by US or MRI has been recorded. Shoulder subluxation on US was defined as α angle >30° measured in IR of the adducted shoulder, and on MRI a type 3 or higher.[69] All procedures related to improving shoulder function have been registered. Harms and complications of treatment were documented.

Three distinctive treatment times were recognized, and patients were arranged accordingly: 1995-1999 (n=53), no shoulder protocol; 2000-2009 (n=101), shoulder protocol under development; and 2010-2019 (n=54), complete protocol in regular use (Table 5). To evaluate the results of the change in the treatment regime, all patients from the aforementioned groups that had reached a minimum five-year (mid-term) FU were compared with regards to shoulder outcome (Mallet score and active and passive ROM). Of the 237 children, 208 had completed a minimum FU of five years; all were born during 1995-2015.

Table 5 Patients and shoulder protocol

Shoulder protocol	Birth year	Patients (n)	Birth weight (kg)	Extent of injury at birth	Plexus recon-struc-tion	3-month test score	Extent of injury at 3 months	Patients 5 year FU (n)	Last FU years	Extent of injury at Last FU
No protocol	1995-1999	53 (1 bilat-eral)	4.3 (3.1-5.6), SD 0.6	26 UP	17	4.3 (0.6-9.3), SD 1.8	30 UP	53	14 (9-17.3), SD 2	47 UP
				24 CP			21 CP			7 CP
				4FUE			3 FUE			0FUE
Protocol under develop-ment	2000-2009	109	4.2 (2.7-5.3), SD 0.5	75 UP	12	6.1 (0-9.3), SD 2.3	78 UP	101	12 (5.2-16.7), SD 2.7	88 UP
				24 CP			24 CP			21 CP
				10 FUE			7 FUE			0 FUE
Helsinki Shoulder Protocol	2010-2019	75 (1 bilat-eral)	4.2 (2.9-5.6), SD 0.6	47 UP	12	5.5 (0-9.3), SD 2.5	54 UP	54 (1 bilat-eral)	5.5 (1-10.1), SD 2.4	59 UP
				19 CP			17 CP			17CP
				10 FUE			5 FUE			0 FUE

Patients arranged by shoulder protocol (birth year). Mean birth weight, 3MTS, age at 5-year assessment and last FU expressed with range and standard deviation.

4.4 Selective neurotization of the infraspinatus muscle using SAN (III)

During 2012 to 2014 we identified 8 BPBI patients from our brachial plexus clinic without IR contracture, congruent shoulder joints, active ER in adduction of less than 10°, and active abduction above horizontal. Patients were offered selective neurotization of the SSNI with SAN. Pre- and postoperative ROM were measured by two independent observers. Adverse effects were recorded. FU was scheduled

at 3, 6, and 12 months postoperatively. Mean age at surgery was 3 years (range 2 to 5 years).

Surgical technique

A transverse skin incision is made at the scapular spine, from which the trapezius muscle is identified and detached. SAN is identified medial to the medial upper margin of the scapula, dorsal to the deep trapezius fascia. The function of SAN is verified using a nerve stimulator, after which the nerve is freed both distally and proximally, preserving as many proximal branches to the upper trapezius as possible. IS is detached from the scapular spine, and the SSNI to the IS is identified at the glenoid notch, where it lies next to the suprascapular artery (Figure 8). The viability of the IS can be verified using a nerve stimulator.

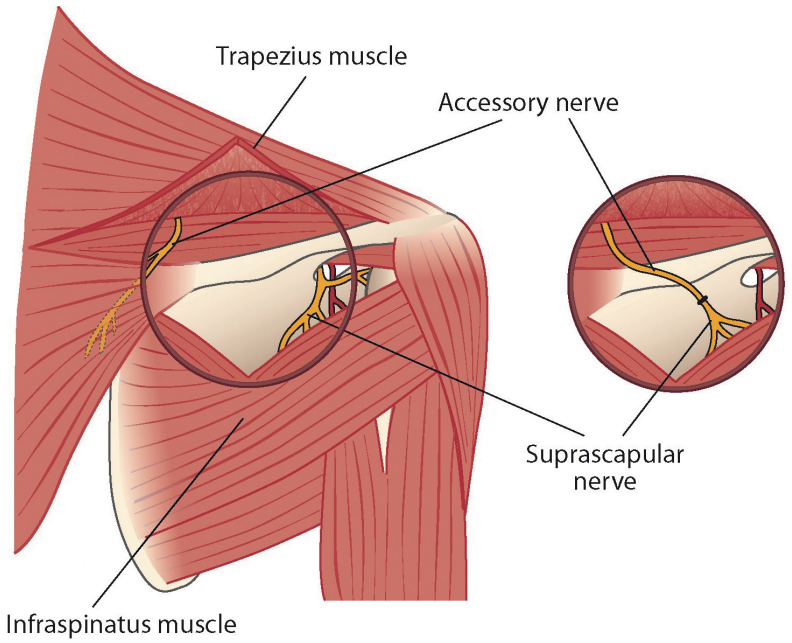


Figure 8 Schematic drawing of SAN transfer to SSNI.

SSNI is transected at the glenoid notch, and SAN as distal as necessary for it to reach the anastomosis site. Neurorrhaphy is performed with two 10-0 non-absorbable sutures and fibrin glue. The shoulder is worked through its full ROM to assess the strength and reach of the anastomosis before the glue is applied. IS and trapezius muscles are reinserted, avoiding compression on the transferred SAN at the scapular spine. Postoperative immobilization is not needed.

4.5 Mid-Term outcome of selective neurotization of the infraspinatus muscle with SAN (IV)

All 14 BPBI patients at our institution that had undergone neurotization of the SSNI with SAN by the technique described in study III in 2012-2016 were assessed, at the least, at the two- year FU. Mean FU time was 4 years (range 2 to 5 years, SD 1). Pre- and postoperative ROM (active and passive) of the shoulder joint were measured using a goniometer by the same independent observers used in study III. Eight of the patients had winging of the scapula pre-operatively.

Among the children 7 of the 14 had undergone preoperative EMG; all seven showed insufficient muscle activation to produce active shoulder ER. EMG was repeated on all 7 at mean 5 years (range 3 to 5 years, SD 1) from the neurotization to evaluate IS and upper trapezius activity using a concentric needle electrode. Possible spontaneous activity (fibrillations, positive sharp waves, and discharges) were recorded. Innervation of the IS was determined by asking the patients to externally rotate the upper arm in adduction: the activation pattern and morphology of the motor unit potential (MUP) was recorded. Quantitative multi-MUP analysis was performed after the examination and the collected MUPs were compared to established normal values and graded.[76]

Parents' satisfaction regarding the functional and cosmetic (scar, scapular winging) outcome was assessed (satisfied vs. not satisfied).

5 STATISTICS

Study I
Sensitivity and specificity for the MRI findings in comparison to the intraoperative findings as well as PMC in relation to root avulsion injury on MRI were calculated. 95% confidence intervals (CI) were calculated using Wilson score intervals. Linear regression models were fitted for GSA difference and model assumptions were visually assessed. The significance level 0.05 was used.

