Neonatal Brachial Plexus Palsy: the role of diminished sensibility of the hand on functional recovery

Buitenhuis, S.M.

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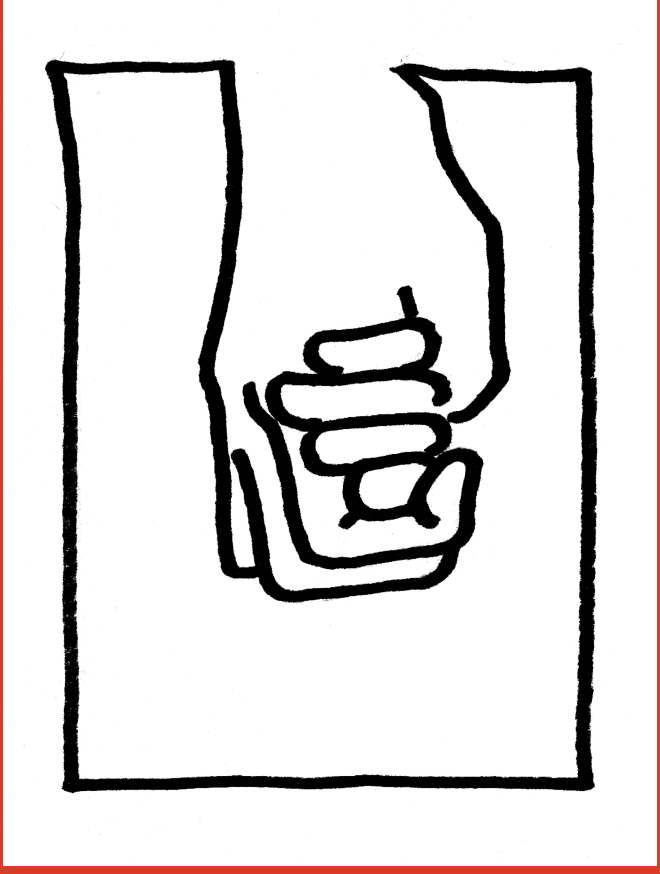

Sonja Buitenhuis

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The printing of this thesis was financially supported by the Scientific College Physical Therapy (WCF) of the Royal Dutch Society for Physical Therapy (KNGF) and by the Department of Physiotherapy LUMC.

ISBN | 978-94-6473-424-9
Design Cover | Chieny Buitenhuis-Boiten
Lay-out | Rob van der Pluijm
Printing | Ipskamp Drukkers BV Enschede

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Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op het gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op dinsdag 11 juni 2024
klokke 16:15 uur

door

Sophia Maria Buitenhuis
geboren te ‘s-Gravenhage
in 1957

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Leden Promotiecommissie

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Contents of Thesis

Chapter 1

General Introduction

INTRODUCTION

The aim of the studies reported on in this thesis is to get a better understanding of the long-term consequences of a brachial plexus injury that occurred during birth, a so-called neonatal brachial plexus palsy (NBPP). NBPP can affect the motor and sensory functions of the shoulder, arm and hand.

The evaluation of sensation following a NBPP has so far not received much attention. Research was merely focused on the outcome in terms of motor function and improving the performance of various motor tasks. Standards for the assessment of sensory outcomes are lacking, which hampers adequate evaluation of sensation and thereby also the development of strategies to improve sensation. Optimization of treatment strategies for NBPP is only possible when all aspects are included, both motor and sensory. This thesis focusses on the assessment of both sensory outcome and motor development, and the relationship between these two.

NEONATAL BRACHIAL PLEXUS PALSY

The brachial plexus is the nerve network connecting the spinal cord with the muscle and sensory end-organs in the shoulder, arm and hand. The plexus is formed by the spinal cord nerves C5 to T1 and the various end-nerves are formed in an elaborate branching pattern. (Figure 1)

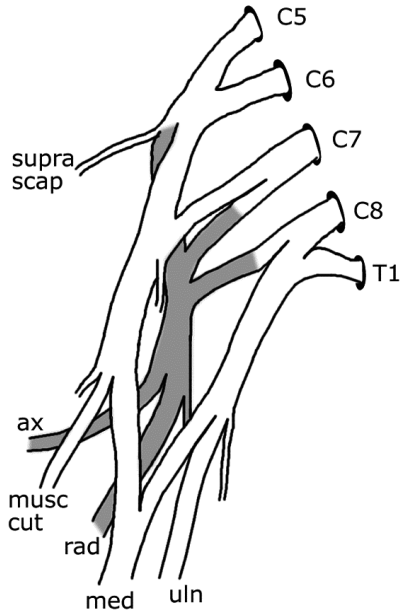


Figure 1 The brachial plexus originates from the spinal nerves C5 to T1 suprascap-suprascapular nerve; ax-axillary nerve; musc cut-musculocutaneous nerve; rad-radial nerve; med-median nerve; uln-ulnar nerve. (from Pondaag[1])

A neonatal brachial plexus palsy (NBPP) is a stretch injury that occurs during delivery when the baby's shoulder is blocked by the mother's symphysis. (Figure 2) Due to lateral movement of the head of the baby, the angle between the neck and shoulder becomes too wide, causing traction to the brachial plexus. The incidence of NBPP is 0.5 to 2.6 per 1000 live births.[2]

Assuming a birth rate of 169,000 live births a year, we can estimate that 85-450 children with a NBPP are born in the Netherlands each year. While the majority will recover spontaneously, 50-150 children will have incomplete recovery, resulting in life-long deficits. The main risk factor for NBPP is high birth weight. In a cohort from our center, we showed a significant correlation between a higher birth weight and a more extensive plexus lesion.[3] Other risk factors, such as gestational diabetes, probably have an indirect effect as they are related to a high birth weight.

Breech delivery carries a high risk of a specific injury type, namely root avulsion of the upper nerves. If a root is avulsed, the nerve root filaments are pulled out of the spinal cord.[4] General textbooks state that the spontaneous recovery of NBPP is good in an estimated 90%

of cases, with complete or nearly complete recovery. A systematic review, however, showed that 20% to 30% of children probably do not recover that well, but have a persistent neurological deficit throughout life.[5] The differences in reported outcomes among studies can be explained by differences in the definition of complete recovery they use and the age of the child at which the level of recovery is established.[6]

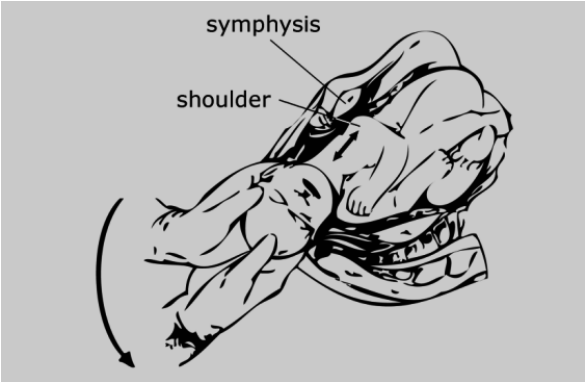
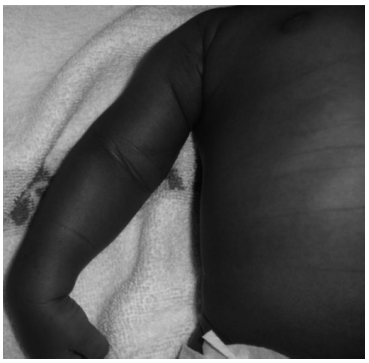
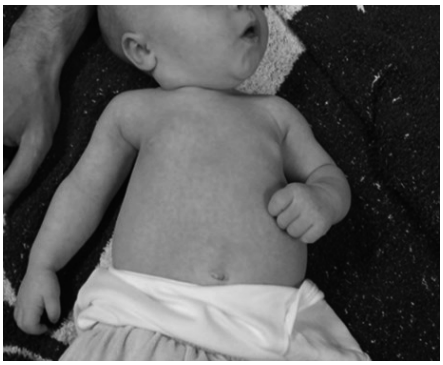


Figure 2 Trauma mechanism of neonatal brachial plexus palsy: the infant's shoulder becomes stuck behind the mother's symphysis during delivery as forces are applied to deliver the child.