Study II
We performed a multivariate analysis of the extent of the injury at birth (UP, CP, FUE) and the 3MTS in a search for predictive signs for development of posterior shoulder subluxation during the first year of life. Group baselines (extent of injury at birth and birth weight) were compared using the Fisher test.
We used the Kruskal-Wallis test for outcome analysis with all three groups compared to each other as well as a pair-wise analysis between the groups using the Mann-Whitney-U test. The minimal statistical difference was set at $p<0.05$.

Studies III and IV
Statistical analysis regarding age and outcome was done using Spearman´s rank correlation analysis.

6 ETHICAL CONSIDERATIONS

Studies I to IV have been approved by Helsinki University Hospital (HUS) ethics committee and HUS New Children's Hospital institutional review board. Approval number: HUS79/E7/2001.

7 RESULTS

7.1 Incidence of permanent BPBI in the hospital district of Helsinki and Uusimaa (unpublished results)

During the study period, 437,454 children were born in the HUS district of Helsinki and Uusimaa. The rate of cesarean deliveries during the same time increased from 17.0% in 1995 to 19.4% in 2019, giving a mean rate of 17.9%.[142] The mean calculated risk for permanent brachial plexus birth injury (BPBI) in the district of Helsinki and Uusimaa was 0.5 per 1000 vaginal live births, while the same for all births was 0.4 per 1000.

The incidence has decreased during the study period to 0.3 per 1000 during the last 5 years (Figure 9). We found an overrepresentation of children born to immigrant parents with an increasing trend. Over the whole study period, 42/179 (24%) were born to immigrant parents. The ethnicity of these children, as described by the US National Institutes of Health, was 31 black, 8 white (including 2 Middle Eastern), 2 Asian (Indian), and 1 Latino. Between 2015 and 2019, 9/18 (50%) children were born to immigrant mothers. Among these, African descent was the most common (6/9). The immigrant population in South Finland (Uusimaa) during the same time period was 14.9%.[143]

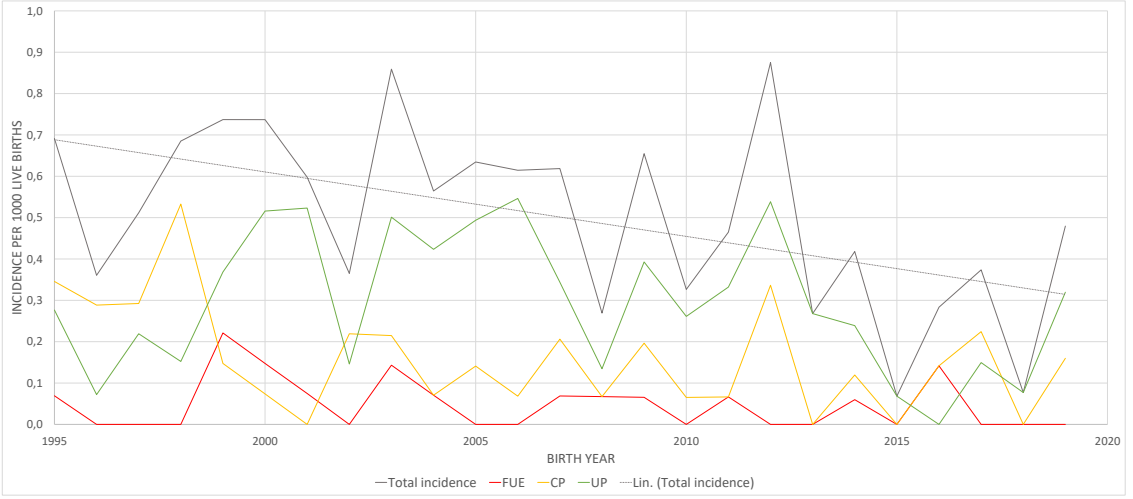


Figure 9 Incidence of permanent BPBI in HUS primary district

Annual incidence of permanent BPBI per 1000 newborns in HUS hospital district of Helsinki and Uusimaa during the last 25 years (grey line) and its trend (dotted grey line). Incidence at birth of UP (green), CP (yellow), and FUE (red) are presented separately.

7.2 Root avulsion diagnosis with MRI (I)

Children with FUE or CP were referred to MRI at mean 2 months of age (range 1 week to 4 months), and the MRI was performed at mean 4 months of age (range 2 weeks to 14 months SD 1). The respective ages of children with UP and no antigravity biceps function by 3 months of age (n=16) were 3 months (range 1 to 6 months) and 4 months (range 2 to 8 months SD 2). Mean time from referral to MRI was 28 days (range 1 to 70 days).

Of the 170 examined root levels, 18 total avulsions were detected in 12/34 patients (Table 6) (Figure 10a and b). Partial avulsions alone were detected in an additional six patients. Thinning of roots were observed in four patients with either total or partial root avulsions. The most commonly totally avulsed root was C8. PMC was seen in association with all 18 total root avulsions and at the level of the avulsion in 6 of the 8 partial avulsions (Table 6). Two patients had PMC without evidence of root injuries. Plexus surgery was recommended to all patients with total avulsion and to seven without (n=19). The 3MTS was less than 3.5 in 18/19 patients. Ten patients with total avulsion and six without agreed to surgery. Three total C8 avulsions, one accompanied by a total C7 avulsion, were left unexplored due to good hand and wrist function at the time of surgery.

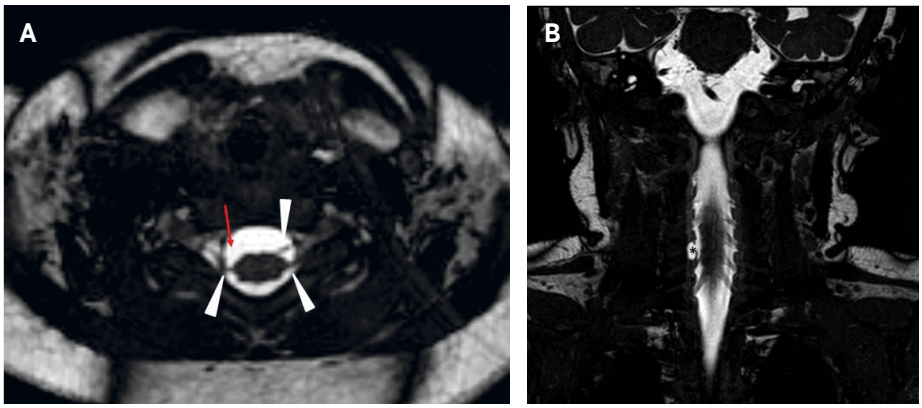


Figure 10 a and b MRI images showing injury to the brachial plexus

a) Axial bFFE MRI (0.5 mm) in a 4 month old girl with right sided BPBI. Partial avulsion of C8 root: ventral C8 root avulsed (red arrow), posterior C8 root intact (arrowhead). Normal left nerve roots (arrowheads). b) Coronal bFFE MRI (0.5 mm) in a 3 month old boy with right sided BPBI. There are complete avulsions of the right C6 roots with a PMC (*) compared to the normal left nerve roots.

Asymmetry of GSA, defined as more than 5° difference to the contralateral uninjured side[69], was found in 22 patients (Table 6). The mean difference was 17° (range 6 to 35). GSA difference was modeled using linear regression with findings at birth and age at MRI as the covariates. Both univariate and multivariate models

were fitted. The findings (FUE, CP, UP) at birth did not significantly associate with the GSA difference in the univariate nor the multivariate models ($p>0.05$ for both FUE and CP when compared to UP in both models). Patient age at MRI significantly associated with both models ($p<0.001$ in both). Glenoid shape was found to be normal in 20 (59%) patients, with a trend toward more severe incongruence in those with MRI done at an older age.

Mean time from MRI to primary surgery was 49 days (range 13-173 days). Intraoperative findings concerning total avulsions were compared to corresponding findings on MRI. Sensitivity and specificity of MRI in detecting total nerve root avulsions was 0.88 and 1.00. Sensitivity and specificity of PMC associated with total avulsion was 1.00 and 0.44.

During the FU, none of the 34 patients underwent full recovery from the injury. When looking at the patient outcome (active antigravity shoulder, elbow, wrist, and finger ROM ratio of injured vs. uninjured), partial root avulsion alone or in combination with thinned rootlets had no clinical significance (Table 7). All patients with CP had a UP at the last FU. Of the patients born with FUE, all but two presented with CP at the last FU. The other two, who both underwent plexus reconstruction, had UP.

Table 6 Patient demographics and findings on MRI

Patient demographics											
Patient	**Extent of injury at birth**	**3-month test score**	**MRI findings**								
			Age (months)	**Total root avulsion**	**Partial root avulsion**	**Thinning of roots**	**PMC**	**GHJ**	**Glenoid shape**	**GSA difference**	**GSA uninjured (°)**
8	FUE*	0	0	C6 7 8		C5vd	C5 6 7 8	N	N	3	-6
15	FUE*	0	3	C8 T1			C8 T1	N	N	6	-7
25	FUE	0	3	C8 T1			C8 T1	SL	PR	25	-15
3	FUE	0	4	C8			C8	D	PG	22	3
20	FUE	1	4	C8	C7D		C8 T1	SL	PR	20	-5
32	FUE*	***	0	C8			C7 8 T1	N	N	5	-10
13	FUE	3	14	C7			C7	N	N	3	-10
9	FUE	0	3	C8			C8	SL	PR	10	-20
17	FUE	0	2					N	N	10	-10
21	FUE*	1	4					N	N	4	-6
22	CP	3	3	C7 8			C7 8 T1	N	N	12	-8
34	CP	2	3	C7 8			C7 8	N	N	5	-10
24	CP	2	4	C8			C8	N	N	2	-7
18	CP	3	3	C6			C6	D	PG	35	-5
1	CP	2	6		C6V 8V		C6 8	SL	PR	21	-9
10	CP	4	3		C8V		C8	D	PG	17	-8
26	CP	2	5		C8V	C7vd	C8	N	N	12	-3
16	CP	5	4		C6D	C6v		D	PG	5	-20
11	CP	1	5					D	PG	34	-6
23	CP	5	4					SL	PR	15	-10
30	CP	5	4					SL	N	10	-10
27	CP	3	4					N	N	7	-8
29	CP	4	3					N	N	4	-1
2	CP	6	5					N	N	3	-5
14	UP	5	7		C6V		C6	D	PG	34	-6
28	UP	5	4		C6D	C6v	C6	N	N	6	-7
31	UP**	3,8/7.6	4				C5-7/ C5-7	N/N	N/N		
19	UP	5	8				C8	N	N	1	-4
5	UP	6	4					D	PG	27	-3
4	UP	6	5					SL	PR	18	-22
6	UP	5	3					SL	PR	10	-15
33	UP	5	4					N	N	9	-11
7	UP	6	3					N	N	8	-12
12	UP	6	2					N	N	0	-5

*Horner sign, **Bilateral injury, ***Surgery before 3 months, FUE = Flail upper extremity, CP = Complete plexus involvement, UP = Upper plexus involvement, V =Ventral root, D = Dorsal root, v =Ventral root thinning, d = Dorsal root thinning, PMC=Pseudomeningocele, GHJ=Glenohumeral joint, GSA= Glenoscapular angle

Patients arranged in descending order of severity of injury at birth, number of root avulsions, and GHJ abnormality.

Table 7 Patient outcome

Patient outcome												
Patient	**Extent of injury at birth**	**Primary surgery**	**Secondary surgery**			**Findings at last follow-up**						
			Specific neurotization	**GHJ relocation**	**Other orthopedic surgery**	**Age (years)**	**Extent of injury**	**Shoulder abduction (%)**	**Elbow flexion (%)**	**Wrist extension-flexion (%)**	**Finger movement (%)**	**Intrinsic (%)**
8	FUE*	CC7				8	CP	91	0	33	0	0
15	FUE*	5 > UT, 6 > MT, 7 > 81, SAN > SSN				4	CP	50	63	72	0	10
25	FUE	5 > 6 ,6 > 1, 7 > 8, SAN > SSN		yes	forearm osteotomy	4	CP	36	50	10	40	20
3	FUE	denied		yes	EIP > EPB, BR > EDC	9	CP	28	73	17	50	0
20	FUE	56 > UT, SAN > SSN	Oberlin		TM > IS	5	UP	78	88	100	100	100
32	FUE*	5 > 8, 6 > UT	SAN > SSNI			3	CP	50	38	25	25	0
13	FUE	SAN > SNN, pRN > pAN				6	UP	39	63	56	100	100
9	FUE	56 > UT, SAN > SSN				7	CP	33	92	10	10	10
17	FUE	56 > UT, 7 > MT, SAN > SSN				6	CP	50	75	11	20	10
21	FUE*	56 > UT, 7 > MT, SAN > SSN			FCU > ECRL/B	5	CP	50	84	17	50	50
22	CP	SAN > SSN				4	UP	38	75	61	100	100
34	CP	denied				2	UP	38	38	25	100	100
24	CP	5 > UT, 6 > UT, 7 > MT, SAN > SSN				4	UP	50	80	100	100	100
18	CP	5 > 6, SAN > SSN				5	UP	83	88	100	100	100
1	CP	denied		yes		5	UP	40	100	100	100	100

10	CP		SAN > SSNI			6	UP	69	81	100	100	100
26	CP	6 > UT, SAN > SSN				3	UP	44	62	100	100	100
16	CP					4	UP	88	91	100	100	100
11	CP	56 >UT, SAN >SSN	Oberlin	yes		6	UP	44	28	61	100	100
23	CP					3	UP	89	91	100	100	100
30	CP		SAN > SSNI			3	UP	92	100	100	100	100
27	CP	SAN > SSN				3	UP	78	81	100	100	100
29	CP		SAN > SSNI			3	UP	72	81	100	100	100
2	CP				TM > IS	7	UP	60	87	100	100	100
14	UP	SAN > SSN				6	UP	66	90	100	100	100
28	UP					2	UP	89	97	100	100	100
31	UP**		SAN > SSNI			3	UP	89	81	100	100	100
19	UP			yes		5	UP	40	56	56	100	100
5	UP					8	UP	94	81	100	100	100
4	UP			yes		2	UP	72	69	100	100	100
6	UP					5	UP	94	100	100	100	100
33	UP		SAN > SSNI			2	UP	81	81	100	100	100
7	UP			yes	TM > IS	7	UP	50	71	36	100	100
12	UP					5	UP	89	100	100	100	100