The most common lesion type, found in around 80% of the cases, is a lesion of the two upper spinal nerves (C5 and C6) of the brachial plexus. This lesion type results in weakness of the shoulder (deltoid, supraspinatus and infraspinatus muscles) and the elbow flexors (biceps, brachialis and brachio-radialis muscles). Immediately after birth, the position of the arm is typically in extension, internal rotation and adduction. When spinal nerve C7 is also damaged, the extensors of the wrist and fingers are weakened as well, leaving the wrist and fingers in a permanently flexed position. This typical position of the arm is commonly referred to as 'Waiter's tip position'. (Figure 3a) In more severe lesions, C8 and T1 are involved as well, which results in a loss of hand function. The most severe lesion form is a complete paralysis of the arm and hand, which is usually called a flail arm. (Figure 3b)[7] Hand function is impaired in about 15 % of patients.[5]



a) Lesion of C5 C6 C7, with the typical 'Waiter's tip' position of the arm



b) Lesion of C5 up to T1: flail arm

Figure 3 Typical arm position in relation to the number of damaged nerves

Classification of nerve injuries

The severity of the nerve injury was classified into three degrees by Seddon in 1942. His classification is still widely used[8]

- Neurapraxia: the structure of the nerve has remained intact and the function will recover completely within a few days.
- Axonotmesis: rupture of axons but basal lamina tubes remain intact. In these lesions, Wallerian degeneration will occur distal to the rupture site. The severed axon will re-grow from proximal to distal to its end-organ, guided by the original basal lamina tube. Depending on the distance between lesion site and end-organ, functional recovery will occur over the course of months. (Figure 4)
- Neurotmesis: axons and basal lamina tubes are ruptured, and in more extended lesions even the perineurium and epineurium are damaged. Axonal elongation is not possible due to the lack of guidance through the basal lamina tube. A neuroma is formed at the lesion site. (Figure 5)

This classification was expanded to five degrees by Sir Sydney Sunderland in 1951.[9] Sunderland's first-degree lesion corresponds with Seddon's neurapraxia, and his fifth degree with Seddon's neurotmesis. Sunderland defined an intermediate degree between axonotmesis and neurotmesis in more detail. In the third-degree injury, not all axons recover; additionally, axonal misdirection will occur, further compromising

recovery. Muscle weakness and/or sensory defect remain. In a Sunderland grade 4 lesion, the internal architecture of the nerve is lost, but the epineurium remains intact. A so-called neuroma-in-continuity is formed.

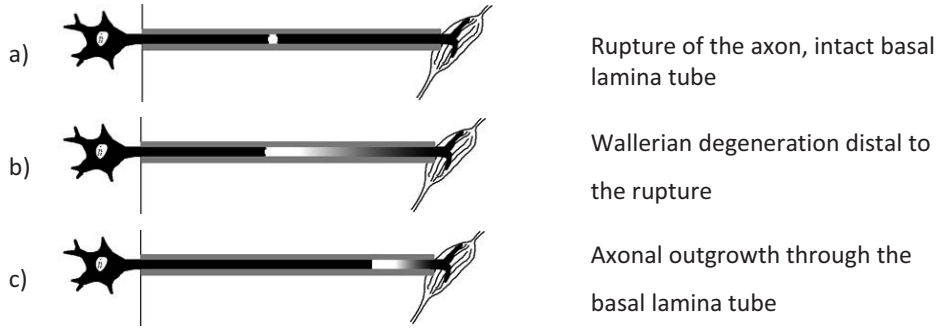


Figure 4 Axonotmesis, schematic representation of one neuron.

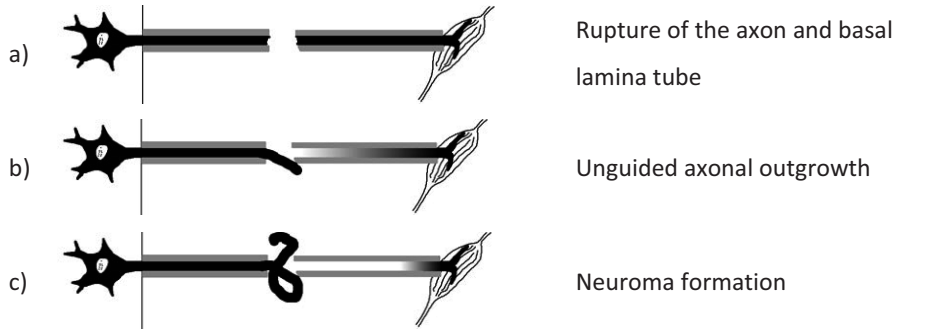
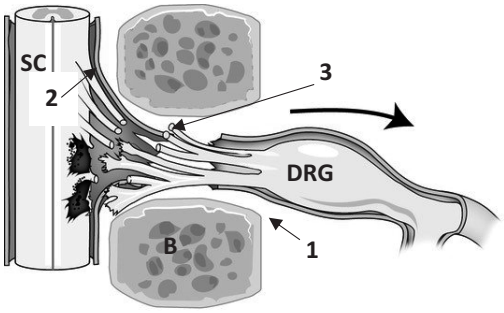


Figure 5 Neurotmesis, schematic representation of one neuron. (from Pondaag[1])

A type of nerve injury which is specific to brachial plexus traction injuries is root avulsion, which is a pre-ganglionic injury in which the root filaments are torn out of the spinal cord. (Figure 6)



In successive order, rupture takes place at:

(1) the fibrous connections between nerve and foramen,
(2) the dura and
(3) the rootlets.

DRG-dorsal root ganglion; B-bony foramen; SC-spinal cord

Figure 6 Avulsion (Copyright ZenuwCentrum LUMC)

Differences between traumatic brachial plexus lesions in adults and NBPP

In contrast to a traumatic plexus lesion in adults, a birth-related lesion will usually not result in complete rupture of the nerve elements. The typical lesion is a neuroma-in-continuity, an intermediate form between Sunderland's grades 3 and 4.[10, 11] Some axons may successfully bridge the neuroma-in-continuity, but their number is reduced and their routing is insufficient. Further focal deficits of myelination have been found in neuroma-in-continuity, contributing to the failure of functional recovery.[10] Some of the damaged axons grow through the neuroma to their original target, but other axons will grow to an incorrect target, which is called misrouting. This phenomenon may explain typical clinical features of NBPP, such as co-contraction of agonistic and antagonistic muscles.[12] Apart from incorrect innervation of motor axons, they may also end up in basal lamina tubes towards a sensory target. Such erroneous outgrowth does not lead functional recovery. In NBPP, the absence of motor control and sensory feedback during the time of development of central motor programs can cause developmental apraxia,[13] whereas in adults these programs are already fully developed.

Prognosis

NBPP is a closed stretch injury of the brachial plexus, with varying severity and extent. A mild nerve damage[11] (neurapraxia/axonotmesis) will completely recover in time, but a severe damage (neurotmesis/avulsion) will cause permanent loss of arm function. The severity of the nerve damage can, at present, not be assessed with certainty at an early

stage, not even with the help of imaging or other ancillary investigations. The severity only becomes clear by observing neurological recovery in the course of time. The difficulty lies in the fact that that the end stage of recovery may be only reached after 18 months to three years. In case recovery is limited and nerve reconstructive surgery is indicated, a critical amount of time has then been lost. After all, the results of nerve surgery are inversely related to the time between trauma and repair.[14] The window of opportunity for nerve reconstruction is limited, due to the intrinsically limited recovery potential of the nerves, and the deleterious effects of denervation on muscles, leading to irreversible atrophy and failure of the development of cerebral control. There is agreement amongst medical specialists that nerve surgery is indicated if spontaneous recovery is insufficient, or severely delayed,[14, 15] and that the time interval after birth is preferentially kept as short as possible. The neurological deficits in mild and severe nerve lesions are initially the same, but the occurrence and speed of recovery will reflect the lesion severity.

Indications for nerve surgery

There are different approaches to assessing recovery, and thus to selecting infants for nerve surgery. The first indicator of poor recovery was defined by Prof. A. Gilbert from Paris: when the biceps muscle (mainly innervated by spinal nerve C6) has not recovered by the age of 3 months, nerve surgery is indicated.[16] Prof. H. Clarke introduced a combined sum score of different movements in an 'active movement scale' at different ages up to 9 months, which is used to decide whether a child should be operated [17] These algorithms estimate the severity of the nerve lesion from the extent and speed of neurological recovery, and serve to support the decision to perform surgical nerve repair in a timely fashion.

The LUMC cohort study (2011)

The Leiden University Medical Centre serves as a tertiary referral center in the Netherlands for complex nerve lesions. We sought to improve early prognostication for children with an NBPP and undertook a cohort study with national recruitment. Children were assessed at the outpatient nerve clinic at three different time points, namely at the ages of one week, one month, and three months. The infants' passive and active joint movements were

assessed, and an electromyography study of the biceps, triceps and deltoid muscles was performed.[18]

These prospectively gathered parameters were then correlated to the presence of a severe nerve lesion, defined as neurotmesis or avulsion, during surgery. Children who were not operated on were followed for two years to ensure that spontaneous recovery occurred. We included 48 infants in the study, which resulted in a model with a correct prediction in 94% of children at the age of one month.[18] We called it the Leiden three-item test.

When to refer to a specialized nerve center: the Leiden three-item test

It is important that children with a severe NBPP with neurotmesis or root avulsion are diagnosed as early as possible, enabling timely referral to a center with the necessary expertise. The three-item test was developed to assess prognosis at one month of age.[18] (Figure 7)

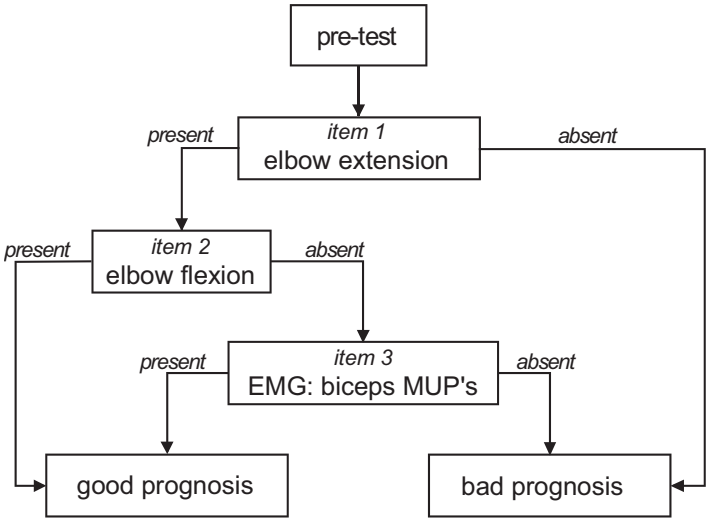


Figure 7 Flow diagram of NBPP assessment at one month of age using the Leiden three-item test. (from Pondaag[18])

In current practice, children are assessed clinically by the referring paediatrician, neurologist or physical therapist, while an electromyogram (EMG) of these very young children is usually performed at our center. The three-item test (Figure 7) starts with clinical examination of elbow extension. (Figure 8)

Figure 8 Testing of elbow extension (mainly triceps muscle): in supine position, bring the arm in anteflexion with the elbow in flexion, and assess active elbow extension.