*positive Horner's sign, **primary surgery before 3 moths of age, pAN = partial axillary nerve, BR = brachioradialis muscle, CC7 = contralateral C7 transfer, ECRL/B = extensor carpi radialis longus and brevis muscle, EDC = extensor digitorum communis muscle, EIP = extensor indicis proprius muscle, EPB = extensor pollicis brevis muscle, FCU = flexor carpi ulnaris muscle, IS = infraspinatus muscle, M = middle trunk, pRN = partial radial nerve, SAN = spinal accessory nerve, SSN = suprascapular nerve, SSNI = infraspinatus branch of suprascapular nerve, TM = teres major muscle, UT = upper trunk

Patients arranged in same order as Table 6, primarily by the extent of injury at birth and secondarily by their 3MTS. Outcome expressed as ratio (%) of active antigravity ROM of the affected side in comparison to the unaffected.

7.3 Shoulder protocol in BPBI (II)

The extent of the injury at birth was registered as UP in 62%, CP in 28%, and FUE in 10% of all 239 affected upper limbs (2 patients with bilateral injury). At the three-month evaluation 68% were UP, 26% CP, and 6% FUE, with a mean 3MTS of 5.5 (range 0 to 9.3, SD 2.4).

There was no statistically significant difference between the three groups with regards to mean birth weight or extent of injury (UP, CP, and FUE) at 3 months. The mean 3MTS was higher ($p = 0.003$) in children born between 2000 and 2009 compared with those born before 2000 or after 2009 (Table 5).

More than half (44/75) of the children born with permanent BPBI in 2010-2019 have been treated with BTX injections, 36 due to dysplastic posterior shoulder subluxation and 8 for internal rotation contracture. Of the additional 48 patients born in 2000-2009 who underwent US screening, 31 received BTX injections. The reason for injection was dysplastic subluxation in 25, and IR contracture in 6 patients. The number of injected patients in the whole study was, thus, 75 with a mean age at the first injection of 5 months (range 2 to 10, SD 7) (Table 8).

Brachial plexus reconstruction was performed on 41 (17%) and shoulder surgery alone on 108 (46%) of the 237 children. GHJ relocation was the most common shoulder surgery (54/237) (Figure 11). The rate of relocation declined during the study period from 28% in children born from 1995 to 1999 to only 7% in children born after 2009. At the same time, the amount of shoulder function augmenting surgery (tendon or nerve transfer) increased from 17% to 36% in the aforementioned groups.

Table 8 Additional information regarding the BTX injections.

Birth year	Patients	Affected shoulders	US screening	BTX injec-tions	injections per patient			Age at 1 st injection (months)	BTX applied (IU)	Target muscles	Spica cast	Duration of cast (weeks)	GHJ relocation
					1	2	3						
2010-2019	75	76	76	44	32*	11	1	5.5 (range 3-10, SD 2.5)	90 (range 60-100, SD 16)	46 SS+PM+TM/LD, 10 SS+PM, 1 TM/LD	53**	5 (range 4-6, SD1)	5
2000-2009	109	109	48	31	26	5	0	5 (range 2-10, SD2)	53 (range 45-100, SD12)	7 SS+PM+TM/LD, 12 SS+PM, 1 SS +TM/LD, 16 SS, 1 TM/LD	23	4 (range 2-8, SD1.5)	34

* 1 refused btx, ** 1 refused cast. US=ultrasound, BTX=botulinum-toxin A, IU=internatonal units, GHJ=glenohumeral joint, SS=subscapular, PM=pectoralis major, TM/LD=teres major and latissimus dorsi complex.

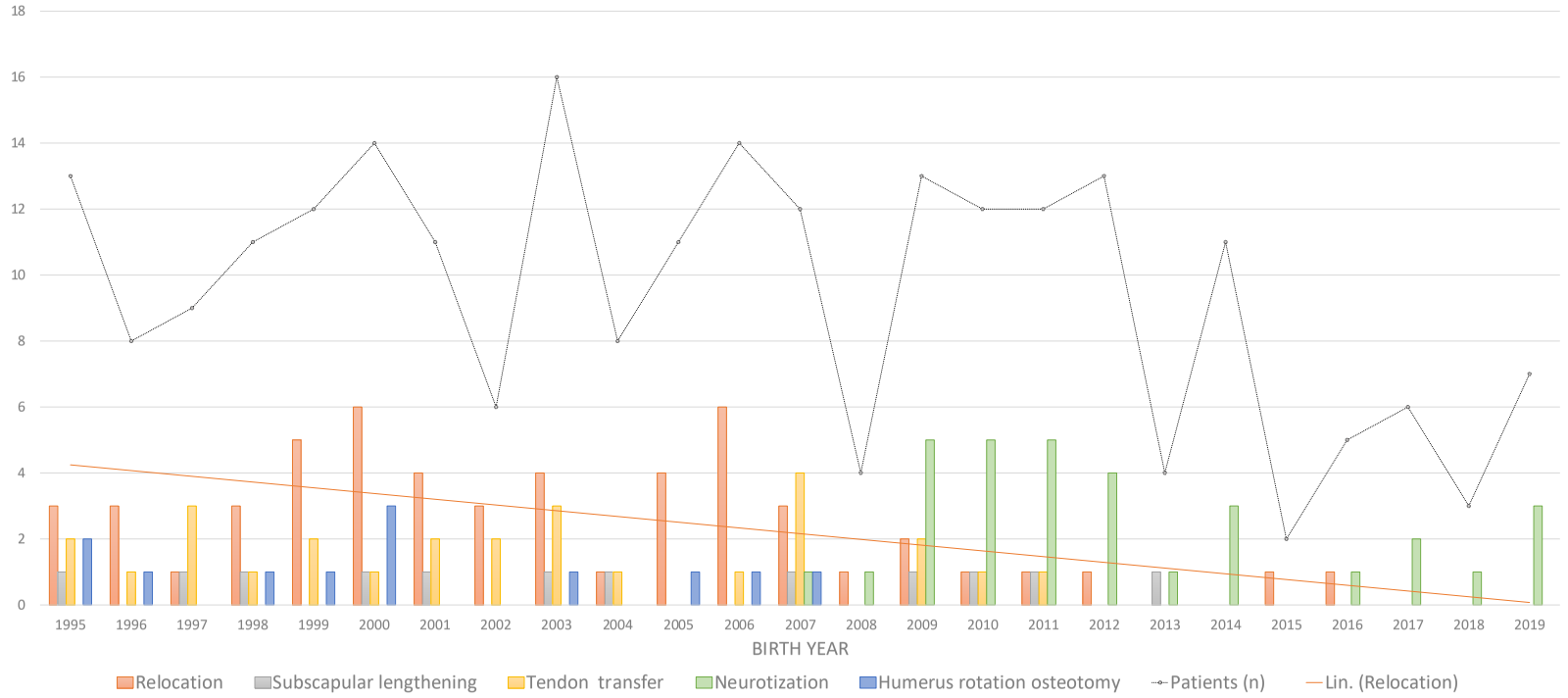


Figure 11 Type of shoulder surgery by birth year

Shoulder surgery has been performed on 108/237 children with 239 BPBI affected shoulders. All children born between 1995 and 2019, number of patients born with permanent BPBI per birth year (dotted grey line). Type of procedure: 54 relocations (red) trend of relocations (red line), 12 SS lengthenings (grey), 27 tendon transfer (yellow), 12 rotation osteotomies (blue), and 32 neurotizations (green). 3 re-do relocations and one re-do humerus osteotomy have been left out.