Failure of elbow extension at one month of age reflects paralysis of the triceps muscle, which signifies involvement of the C7 / C8 / T1 roots, and carries a poor prognosis. These children should be referred to a specialized center. When active elbow extension is present, the second item to test is elbow flexion. (Figure 9)

Figure 9 Testing of elbow flexion (mainly biceps muscle): in supine position, bring the arm in 90^{o} abduction and external rotation, and assess active elbow flexion.

If elbow flexion is present (or has already recovered) at one month of age, the prognosis is considered favourable. If elbow flexion is absent, the next step is to perform an EMG of the biceps muscle. The presence of motor unit potentials (MUPs) signifies that subclinical recovery of the biceps has taken place and the prognosis for recovery is good. If no MUPs are found, the prognosis is poor.

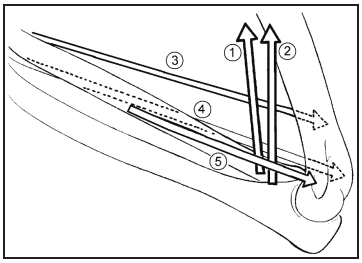
The three-item test is used for prognostication at the age of 4-6 weeks, and is highly helpful to inform parents of the expected outlook at an early stage. Additionally, it helps in the planning of ancillary investigations (MRI) and surgery.

Irrespective of the estimated prognosis, children are re-examined at the age of three months for a definite indication for nerve surgery. If hand function remains diminished (involvement of C8 or C8 and T1), there is an absolute indication for surgical reconstruction of the nerve. In other cases, lack of recovery of the biceps muscle is a reliable indicator of

severe lesion of the upper nerves (C5 and C6). In this respect it is of eminent importance that 'trick' movements are recognized during the execution of elbow flexion, as they wrongly suggest recovery of the biceps muscle (and thus of C5 and C6 spinal nerves), but are in fact executed by other muscles (and other nerves). A commonly observed trick movement to flex the elbow in supine position is by swinging the arm forward using the pectoralis muscle. The elbow will then flex and the hand can be brought to the child's mouth using the effects of gravity and relaxation of the triceps muscle, whereas it suggests active elbow flexion based on biceps muscle recovery.

Trick movements: the Steindler effect

A frequently seen trick movement has been named 'the Steindler effect'. The name is derived from the operation according to Steindler, in which the origin of the wrist and finger flexor muscles is moved more proximally on the humerus. As a result, the forearm flexor muscles will also act as flexors of the elbow joint. Likewise, some infants are able to flex the elbow by other muscles than the original prime movers, especially by the extensor carpi radialis muscle (in combination with the pronator teres muscle), when its origin is located just above the elbow joint. One main characteristic of elbow flexion based on the Steindler effect is that the lower arm is in pronation. The extensor carpi radialis muscle can act in this way, as it is a bi-articular muscle spanning both wrist and elbow. (Figure 10)



1 *biceps brachii muscle (C5) / C6 – musculocutaneous nerve*
2 *brachialis muscle (C5) / C6 – musculocutaneous nerve*
3 *brachioradialis muscle C6 – radial nerve*
4 *extensor carpi radialis longus muscle C7 – radial nerve*
5 *pronator teres muscle C7 – median nerve*

Figure 10 Elbow flexion can be executed by other muscles than the biceps brachialis and brachioradialis muscles.

We performed a study to assess which type of nerve lesion (axonotmesis, neurotmesis or root avulsion) was found in children who clinically showed elbow flexion using the Steindler effect.[19] We identified 28 children with NBPP (born between 1997 and 1999) at our outpatient clinic at the LUMC who executed elbow flexion partially or completely using the

Steindler effect. Among these children, 20 (72%) were found to have a severe nerve lesion, for which nerve reconstruction proved necessary. Six weeks after their surgery, in which the nerves to the biceps, brachialis and brachioradialis muscles were interrupted, these children could still bend their elbow with the same Steindler effect. This finding proved that it is possible to flex the elbow without using the biceps, brachialis, or brachio-radialis muscles. (Figure 11)

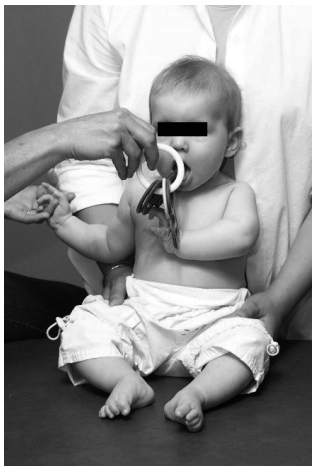


Figure 11 Child flexing the elbow with a Steindler trick at the age of 3 months.

Legend Figure 11

Six weeks after surgery with nerve grafting of the C6 nerve outflow towards the biceps muscle, the child was still able to flex her elbow using the Steindler trick. This finding proved that it is possible to flex the elbow without the m. biceps, as it was too early after nerve surgery for the latter to be reinnervated.

From this study we learned that proper differentiation between elbow flexion based on biceps muscle activity and the Steindler effect is crucial to avoid inadequate neurological assessment. Imprecise assessment may lead to underestimation of the severity of the nerve lesion, while a severe lesion carrying an indication for surgical nerve repair may actually be present.

Some children may use a combination of flexing the elbow and the Steindler effect, and with some biceps as shown by the hand position in supination. These children may be in a recovery phase. Palpation of the biceps muscle to see whether it contracts during flexion may be difficult and is therefore not always reliable. We recommend that children in whom it is difficult to differentiate between elbow flexion based on biceps function and on a

Steindler effect should be monitored by a specialized team to evaluate whether neurological recovery occurs.

We clinically observed that many children in the first month of their life flex their elbow with a 'natural' Steindler effect, alternating between flexion with and without supination. Perhaps supination of the forearm would be a better criterion to assess recovery of the biceps, and thereby of the superior trunk, but this has not been sufficiently studied.

A variant of the Steindler effect has been observed where elbow extension is executed in a situation in which the triceps muscle is paralyzed. The extension is then executed with the flexor carpi ulnaris muscle. This trick (‘reversed Steindler effect’) can be recognized by noticing that the wrist is moved into ulnar deviation.

TREATMENT OPTIONS

Nerve surgery

Severe nerve injuries (neurotmesis / Sunderland grade 4 lesion or root avulsion) will not recover spontaneously, and nerve surgery may improve the outcome significantly compared to what the natural course would have been. Nerve surgical repair techniques which can be used include nerve grafting and nerve transfer. Nerve grafting consists of resection of scar tissue and the neuroma and subsequently bridging the gap between the proximal and distal stumps with a nerve graft. The graft serves as a guide for the outgrowing axons. (Figure 12)

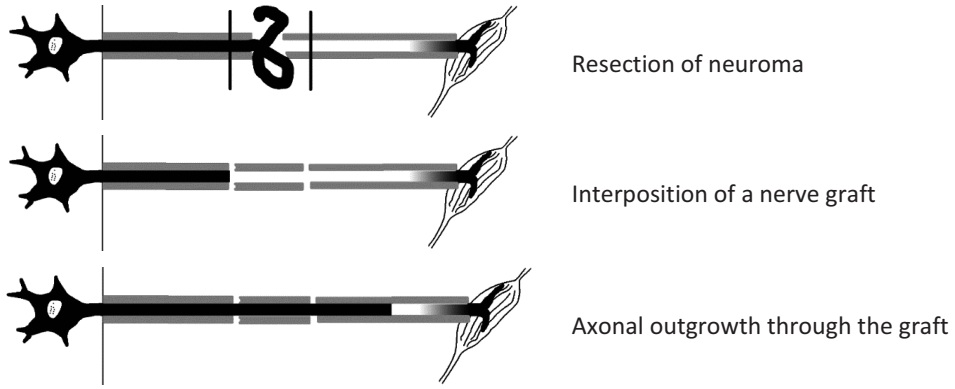


Figure 12 The principle of nerve grafting (from Pondaag[1])

The best graft to bridge the gap is an autologous nerve, for which the patients’ sural nerve is usually used. In our hospital, we harvest the sural nerves using an endoscope, via three

incisions in the leg, the scar being hardly visible after one year.[20] The use of the sural nerve causes loss of sensation on the lateral side of the foot, which does not compromise the function of the leg and foot.[21] A prerequisite for nerve grafting is the availability of a healthy proximal nerve stump that can serve as an outlet, so this technique cannot be employed in avulsion injuries. In such lesions, a nerve transfer can be applied. This technique involves cutting a healthy nerve in close proximity to the damaged nerve and coapting the healthy proximal stump to the denervated distal stump of the damaged nerve. (Figure 13)

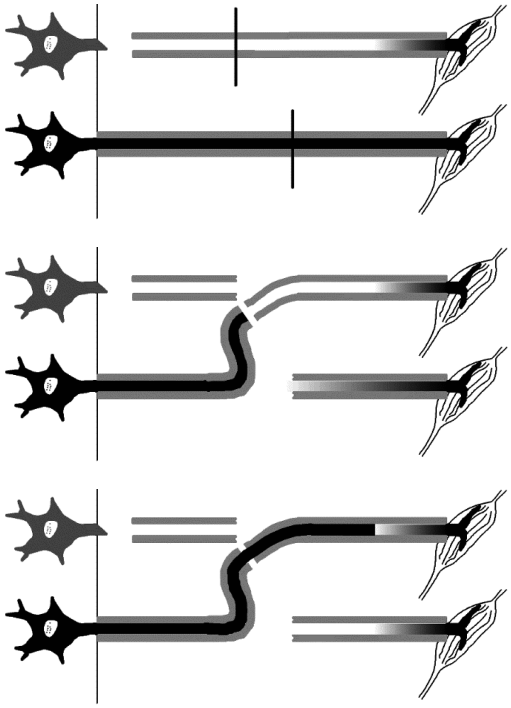


Figure 13 The principle of nerve transfer (from Pondaag[1])

At the Leiden University Medical Center, nerve surgery is performed preferably at an age of 3 to 5 months. After the surgery, the baby is immobilized to prevent loss of the nerve repair. For the first two weeks, the baby is immobilized in a synthetic shell, followed by three weeks with the arm under the shirt. (see Figure 14)

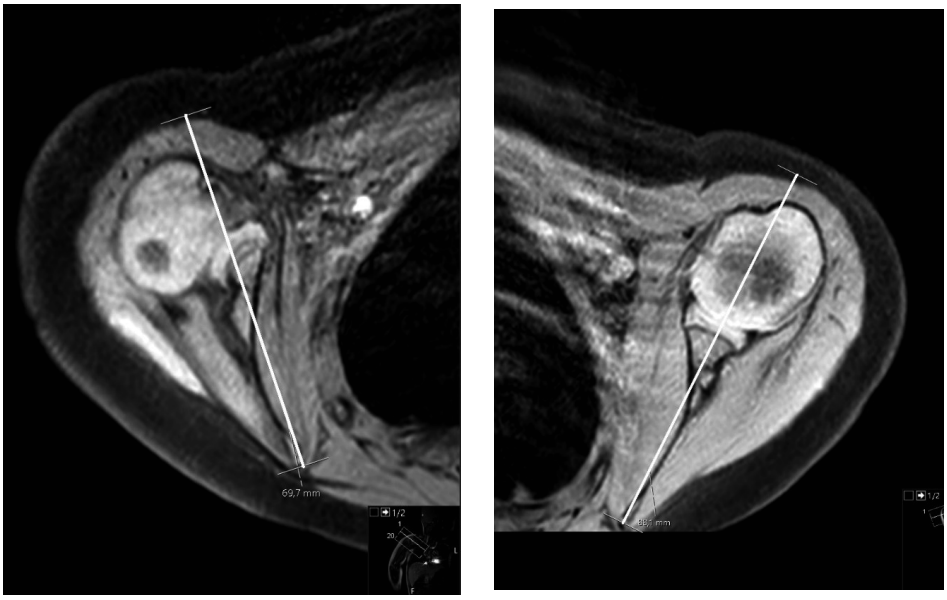
Figure 14 Immobilized arm after nerve surgery using a synthetic shell

Neurological recovery takes place only after the axons have reached the target end-organ. As axons grow approximately 1 mm per day under ideal laboratory conditions, recovery of function following NBPP repair can take up to 2.5 years for an upper brachial plexus lesion and 5 years for a total brachial plexus lesion.

The results of nerve surgery of the upper brachial plexus lesion are generally good. Results of elbow flexion recovery are excellent: approximately 95% of children will regain elbow flexion against gravity (unpublished data). On the other hand, true glenohumeral external rotation will only recover in 40% of children after reconstruction of the suprascapular nerve. A functional analysis after nerve surgery, however, found that 90% of the children can reach their mouth with their hand, and 75% are able to put their hand on their head.[22] Hand function restoration after nerve reconstruction in case of a total lesion is feasible. We found that recovery to the functional level of an assisting hand is around 65%.[23]

Secondary surgery

Secondary surgery to improve function involves bone, joint or tendon surgery. The principle of a tendon transfer is that a functioning muscle's tendon is detached from its original insertion and attached to a muscle that is not working. The indication for secondary surgery procedures may be either to treat joint deformities, or to improve function in case of insufficient neurological recovery. The most frequent indications for secondary surgery are addressed below. Concerning the shoulder, one of the key challenges is to keep the glenohumeral joint mobile. Recovery of the infraspinatus muscle following suprascapular nerve reconstruction is usually poor.[22] An ongoing internal rotation position may lead to secondary deformity of the shoulder joint. This may be an indication for internal contracture release and tendon transfer of the latissimus dorsi and/or teres major muscles.[24, 25] Surgical treatment of a progressive internal rotation contracture is only possible when the glenoid and head of the humerus are not dislocated or deformed. (Figure 15)



a b

Figure 15 a) Affected shoulder with dislocated and deformed glenoid and head of the humerus;
b) the non-affected shoulder for comparison.
(Copyright ZenuwCentrum LUMC)

In case of a fixed supination deformity, a pronation osteotomy of the ulna and/or radius can be performed to improve the functional position of the hand.[26, 27] When the wrist extension is weakened, a better grip function can be obtained by tendon transfer of the pronator teres muscle to the extensor carpi radialis longus and brevis muscles.[28]
To treat weakness of the extension of the fingers and thumb, a muscle transfer of the flexor carpi radialis muscle to the extensor communis muscle and of the palmaris longus to the extensor pollicis longus muscle may be performed.[27-29]

Splinting / bracing

There are two indications for splinting following an NBPP. The first is to functionally support a weak joint, for example using a brace that keeps the wrist in neutral position to improve functionality of the hand. The second is to treat contractures. The contracture that we encounter most frequently is the elbow flexion contracture. The prevalence of elbow flexion contracture, defined as a fixed position of the elbow, is nearly 50%.[30] Severe elbow flexion contracture, defined as more than 30 degrees, has been found in 21% to 36%.[30, 31] The etiology is multifactorial. It is presumed to result from a combination of passive tissue restrictions (the joint itself, the muscle fascia, the subcutis and the skin), active resistance caused by muscle contraction and poor coordination between m. biceps and m. triceps. There is strong evidence that elbow flexion contractures are largely due to the effects of denervation, which causes failure of the growth of the affected flexor muscles.[30] The muscle phenotype in elbow flexion contracture has been compared in children with NBPP and children with cerebral palsy. Both contractures are caused by lack of muscle length rather than excess of muscle strength.[32] These findings imply that contracture treatments should aim to lengthen rather than weaken the affected muscles. The efficacy of treating an elbow flexion contracture did not differ between serial casting and a dynamic orthosis.[33] It has been suggested that contracture of the glenohumeral joint can be prevented by applying the SupER splint.[34, 35] This SupER splint holds the arm in supination and in externally rotated position, and is recommended to be worn 22 hours per day. Unfortunately, long-term results of the SupER splint have not been analyzed.

Botulinum toxin

Botulinum toxin is a neurotoxic protein produced by the bacterium *Clostridium botulinum*. It prevents the release of the neurotransmitter acetylcholine at the neuromuscular junction. It causes a flaccid paralysis that lasts for several months. In children with NBPP there are a few indications for this treatment, although controversy exists regarding its efficacy.[36] Firstly, Botulinum toxin can be used to counter a progressive internal rotation contracture.[37] At our center, children with limited dysplasia of the glenohumeral joint are treated with Botulinum toxin injection of the m. subscapularis.[38] This procedure is performed under general anaesthesia, immediately after MRI imaging of the shoulder has been performed to determine the severity of the shoulder dysplasia. We found that it may be effective in preventing the need for tendon transfers in selected patients[38], but other authors found that the effect of Botulinum toxin was not sufficiently sustained over time to be of clinical benefit.[36] A second indication for Botulinum toxin is the treatment of co-contractions of agonist and antagonist muscles after misrouted reinnervation. Currently, the most common indication is the treatment of co-contractions of the biceps and triceps muscles. The triceps muscle is weakened by the injection of Botulinum toxin, followed by rigorous physiotherapy training of elbow flexion.[36]

OUTCOME ASSESSMENT

Outcome and functioning: the ICF model

Outcome assessment for children with NBPP may include a number of aspects, which can be classified according to the International Classification of Functioning, Disability and Health, which is a model developed by the World Health Organization. (Figure 16) The model includes a number of domains. The first domain is 'Body Functions and Body Structures' which includes features like motor function, strength, sensibility, contractures, pain, but also cosmetic deformity and developmental apraxia. Outcomes in the 'Activity and Participation' domain include aspects like self-care, mobility, school and leisure activities. The domains are influenced by 'Personal factors' and 'Environmental factors'. Ideally, outcome is assessed for all domains and factors. A systematic review, however, showed that the majority of studies focus on 'Body Functions and Body Structures' only.[39] Recent papers have started to assess outcomes in other domains.[6, 40, 41] Each domain of the ICF model is relevant for all ages, but one should realize that treatment priority may shift from 'Body

structures and functions' at early ages (from birth to toddler) to 'Activity and Participation' as the child gets older.[6] Perspectives of functioning and health in the ICF model may differ between patients and their parents versus healthcare professionals.[42]