Radiological shoulder outcome

The rate of radiologically verified posterior shoulder subluxation was 44% in children born in 1995-1999 (all 24 verified by MRI), 50% in children born in 2000-2009 (40 verified by US and 14 by MRI), and 47% in children born in 2010-2019 (all 36 verified by US). There was no statistically significant difference regarding the rate of subluxation between the groups ($p>0.05$). Mean age at detection of first subluxation dropped from 5 years (range 4 months to 9 years, SD 29) for children born in 1995-1999 to 17 months (range 1 months to 10 years, SD 25) for those born in 2000-2009, and further to 5 months (range 1 to 12 months, SD 3) for children born in 2010-2019. Mean α angle at detection of shoulder subluxation in all children was 45° (range 32 to 80, SD 12), with a mean difference to the uninjured side of 21° (range 10 to 30, SD 10). Mean passive ROM for ER in adduction at detection of subluxation was 63° (range 20 to 90, SD 16).

Primary shoulder subluxation was not detected in any of the children who had undergone the US screening protocol (n=123, 75 born in 2010-2019 and 48 born in 2000-2009) at later than 12 months of age.

Functional shoulder outcome and predictive signs for shoulder sequelae

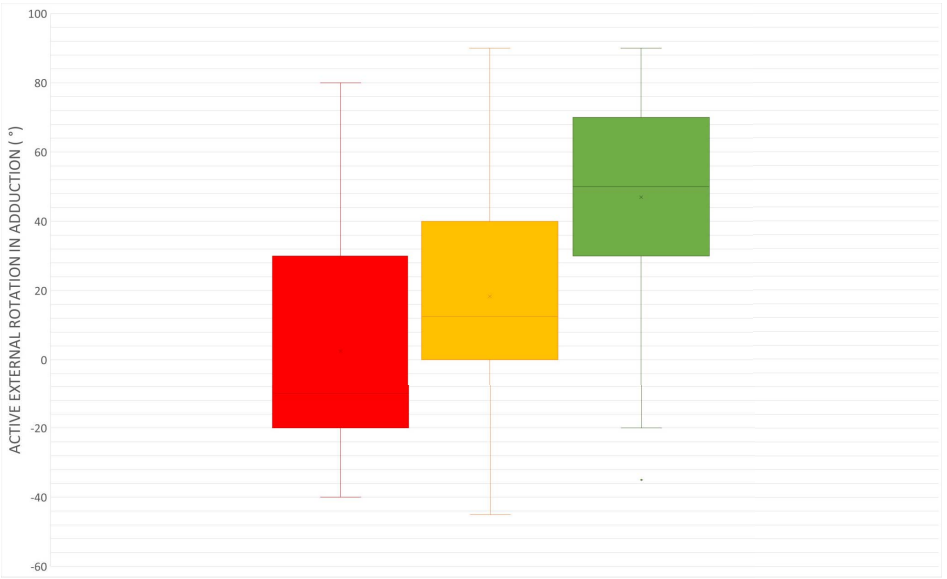
Functional shoulder outcome was assessed in 208 children at a mean age of 5 years (range 4 to 6 years, SD 1). Active and passive shoulder ER in adduction and modified Mallet scores were better in children born after 2009 compared to children born in 1995-2009 ($p=0.0$ for both) (Figure 12 a and b, 13 a-c): mean active ER in adduction at the five-year FU was 2° (range -40 to 60, SD 34) in children born before 2000, 18° (range -45 to 80, SD 31) in children born in 2000-2009, and 46° (range -35 to 80, SD 28) in children born in 2010-2015. Mean passive ER in adduction was 40° (range -20 to 90, SD 35), 54° (range -20 to 90, SD 27) and 72° (range 0 to 90, SD 20).

The mean modified Mallet scores for global ER at the same time point and groups were 3 (range 2 to 5, SD 1), 3 (range 2 to 4, SD 1) and 4 (range 2 to 5, SD 0.5).

No difference ($p>0.05$) between the groups was seen with regard to the Mallet scores of global IR with mean 3 (range 2 to 5, SD 1) vs. 3(range 2 to 5, SD 1) vs. 3 (range 2 to 5, SD 1) nor between mean active shoulder abduction: 130° (range 60 to 180, SD 40) vs.140° (range 45 to 180, SD 40) vs. 135° (range 45 to 180, SD 40).

A 3MTS between 3.3 and 7.4 correlated positively with dysplastic posterior shoulder subluxation during the first year ($p=0.004$). No association of the birth weight nor the extent of BPBI at birth to dysplastic posterior shoulder subluxation ($p>0.05$) was found.

a



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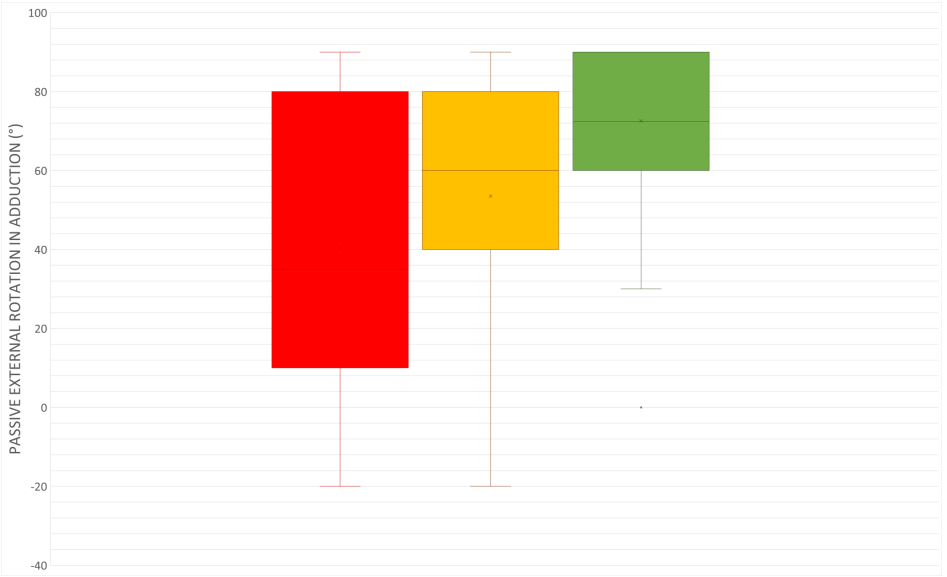

Figure 12 a and b Active and passive external rotation at five-year follow-up

Active (a) and passive (b) ER in adduction at the five-year FU. Figures express range, mean (x), median (horizontal line), and 2SD (box) values. Red: Children born in 1995-1999, no shoulder protocol (53 patients, one bilateral). Yellow: Children born in 2000-2009, shoulder protocol under development (109 patients). Green: Children born in 2010-2019, institutional shoulder protocol in routine use (54 patients, one bilateral).