Most children had little knowledge of the etiology of the brachial plexus birth lesion. The health care specialist needed to explain the parents and their child about the cause of the condition.[40] Impact on the parents and family of having a child with a NBPP is an environmental factor that health care specialists should take into account to provide effective care from an early stage on.[41]

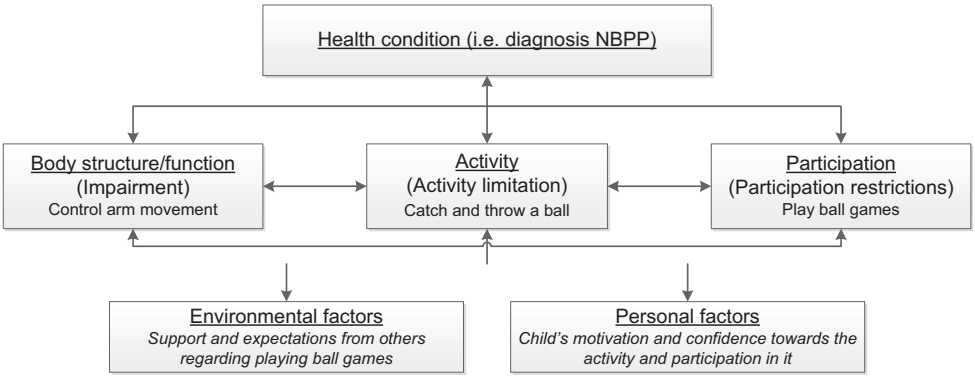


Figure 16 ICF model in relation to possible NBPP problems (Holst, van der[43])

Outcome evaluation

A large number of measures have been used to assess outcomes.[39] This is why it is difficult to compare studies, or pool data from different centers. In this respect, it would be desirable to have a standardized core outcome set. The Leiden Nerve Center has launched the first initiative towards such a core outcome set, which was named: iPLUTO: international Plexus oUtcome sTudy grOup.[44] A Delphi round of surveys was employed using a nine-point Likert scale to rate the suitability of different outcome measures. Consensus was defined as a rating of 7/8/9 out of 10 by >75 % of the participants. International consensus was reached that evaluation should take place at specified follow-up moments based on the age of the child, namely 1, 3, 5, 7 and 15 years. The evaluation should include (1) passive range of motion (measured in degrees) of joint excursions; (2) active range of motion (also

measured in degrees); and (3) the Mallet score.[45] The Active Movement Scale and MRC grading of strength did not receive sufficient support to be endorsed in this survey.

In the first iPluto study, consensus was only reached on motor items from the 'Body Function and Structure' domain. Consensus regarding additional ICF domains (functionality, quality of life), will be addressed in future research.[44]

THE PEDIATRIC PHYSIOTHERAPIST

The ICF model can be applied at all ages. The treatment priorities after NBPP, however, typically shift from a strong emphasis on body structure and body function in infancy toward greater emphasis on activity and participation as the child gets older.[6] The main goal for pediatric physiotherapists has been defined for different ages of the child: baby, toddler, pre-school, school age and adolescent. Depending on the setting, pediatric physiotherapists or occupational therapists perform these tasks in some countries.

Babies

The focus in this period is on the domains of body structure, active functioning and environmental factors. The environment involved consists mainly of the child's parents. As early as possible (preferably within one week after birth) a baby with a brachial plexus lesion will be assessed by a physiotherapist. In the early phase, the treatment primarily consists of providing information about the nerve lesion to the parents. It usually takes a great deal of repetition for the parents to grasp all available information. Most parents have experienced the birth as a traumatic life event. Feelings of guilt and failure may have emerged, besides feelings of anger towards the gynecologist, obstetrician, or midwife. The second objective is to perform exercises to prevent contractures. It is of eminent importance to start exercising as soon as possible. Joint movements relating to the paralyzed muscles must be applied by the parents multiple times a day. The parents are often afraid to move the affected arm, as they think that the nerve lesion may worsen or that rest is better to allow the nerves to recover faster. The only indication for immobilization of the affected arm is a clavicle or humerus fracture, and it will usually last for three weeks. In all other situations, the arm has to be moved at the joints as much as possible to prevent contractures. Comparison of joint excursions with the unaffected arm

can thereby be very helpful. The advice is to perform the exercises during every diaper change, resulting in practicing at least six times a day, for around five minutes. The joint movements at risk for contracture in case of a lesion of C5 and C6 are: external rotation, abduction, elbow flexion and supination. When C7, C8 or T1 are damaged too, care should be taken to include mobilization of wrist extension and radial abduction. When the hand is paretic or paralyzed, the joints of the fingers should be mobilized as well: ossa metacarpi (MCP) in flexion, but also phalanx proximal (PIP) and the phalanx distal (DIP) in extension. The physiotherapist provides the parents with instructions and advice on how to dress, undress, lift and bathe the child, with special focus on handling of the affected arm. In the early phase, these basic procedures may be challenging for the parents. The rule of thumb is that the postures and movements of the healthy side should be reproduced at the affected side. Care should be taken to prevent unphysiological positions or extreme movements, especially in case of a flail arm.

The child often exhibits a gaze preference towards the unaffected side, perhaps because it perceives movements of the unaffected arm and hand and successfully brings the unaffected hand to the mouth. (Figure 17) The physiotherapist must instruct the parents on how to stimulate the child to also look towards the affected side. This can be done by turning the head in that direction, or by drawing visual attention to the affected side.

The third objective is to help the child gain awareness of the affected arm and hand, so that the child can incorporate the affected side in their cerebral body image. This can be achieved and stimulated by bringing the child's affected hand in contact with different kinds of materials. It is important to stimulate playing with two hands together and engage the affected hand in activities. Providing stimuli drives sensibility development. Figure 18 shows an example of how a child brings his affected hand to his mouth to lick yoghurt from his fingers.

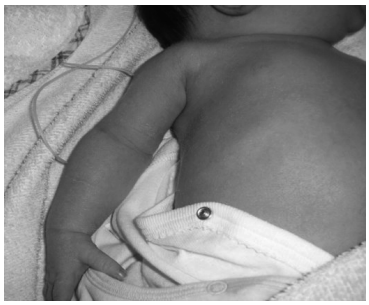


Figure 17 One-week-old baby with a NBPP

Figure 18 Child (NBPP C5 to T1) brings his affected hand to his mouth, because he wants to lick yoghurt, an exercise helping the child to be aware of his hand.

Postoperative regimen after nerve surgery

Immobilization is indicated during the first weeks after nerve reconstruction. Different hospitals apply different immobilization schemes. In our hospital, the baby's head, shoulder and arm are strictly immobilized in a cast for two weeks. (see Figure 14) This period is followed by three weeks of relative immobilization, where the head and neck can move freely, but abduction and external rotation in the glenohumeral joint are immobilized by putting the arm under the shirt. After this period, the physiotherapist and parents can restart the exercises to treat joint contractures.

Toddlers, pre-school and school age

The shift in treatment goals once the toddler age is reached is towards the domains of activity and participation, paying attention to environmental and personal factors. The end stage of neurological recovery is reached between the ages of 2 and 4 years, either from

natural recovery or recovery after surgery. In case of diminished hand function, recovery will take even longer.

Some situations may require special attention. At toddler age, a diminished balance may develop due to a favourite position veering towards the healthy side. (Figure 19) The reflex to break a fall by stretching out the arm is impeded by the NBPP and may necessitate extra support in learning how to walk.[46]

Figure 19 A child with a right-sided NBPP of C5 to C7 puts his body weight on the non-affected left site. His right knee is supporting his affected arm to keep it in elbow flexion.

Most children compensate for the lack of glenohumeral movement (both active and passive) by compensatory activity of the scapula. Such superfluous scapular movements, combined with internal rotation contracture and/or abduction contracture, are sometimes referred to as winging of the scapula. Another form of compensation can occur at the level of the spine, resulting in a compensatory scoliosis. (Figure 20)

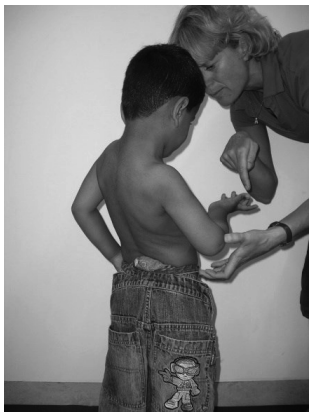


Figure 20 Rotation of the spine, because the child compensated for the lack of active gleno-humeral external rotation

Riding a bike is sometimes a challenge, due to the asymmetric arm positions. When this is caused by the elbow flexion contracture, a night brace can help to reduce the contracture. If the difference in position between the two arms persists, an adjustment of the handlebar is an option to allow the child to sit straight on the bike. (Figure 21)

Figure 21 Adjustment of a bicycle handlebar for a child with a right-sided NBPP

Self-care requiring bimanual activities, such as dressing or making a ponytail, may need extra support. Participation in sports and gymnastics at school (like throwing and catching a ball with two hands) may be hindered, in which case the gymnastics teacher (or swimming teacher) may need extra education and explanations.
Determining the best hand to write with may be troublesome in school. Most children with a right-sided NBPP will change the dominant hand to left side.[47, 40, 48]

Adolescents

Adolescence may warrant extra guidance and advice to make choices regarding sports[49], education and future profession.[50] It is important to help adolescents find a balance between ability and capacity, which may be needed to prevent the development of pain and stress due to overuse. Health care professionals should be on the alert for signals of mental problems, as adolescents with NBPP may experience being different from their peers, or they may be teased or bullied because of their arm, which may cause disability-related distress and worries.[48] Regularly explaining what has happened to their arm is necessary for children and adolescent to learn about their own capacities.

Teamwork

It is important that children with an NBPP are treated early after birth by specialized health care professionals. The pediatric physiotherapist is the starting point for diagnosis and monitoring of these children, especially within specialized brachial plexus teams. Such multidisciplinary teams should also include specialized surgeons who can perform nerve repair and secondary surgery. Other treating specialists in the team may be a neurologist, and an occupational therapist. Early treatment may prevent a delay in sensorimotor development and secondary joint disorders. Early interventions may help the child integrate the arm as much as possible into its own body image. Possible psychological problems in children and parents can be recognized and treated in a timely manner.

CHILDREN WITH A NBPP AND THEIR SENSIBILITY

Importance of sensibility

The importance of the sensibility of the hand was expressed by Lundborg as follows: “A hand without sensibility is usually a hand without function”.[51] The hand can be regarded as the interface between the brain and the environment, and the philosopher Descartes consequently called it “the outer brain”.[52] The mechanoreceptors in the hand react to tactile stimulation, and the resulting neural impulses are conducted by the peripheral nerves along the spinal cord to the somatosensory cortex of the brain. Sensory functions may be categorized as localization of touch and discrimination of touch, enabling the recognition of objects without using the eyes. Roughly speaking, one could say that vital

sensibility can warn against external influences which may disrupt the normal course of life, while gnostic sensibility serves to analyze these influences in more detail.

Current knowledge about sensibility

In many facets of the ICF domains of impairment, activity and participation, recovery of motor function is the primary focus. There is currently a knowledge gap as regards the sensibility of the hand in children with NBPP. Studies reporting assessment of sensibility have been rare and reported conflicting outcomes. Some of these studies described normal sensibility[53-56], while others reported diminished sensibility.[57-59] These different studies are described in detail in the Appendix to this thesis. We felt that the currently available studies fell short in terms of methodology. One major limitation is that only two studies employed a control group.[59, 60] In many studies, the contralateral arm was used as control, which may be affected by the effect of a limb preference shift, which often occurs. We chose to include a control group and compare the affected arm with the non-dominant arm in the controls.
A normal sensory input to the somatosensory cortex in early life is essential for the development of motor skills.[13, 61] The hypothesis in the present thesis is that the sensory development of children with NBPP is affected to a significant degree, and this in turn will have a major effect on motor performance, as the NBPP lesion occurs during a critical time window of brain development. The sensibility of the hand provides crucial feedback information to the central nervous system during development. Erroneous sensory input to the brain will lead to central apraxia or dyspraxia.[13] One example is the absence of automated swing of the affected arm when the child is walking or running, even when this movement can be executed voluntarily.[62, 63]

PAIN

The literature on pain in children with a NBPP is scarce. It seems that the issue of pain is less important to assess for treating physicians than it is for patients.[42] One often-cited paper found 'no evidence of chronic pain behavior' in their cohort, although pain was not assessed at all during outpatient evaluation; it was simply not spontaneously reported by the children or their parents.[53] One study that actively and systematically documented pain in a cohort of 65 surgically treated children found a lifetime prevalence of 66%.[64] These authors reported no difference between children with upper or total plexus lesion. Another

study reported that 78% of the 37 children with NBPP (22 with orthopedic reconstructive surgery, 9 with orthopedic and nerve surgery, 1 with nerve surgery only and 5 with no surgical intervention) aged between 8 and 18 years experienced pain.[65] A factor that may play a role is that children may not only experience pain in a different way than adults, but that they may also use other words to describe pain.[64] Children may express pain as 'pain', but also as an 'unpleasant feeling' .

Self-mutilation may be considered another form of pain behavior. The incidence of biting fingers following NBPP was reported to be 11% (4/37) in children with a total NBPP and 2% (2/90) of children with a upper NBPP.[66] None of the children who exhibited this form of self-mutilation reported spontaneous pain. The third form of pain is that reported by adolescents or adults who experience pain of the affected shoulder caused by overuse of the muscles or shoulder joint. This pain is usually regarded as musculo-skeletal, and is thus not discussed in further detail here.

OUTLINE OF THIS THESIS

Chapter 2 describes the results of the assessment of the hand sensibility in healthy young children using instruments validated for adults. Testing in healthy children enabled us to identify which test tools are suitable, to adapt them as necessary, and to compare the dominant and nondominant sides.
After this standard had been set, the study reported on in **Chapter 3** assessed the sensibility of the hand in children with NBPP involving the upper nerves C5 and C6, and correlated the results with dexterity. **Chapter 4** describes an in-depth analysis of tactile hand sensibility, to correctly localize a sensory stimulus on the fingers. **Chapter 5** focusses on subjective experience of both the children and their parents regarding the perception of touching their hands.
In the study reported on in **Chapter 6**, we assessed the grip force of children with a C5 - C6 NBPP. Such an upper lesion should only affect shoulder muscles and elbow flexor muscles. Our clinical observation was, however, that children with an upper NBPP employed their hand less often in daily life. This is why we were interested in grip force and dexterity of the hand (as assessed in Chapter 3).

The consequences of NBPP regarding hand function cannot be explained solely by action mechanisms involving the peripheral nerves; the development of cortical programs must be involved as well.

Chapters 7 and 8 discuss other aspects of cortical development. In the study reported on in **Chapter 7**, we assessed whether children with NBPP have a higher incidence of central developmental disability compared to the general population, and related central delay to fidgety movements.

Chapter 8 concerns one gross motor milestone in children with NBPP, namely the age of walking independently, which we compared with a control group from the literature.

Chapter 9 summarizes all aspects, followed by a general discussion, and suggestions for further research. **Chapter 10** comprises a summary of this thesis in Dutch.

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CHAPTER 2

Hand Sensibility in Healthy Young Children

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Pediatric Neurology
2018 Sep; 86:52-56

ABSTRACT

Objective

The aims of the study were (1) to assess hand sensibility in healthy young children using instruments validated for adults; (2) to identify which test tools are suitable; and (3) to compare the dominant and non-dominant sides.

Patients and Methods

Twenty-five healthy children aged 7-11 years (mean 9.5 years) were investigated. Sensibility was assessed with the Semmes-Weinstein Monofilament test (SW), two-point discrimination (2PD), localization test (LOC) and stereognosis object recognition (SOR). Sensory stimuli were administered to fingertips.

Results

The thinnest SW filament (D; 2.83mm) was felt at 94% of examined points. A 2PD at the smallest distance of 2 mm was found in the thumb in 84% of children and in the index finger in 94%. Only 60% felt this distance in the fifth digit. The difference between little finger and index finger was statistically significant ($p = 0.001$). Near-maximum value on the LOC was scored in both hands. All children had a 100% score for both hands in the SOR.

Conclusions

Most children can detect touch in the digits at low pressure. The majority are able to discern two points 2 mm apart in the first and second digits, but significantly less so in the fifth digit. Children are well able to localize on which side of a fingertip pressure is applied. Objects are recognized very well, and occasionally too quickly to record. There appear to be no differences between the dominant and non-dominant hands in either test. Adjustment of sensory test protocols routinely used in adults is necessary to optimize hand sensation testing in children, in view of the detection limits.

INTRODUCTION

Hand sensation provides crucial feedback information to the central nervous system, regarding aspects like pressure to adjust grip in specific tasks, or pain to warn against danger. Hand function is affected when sensory feedback is disturbed due to disorders of the central or peripheral nervous system. The most serious situation is that of a 'blind hand', where visual control is needed to compensate for the absence of sufficient sensory input.[1]

It is not clear why, so far, little effort has been made to objectify hand sensation in children, whereas it is known that sensory deficits have a negative impact on their functioning as adults. Moreover, normal afferent input is of eminent importance for the correct development of the brain, and disturbances may lead to 'developmental apraxia'.[2] This lack of instruments hampers objective evaluation of the sensory status of the hand, frustrating proper interpretation of its function. In addition, it means that efficacy of treatment is difficult to evaluate.
It was recently published only about 10% of all axons in a mixed peripheral nerve are efferent (motor) fibers and that the majority of fibers are afferent (sensory).[3] These afferent fibers are seldom evaluated as outcome parameter after recovery of nerve lesions, resulting either spontaneous recovery or from nerve reconstruction. Especially in NBPP, the literature on sensory outcome is scarce, compared to results of motor outcome.