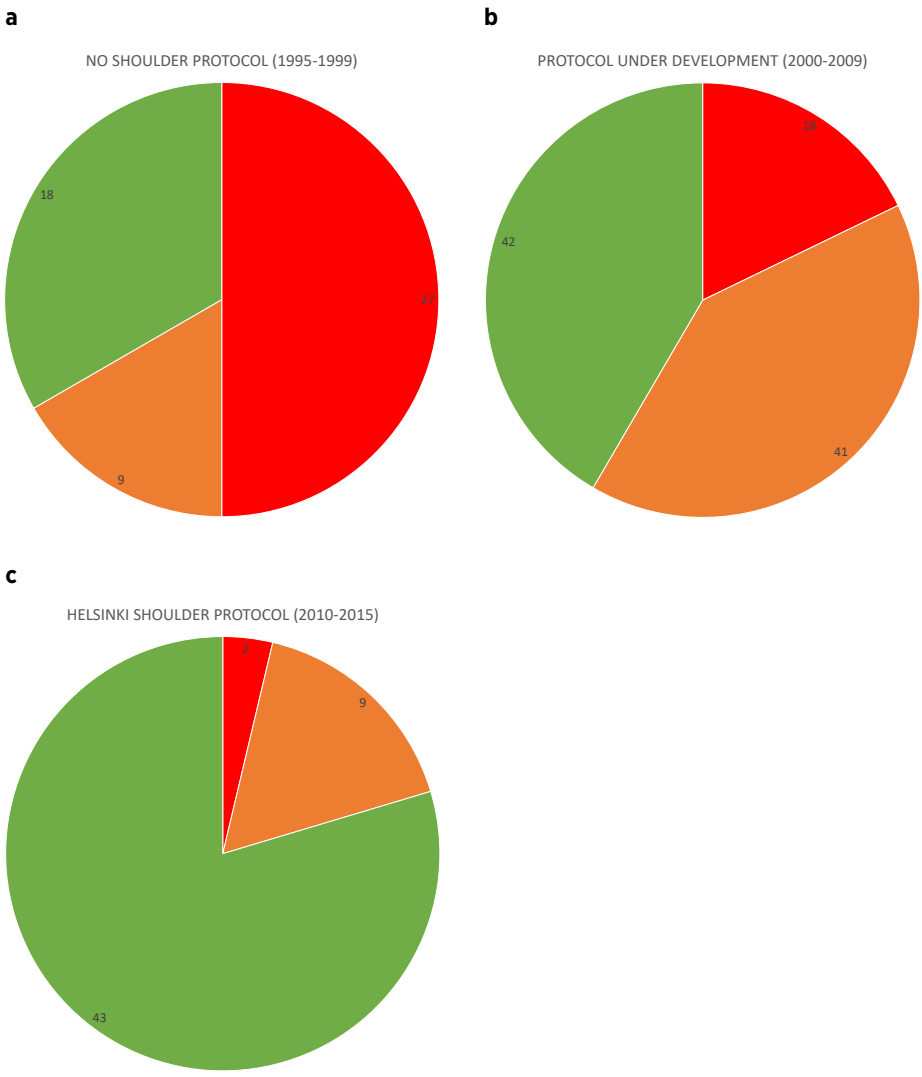

Figure 13 a-c Pie charts showing differences in modified Mallet scores for global external rotation between treatment groups.

Modified Mallet score measured at 5-year follow-up. Patients arranged by treatment group as follows; a) no shoulder protocol, children born 1995-1999, b) shoulder protocol under development, children born 2000-2009, c) institutional shoulder protocol in use, children born 2010 -2015. Color of slice signify Mallet grades; 2 (red), 3 (yellow), 4 or higher (green). Numbers inside each slice signify number (n) of examined shoulders. Children born 2010-2015 had significantly better modified mallet scores for global external rotation (p=0.00).

7.4 Selective neurotization of the infraspinatus muscle using SAN (III)

All patients improved active ER in adduction and abduction. The earliest signs of improvement were seen at three months post-operatively (5/7). At the one-year FU, mean improvement of active ER in adduction was 47° (range 20 to 85) and in adduction and 49° (range 5 to 85). Active abduction improved mean 16° (range 0 to 60). Patient age at the time of surgery did not affect the outcome. No serious adverse effects were noted. One patient developed a keloid scar.

7.5 Mid-Term outcome of neurotization of the infraspinatus muscle (IV)

Among the patients 12 of the 14 improved active ER in adduction to mean 57° (range 40 to 95, SD 20). All 14 improved active ER in abduction to mean 56° (range 30 to 85, SD 20), as well as active abduction to mean 27 ° (range 10 to 60, SD 13) (Figure 14 a and b).

Postoperative EMG showed reinnervation of the IS in all seven examined patients with mild to moderate signs of old recovered nerve injury. Upper trapezius function was assessed in six of the seven patients as one patient refused assessment. All six showed normal upper trapezius function.

One patient developed shoulder IR contracture and another a posterior shoulder dislocation treated by relocation three years after the neurotization. Six patients developed a hypertrophic scar, which healed with local silicone treatment. One developed a Keloid scar but refused further scar treatment. Scapular winging was evident in five patients at the last FU. All but one patient's parents were satisfied with the functional and cosmetic outcomes of the neurotization. No correlation between age at surgery and outcome was found.