Tests to obtain objective information regarding specific qualities of hand sensation in adults have been validated.[4] These tests are also used in children, but it is not well established whether these tests provide equally useful information and, therefore, whether they should be applied in children. The need for a reliable test method to evaluate hand sensation in children has become relevant in view of developments in peripheral nerve reconstructive surgery, especially for severe neonatal brachial plexus palsy (NBPP), peripheral nerve lesions and cerebral palsy. Sensory testing in adults with NBPP who were conservatively treated showed abnormalities in the outcomes of the Semmes-Weinstein monofilament test, two-point discrimination, object recognition and a locognosia test.[5] Children with severe NBPP are surgically treated and the focus of outcome evaluations so far has been on motor function recovery. Much less emphasis has been put on sensory function recovery. It remains to be established how sensation affects functional outcome and can be optimized.

There is therefore a need for objective evaluation outcome measures to compare results of specific surgical repairs and hand therapy support, in order to optimize treatment strategies. The current literature does not provide clear information on ways to evaluate sensory function in children and the best tests to use.

Monofilaments exerting different pressures have been used before to detect touch in children. One study of 43 children aged between 6 and 12 years applied monofilaments to the shoulder (C5), index finger (C6), thigh (L3) and external malleolus (S1). The results were compared with data from the literature regarding adults. The analysis showed that children and adults obtained similar sensory scores. Sex, age and laterality did not have a significant effect on the findings. The index finger proved to be the most sensitive site to test.[6]

Two-point discrimination (2PD) can be used in children aged 7 years and older; its reliability is decreased in younger children.[7] The tip of the index finger was found to be more sensitive in children, compared with the thenar eminence of the hand and the external malleolus of the foot.[8]

The primary aim of the current study was to establish values for hand sensation in healthy young children using test methods validated for adults. The secondary aim was to identify which assessment tool might be suitable to diagnose diminished sensibility in clinical practice. The third and final aim was to assess whether differences in sensibility exist between the dominant and non-dominant hands in healthy children.

PATIENTS AND METHODS

Participants

Twenty-five healthy children aged 7-11 years (mean 9.5 years), without any history of disease or trauma potentially effecting sensation or cognition, participated in this study. The children were recruited at the Montessori school in Voorburg, The Netherlands. The study was announced on the school's message board. The school provides regular Dutch standard level education. The minimum age was set at 7 years, as from this age up children are able to take part in threshold testing.[7] Additionally, this is the age at which blind or visually impaired

children start training for tactile writing systems (like Braille), and hand dominance becomes clear.[9]

The study protocol was approved by the Medical Ethics Committee of Leiden University Medical Center (ABR nr. 48977) and informed consent was given by the parents.

Sensory Testing

The sensibility of both hands was assessed using four different methods: (1) Semmes-Weinstein Monofilament test (SW); (2) two-point discrimination (2PD); (3) localization test (LT) and (4) stereognosis object recognition (SOR).

Modifications were made to suit the smaller size of the children's hands and their ability to understand and remain concentrated. These modifications were tested first in a pilot involving a number of healthy children, before the actual study was performed. A screen was positioned such that it prevented the children from seeing the hand being tested. Sensory stimuli were given on the palmar side of the fingertips. The hand was categorized as dominant if it was their writing hand. Both hands were studied with all test methods, in the same order. Each method was used first on the dominant hand. Each test started with a demonstration and a short practice period.

Semmes-Weinstein Monofilament Test (SW)

Monofilaments of three different diameters (D 2.83 mm; F 3.61 mm; J 4.31 mm) were applied two times, with a 1.5 second interval, for each fingertip, going from the thumb to the little finger. Each filament was vertically positioned on the fingertip and pressed until it bended, for 1 second. Thus, the pressure applied to the fingertip corresponded to the diameter of the filament.[10] The thinnest filament, D, was used first, followed by the filaments with a larger diameter. The SW test was scored positive if at least one of the two stimuli per finger for each monofilament was felt. Once a filament had been felt, thicker filaments were no longer applied.

Two-point discrimination (2PD)

The McKinnon-Dellon Disk-Criminator® was used for 2PD testing. The Disk-Criminator® consists of a plastic frame with on its outer rim pairs of metal dots and one single dot. The distances between the paired dots range between 2 mm and 6 mm. The weight of the instrument was placed on the fingertip with the two points in the longitudinal direction of

the finger in order to ensure equal pressure each time. The tips of the thumb, index finger and small finger were statically tested in both hands. The children were asked to indicate whether they felt one dot or two dots as varying dot distances were applied in both descending order (from 6 mm to 2 mm) and ascending order (2 mm to 6 mm) as described previously.[11] The order varied for each finger. A score was considered positive if the child correctly discriminated two points five consecutive times. The smallest distance between the dots that could be discriminated was documented as the best score.

Localization test (LT)

The test protocol described by C. Jerosch-Herold et al. was used.[12] The thickest SW monofilament was pressed for 2 seconds on the radial or ulnar half of the fingertip. The children were asked to indicate in which part of the hand they felt the pressure. A drawing of the hand with numbered regions of the fingertips was shown to them during the test to help them describe the localization. (Figure 1)

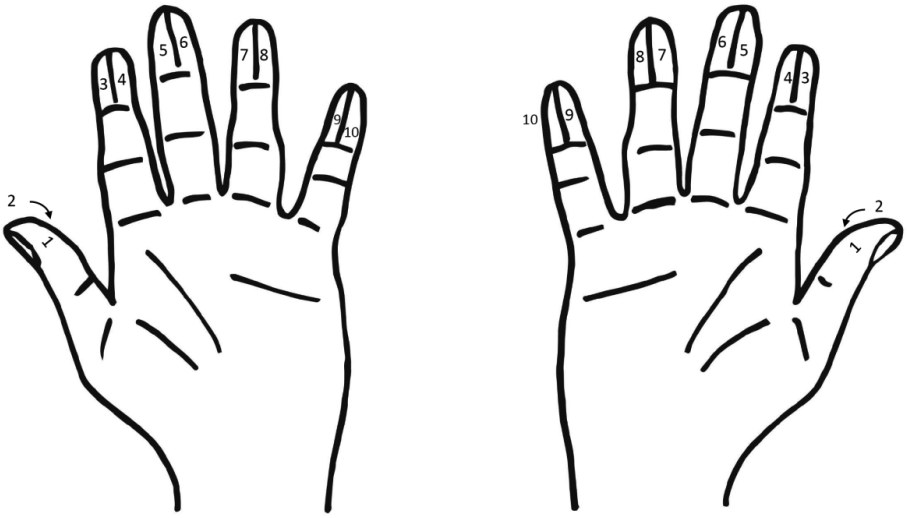

Figure 1 Localization areas on fingers

Each region that was correctly identified scored two points. One point was scored if the pressure was localized either in the correct half but on an adjacent finger, or in the wrong half of the correct finger. The individual scores were added to form a sum score. Thus, the maximum score that could be attained per hand was 40. For each finger, both halves were scored and a maximum of two points was given; two test rounds were performed (5x2x2x2).

Stereognosis: object recognition (SOR)

Both hands were put behind a screen.[13] Six small objects (eraser, small paper ball, Lego brick, bead, coin, button) were successively placed between the fingertips, in alternating sequence, starting with the dominant hand. The child had to identify the object. A similar series of objects remained in sight in front of the screen to facilitate recognition.

Statistical analysis

Paired t-tests for continuous variables and McNemar tests for categorical/dichotomous variables were employed. Data were analyzed with SPSS Statistics for Windows, version 22 (IBM Corporation, Armonk, NY, USA).

RESULTS

A total of 50 hands were analyzed. One of the 25 children was left-handed.

After the analysis of the first 25 children, an interim-analysis showed that the findings in these children were very similar. For this reason, recruitment of a larger group was judged not necessary.

The standard deviations of the results in all three tests were relatively small, therefore, we concluded that testing more children to obtain a larger group size would not lead to other conclusions. (Table 1).

Table 1 Comparison of dominant versus non-dominant hand in three tests (25 pairs).

	Mean score (St.Dev)		Paired sample t-test		
Test	**Dominant hand**	**Non-dominant hand**	**Difference of means**	**Confidence Interval (95%)**	**Significance (2-tailed)**
SW	4.56(1.26)	4.68(1.14)	-0.12(0.12)	(-0.37 - 0.13)	0.33
2PD	2.20(0.27)	2.23(0.34)	-0.03(0.06)	(-0.15 - 0.10)	0.66
LT	36.20(3.57)	37.24(3.60)	-1.04(0.55)	(-2.18 - 0.10)	0.07

Legend Table 1

Mean scores on SW, 2PD and localization tests, for each hand, dominant versus non-dominant, and results of the paired-sample t-test.

Semmes-Weinstein Monofilament

The thinnest filament (D 2.83) was felt 235 times (94%) and the second thinnest (F3.61) was felt the remaining 15 times (6%). The thickest filament (J.4.31) thus did not need to be used for testing. For statistical analysis, a score of 1 was noted when the thinnest filament (D 2.83) was felt, and a score of 0 when the second thinnest filament (F3.61) was felt. We compared pairs of fingers, grouped by hand dominance, to assess whether one of the fingers was more sensitive than the other. In 88-92% of cases, the same (thinnest) monofilament was felt in both fingers. (Table 2) The average sum score for all fingers was 4.56 for the dominant hand and 4.68 for the non-dominant hand. (Table 1) We found no significant difference between the fingers of either the dominant or the non-dominant hand.