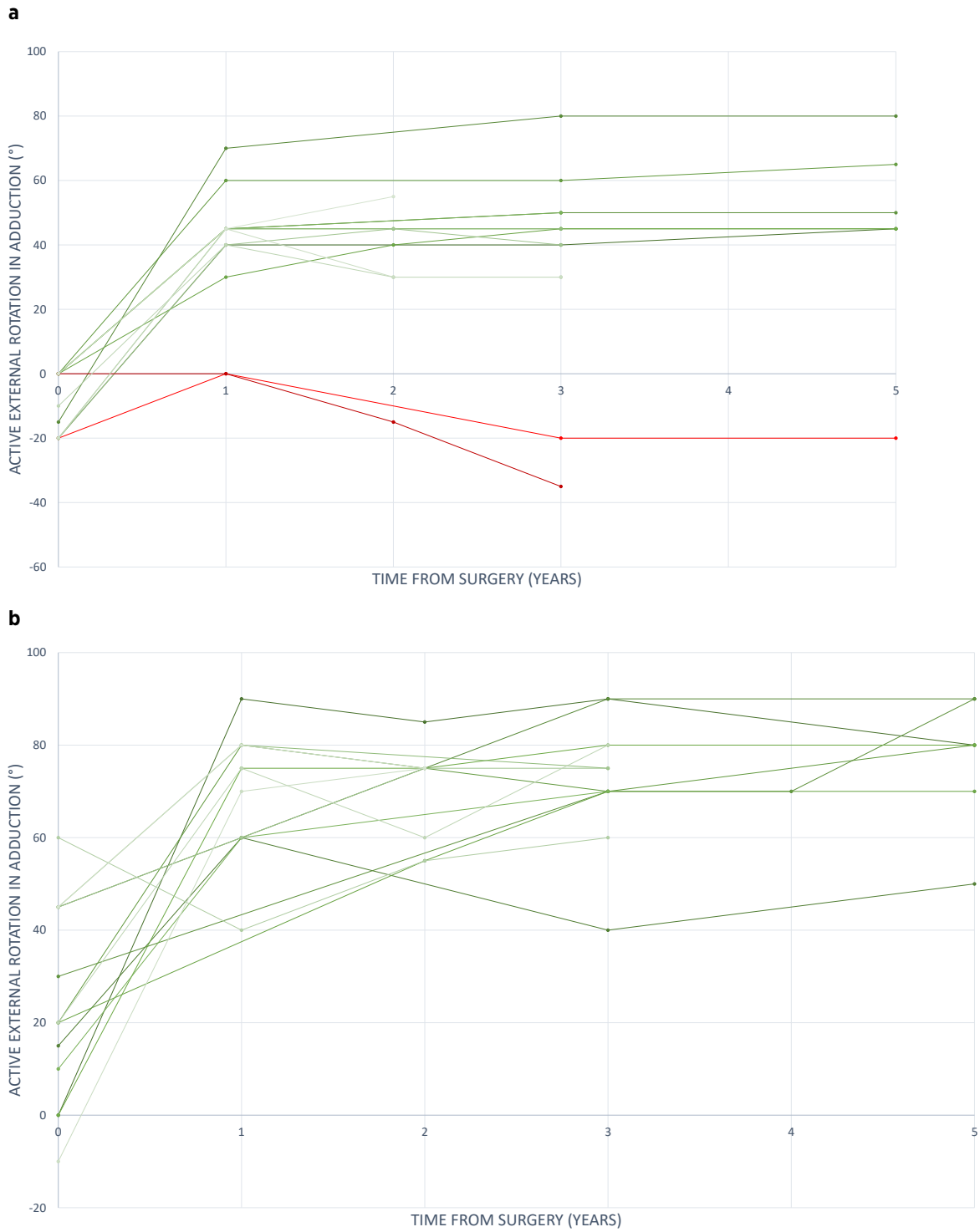

Figure 14 a and b Mid-term results of SAN pro SSNI

Active shoulder ER improved in adduction (a) in 12/14 patient (green lines), and in abduction (b) in all patients. Two patients developed shoulder IR contracture with decreased active shoulder ER (red lines) (a).

8 DISCUSSION

The reported overall incidence of BPBI in Finland is between 2.5 to 3 per 1000 births[18,144] while incidence for permanent injury is reported to be 0.64 per 1000 live births.[11] We found a large variation (nine-fold) in the annual incidence of permanent BPBI with a decreasing trend to a mean of 0.3 per 1000 during the last five years of the study (2015-2019). The literature reports an incidence for permanent injury in all births between 0.1 and 1.6 per 1000,[9,19,20] while the incidence for vaginal births is reported between 0.2 and 0.3 per 1000.[19,20] The results of this study are well in line with these earlier findings. We are not aware of any previous population-based studies reporting such a high annual variation in the incidence of permanent BPBI.

During the study period, there was a 2.4% total increase of cesarean deliveries from 17% in 1995 to 19.4 % in 2019.[142] This increase alone cannot explain the drop in permanent injuries during the last five years of the study. No significant changes in the mean birth weight over the study period were found. Another big question is the overrepresentation of children born to immigrant parents, especially from Black families. Studies from both England and the United States have reported an overrepresentation of Blacks, Hispanics, and Asians.[16,21] It has been hypothesized that the difference could be related to healthcare access particularly high-quality perinatal care.[16,21] All Finnish residents are covered by the public health care system, which should guarantee equal accessibility and the same treatment standard to all. Thus, we cannot explain the reason for the relatively higher risk of sustaining a permanent BPBI in immigrant children.

We developed our MRI protocol to assess whether root avulsion injuries could be reliably detected preoperatively, but also to evaluate whether it could be of use in decision-making and planning of plexus surgery in children with permanent BPBI. Apart from evaluating the brachial plexus itself, both shoulders were assessed. CT myelography has long been the gold standard in BPBI diagnostic imaging, but in recent years, there has been a clear trend towards MRI, possibly due to the fact that MRI does not involve ionizing radiation or the need for intrathecal contrast injection. Earlier MRI studies with evaluation of the presence of PMC only[141] or of nerve root integrity with 1.5 mm MRI slice thickness[145] have demonstrated only moderate sensitivity or specificity levels for root avulsions. In contradiction to these earlier reports we found an excellent correlation between complete root avulsions and surgical findings using 1.5 T MRI with 0.5 mm slice thickness in axial and coronal views. Sensitivity and specificity for complete root avulsion on MRI in our study are in line with the more recent studies of Somashekar et al.[72] and

Menashe et al.[146] Our study further confirmed that PMC has a high sensitivity but low specificity for total nerve root avulsions on MRI.[145,147] We found that a total root avulsion on MRI is a good indication for brachial plexus surgery. Partial avulsions and thinned roots did not influence outcome, so this finding alone should not be an indication for plexus exploration.

The risk of posterior shoulder subluxation during the first year is ≥30% in patients with permanent BPBI according to Pöyhiä et al.[11] She found that half the patients that are to develop posterior shoulder subluxation do so by 3 months of age. This is in accordance with our findings in study I, where the first signs of GHJ incongruence were recognized on MRI in patients less than 2 months old. If left untreated, posterior shoulder subluxation leads to permanent restriction of ROM and GHJ deformity,[148,149] so early detection and intervention are important.[98,149,150] US has been shown to detect posterior shoulder subluxation more reliably than clinical examination.[11] In our population-based material (study II), shoulder incongruence and deformity developed in nearly half of the children who had sustained a permanent BPBI, while in study I, we found signs of glenohumeral dysplasia (type II or higher) in 20/35 shoulders.

Maintenance of good passive shoulder ROM, treatment of posterior subluxation with BTX injections, and early surgical reduction of the shoulder subluxation/dislocation may prevent adverse shoulder sequelae in BPBI.[98,149,150] The main goal of early BTX treatment is to restore congruence of the shoulder joint and ease passive shoulder ROM exercises while awaiting possible IS recovery. No consensus exists about the right dosage, targets, timing or efficacy of BTX injections.[94] Reported dosage varies between 7.4 and 10 IU/kg and it has been administered to both the SS and PM muscles or equally divided between all four internal shoulder rotator muscles.[94-98]

BTX treatment in itself is seldom sufficient enough to maintain shoulder congruence, thus, children who do not regain active Mallet grade III or higher global external rotation should be considered for either tendon or nerve transfer.[70,82] Greenhill et al.[95] and Singh et al.[96] found that BTX treatment in itself resulted in good active ER in adduction without the need for further procedures in ~15% of their patients. In both aforementioned studies, ~65% of the patients underwent secondary shoulder procedures during a mean FU of 2 and 5.4 years, respectively. The mean age at first BTX injection was 11.5 and 12 months, and the mean passive ER in adduction was 6-23° at the time of injection in these two studies. We administered a high dose of BTX at an earlier age to children with less severe contracture at time of injection. This could explain our lower rate of post-BTX shoulder surgery (45% patients 2010-2019) and better functional outcome.

A congruent shoulder is again a prerequisite for both tendon or nerve transfers, which underlines the importance of early diagnosis and treatment of posterior

shoulder subluxation. Today, several authors advocate surgery to restore missing shoulder ER before 3 years of age in an aim to maintain shoulder congruence and possibly prevent glenohumeral deformity.[70,125-127] Shoulder ER can be improved in abduction with LD and/or TM to infra/supraspinatus tendon transfer and in adduction with the lower trapezius to infraspinatus tendon transfer.[71,135,136] Similar results can be achieved with neurotization of the whole SSN or the SSNI with SAN.[83,151]

We have shown that IS function can reliably be restored by the technique described in study III. As spontaneous recovery of IS function is unlikely after 1.5 years,[9] we recommend neurotization at 2 years of age. We did not find an upper age limit for the procedure, as our oldest patient who benefitted from the surgery was 4.7 years. However, we believe our study population to be too small for reliable statistical calculation regarding this issue. We have discontinued the use of pre-operative EMG and MRI studies, as we aim at doing the procedure at 2 years of age. We still believe both EMG and MRI can be beneficial, especially when evaluating older patients for the procedure.

The gain from tendon transfers subside over time,[152] and while our midterm results (study IV) are promising, we still have no way of knowing how the presented technique will stand the test of time. Both our patients that failed to benefit from the nerve transfer had developed an IR contracture during the waiting time, with only 30° of passive ER at the day of surgery. It is possible that the outcome of these two patients would have been better if subsequent lengthening of the SS were done.

9 STRENGTHS AND LIMITATIONS

This study has several limitations. We can only speculate on the reason for the recent decrease in the incidence of BPBI in Southern Finland. We did not explore the lower plexus in children with good hand function and could not therefore verify all our MRI findings. We have no way to assess not only whether we have performed plexus reconstructions or shoulder surgery on the right patients but also whether we have performed them technically correctly. The rate of dysplastic posterior shoulder subluxation in children born after 2015 could be an underestimate, as the FU of these children is still short. It is impossible to know the relative importance that patient-related factors (extent and type of BPBI) and interventions (passive ROM exercises, clinical and US screening, BTX-injections, ER bracing or specific surgery) have in keeping the shoulders in place. We have addressed the rate of posterior shoulder subluxation, but not other dysplastic changes, such as size and shape of the humeral head and the glenoid. As of today, there are no studies comparing tendon transfers aimed at restoring shoulder ER to nerve transfers, so we can only speculate on the possible superiority of one over the other.

10 CONCLUSION

1. The annual incidence of permanent BPBI shows great variation. The incidence of permanent BPBI injury in vaginal delivery is ~0.3 per 1000 births in the HUS district of Helsinki and Uusimaa. Children of immigrant parents have a significantly higher risk for sustaining a permanent BPBI, but the reason for this is unknown.

2. Root avulsions can be reliably detected by cervical MRI. Partial avulsion seem to have little or no impact on outcome.

3. Daily passive ROM exercises of affected joints from birth, US screening for posterior shoulder subluxation, BTX treatment of internal rotators in combination with six weeks of spica bracing if IR contracture or subluxation is detected during the first year, and specific surgery to enhance active shoulder ER appear to reduce the need for shoulder relocation.

4. Active shoulder ER can be reliably restored and maintained with specific neurotization of the infraspinatus muscle with SAN in a subset of children with congruent shoulders and active abduction above or at horizontal, without IR contracture.

11 TREATMENT PROPOSAL FOR PREVENTION AND MANAGEMENT OF SHOULDER SEQUELAE IN PATIENTS WITH PERMANENT BPBI

In line with our findings we propose that the birth hospital give all patients with BPBI instructions for daily passive ROM exercises. Special emphasis should be put on passive shoulder ER in adduction. Children whose injury does not fully reslove during the first three months should undergo dynamic US screening during the first year. If restriction of passive ER in adduction is observed (<70°), or subluxation is detectedon US, BTX injections to all internal rotators should be administered in combination with a six-week continuous spica brace (Figure 5 and 15).

If active ER rotation in adduction is <0° at 1.5 years SAN pro SSNI or tendon transfer should be considered. Passive ROM exercises of all affected joints should be continued throughout growth.

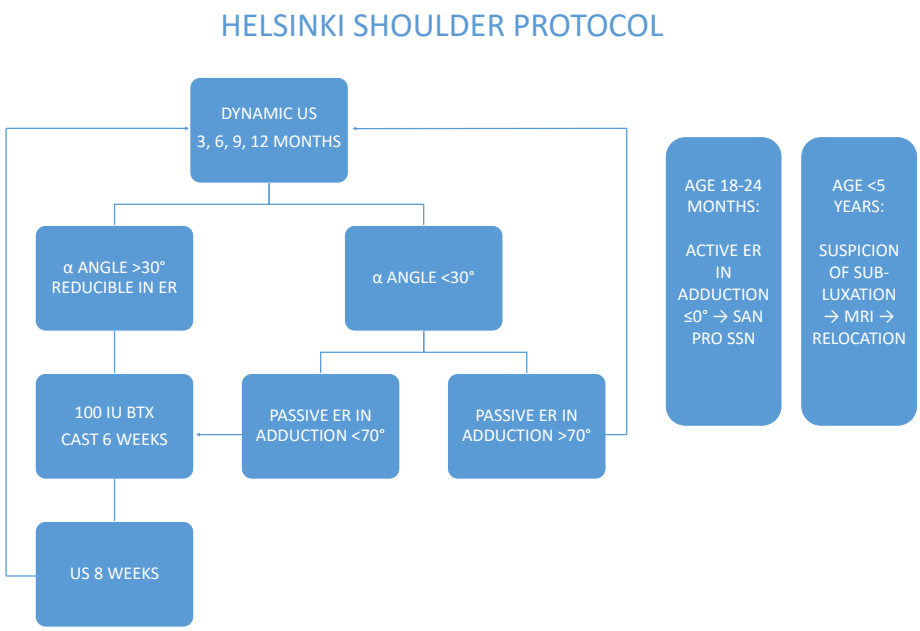

Figure 15 HUS protocol for treatment of shoulder sequelae in patents with permanent BPBI

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