Table 2 Results of SW testing.

Side		DD	FF	FD/DF	p*
	dig 1 vs dig 5	88%	4%	8%	0.5
dominant	dig 1 vs dig 2	88%	8%	4%	1.0
	dig 5 vs dig 2	92%	4%	4%	1.0
	dig 1 vs dig 5	92%	4%	4%	1.0
non-dominant	dig 1 vs dig 2	92%	8%	0%	1.0
	dig 5 vs dig 2	92%	4%	4%	1.0

Legend Table 2

DD: both fingers felt the D (thinner) filament;
FF: both fingers felt the F (thicker) filament;
FD/DF: combination of thick/thin or thin/thick;
*: p-value from Mc.Nemar test.

Two Point Discrimination

The average 2PD for thumb, index finger and little finger was 2.20 mm for the dominant hand and 2.23 mm for the non-dominant hand. On the thumb (digit 1), the children were able to detect two points with a 2 mm distance in 84% of cases. For the index finger this was 94%, but for the small finger only 60%. The difference between little finger and either the thumb or the index finger was statistically significant. (Table 3) It was found that 5 and 6 mm testing was useless, and only took up precious time.

Table 3 Comparison of two-point-discrimination in pairs.

Side		Mean 2PD* (mm)	p**
dominant	dig 1 vs dig 5	-0.160	0.161
	dig 2 vs dig 5	-0.320	0.003
non-dominant	dig 1 vs dig 5	-0.360	0.001
	dig 2 vs dig 5	-0.400	0.001

Legend Table 3

* mean difference between pairs;

** p-value from 2-tailed paired-samples t-test.

Localization test

An almost maximum score was achieved in both hands. The average for the right hand was 36.2 and for the left 37.2. Scores did not differ significantly between the fingers. (Table 4)

Table 4 Localization test, comparison between different pairs of fingers.

Side		Mean*	p**
dominant	dig 1 vs dig 5	-0.36	0.19
	dig 1 vs dig 2	0.08	0.80
	dig 2 vs dig 5	-0.44	0.16
non-dominant	dig 1 vs dig 5	-0.12	0.50
	dig 1 vs dig 2	0.00	1.00
	dig 2 vs dig 5	-0.12	0.45

Legend Table 4

* mean difference in score between pairs;

** p-value from 2-tailed paired-samples t-test.

Stereognosis test

All children had 100% scores for both hands. The objects were recognized very rapidly with each hand, making it impossible to measure the time taken to recognize a single object. The time taken to identify all objects in both hands was 64 seconds.

DISCUSSION

The primary aim of the current study was to determine normal values of hand sensation in healthy young children by applying sensibility test methods validated for adults. We found that only light pressure with an SW filament (D; 2.83mm) was needed for the stimulus to be detected in 94% of the examined points on the fingertips. The best ability to distinguish two adjacent points was found for the index finger, closely followed by the thumb, but it was significantly less in the little finger. Both in the dominant and non-dominant hands, localization scores were close to the maximum. Scores for object recognition were 100% for both the dominant and non-dominant hands. Overall, we observed no significant difference between the dominant and non-dominant hands in any of the four tests.

Previous studies have found that the index finger (C6) is the most sensitive site on the human body to detect touch, more so than the shoulder (C5), upper leg (L3) or lateral ankle (S1).[4] Obviously, this ability is useful since objects, textures and pinch are felt predominantly with the thumb and index finger.

Menier found a mean 2PD of 2.2 mm for the index finger in children aged between 6 and 13 years, which is similar to our results.[8] A previous study found that the 2PD threshold was lower in 5-year-old children than in children aged 11.[14] We did not include such very young children in our study, but more recent studies did not confirm this finding.[6,8] Minor differences between those aged 6 and 13 years have been reported, but without statistical significance. One explanation might be the small sample size (n = 11) in one of these studies.[8] The sample size in our own investigation was too small to enable a definite conclusion on a relationship between age and 2PD. A decrease in threshold values has been shown to occur in adults with increasing age from 20 years up in a large population of 427 subjects.[11]

The secondary aim of our study was to identify which test tools might be suitable to diagnose a diminished sensibility among children in clinical practice. The thinnest SW filaments (D 2.83) and a 2PD distance of 2 mm on the index finger were detected by the majority of the children. We conclude that these two tests should actually be made more sensitive for the pediatric population. This would require including a monofilament with a

diameter smaller than 2.83 mm, and a 2PD test with a distance between two dots of less than 2 mm. The value of the current tests for children with a peripheral nerve lesion, for instance NBPP needs to be assessed. The scores found in the present study may imply that it is important to use a more precise measurement tool allowing the exact measurable distance in mm to be read. Simply using a bent paper clip is insufficient.

The little finger appeared to be less sensitive than the thumb and index finger. This might indicate that the density of sensory receptors in the tip of the index finger is higher than in the other fingertips. This is relevant if superior trunk or median nerve lesions have to be identified by comparing sensation with that of an area innervated by an intact inferior trunk or ulnar nerve.

We observed that the localization test required a lot of concentration of the children. Some of the youngest children had to be actively encouraged to complete the test. The reason might be the large number of points that were examined. Interestingly, many of the children asked if they were allowed to quickly move their fingers in between stimuli. They commented that they could feel better when they moved their digits. It appears that active finger movement is required for optimal conditions to localize a stimulus.

The stereognosis test as we performed it proved to be of no value in assessing sensibility. The objects were too easily recognized. Children were able to name the object immediately after it was put between their fingertips. It was not even necessary for them to flex their fingers around the object. As a result, the time recording mainly recorded how quick the examiner was at putting the objects on the children's fingertips. In view of these results, we feel that although this test might be valuable in showing gross pathology, it will not help to discriminate subtle sensory differences.

The third and final aim was to assess whether differences in sensibility exist between the dominant and non-dominant hands. We did not find any significant differences with the tests we applied, which is important if either the dominant or non-dominant hand is involved in a condition affecting sensation.

Validated measurement tools for sensibility in children are lacking. We adapted and tested a set of four methods routinely used in adults. Future research should determine the need to develop specific tests for children, taking into account children's understanding, concentration span and the smaller size of their fingers.

CONCLUSIONS

Testing hand sensation in children by applying the tests routinely used in adults provides useful information, but has limitations as well. Optimizing the detection of diminished sensation requires adaptation by compensating for intrinsic differences in sensation and concentration span related to the young age.

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CHAPTER 3

Sensibility of the hand in children with conservatively or surgically treated upper neonatal brachial plexus palsy

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Pediatric Neurology
2018 Sep; 86:57-62

ABSTRACT

Objective

The aim of this study was to assess the sensibility of the hand in children with a neonatal brachial plexus palsy (NBPP) involving the upper nerves C5 and C6, and to correlate the results with dexterity.

Patients and Method

Fifty children with NBPP (mean age 9.8 y) and 25 healthy controls (mean age 9.6 y) were investigated. In the NBPP group, nerve surgery had been performed in 30 children and 20 children had been treated conservatively. Sensibility was assessed with two-point discrimination (2PD) and Semmes-Weinstein (SW) monofilaments. Dexterity was evaluated with a single item from the Movement Assessment Battery for Children-2. We compared the affected side of the NBPP group with the non-dominant hand of the control group.

Results

The sensibility in the first and second fingers was significantly lower in the NBPP group than in the control group for both the 2PD ($p = 0.005$ and $p = 0.014$ respectively) and the SW monofilament test ($p<0.001$). Dexterity was significantly lower in the NBPP group than in controls, corrected for age ($p = 0.023$). There was a significant difference toward decreasing hand function with decreasing sensibility according to the SW test for the thumb (Jonckheere-Terpstra non-parametric trend test, $p = 0.036$)

Conclusions

The sensibility of the thumb and index finger in children with an upper plexus lesion (either surgically or conservatively treated) is diminished. The decreased sensibility has a negative impact on hand function. Appreciation of diminished hand function in patients with NBPP involving C5-C6 is important to optimize treatment.

INTRODUCTION

The neonatal brachial plexus palsy (NBPP) is a traction injury that occurs during birth. The most common type is a lesion of the two upper nerves (C5 and C6) of the brachial plexus. In more severe cases, C7, C8 and T1 can be involved in the lesion as well.[1] Studies have observed that a certain clumsiness of the hand exists in patients with NBPP with a C5-C6 lesion.[2] This is remarkable, as the motor function of the hand is innervated by the lower nerves of the brachial plexus, mostly C8 and T1, which are intact in C5-C6 lesions. One explanation for this phenomenon may be that the diminished hand function is the result of a reduced sensibility in the hand. The sensory innervation area of spinal nerve C6 consists of the lateral ventral lower arm, the radial side of the palm of the hand, and the palmar side of the thumb and index finger. Sensibility in these areas has been found to be reduced in adults with NBPP.[3] Reduced sensory feedback of these two fingers to the brain may have a negative influence on dexterity. Reports on sensibility of the hand in patients with NBPP are limited, and conflicting.[4] Some papers reported normal sensibility, while others reported diminished sensibility.[5, 6, 7]

The current study was performed to assess sensibility in young children with NBPP, with two goals: (1) to see whether we could detect a decreased sensibility and (2) to correlate sensibility with hand function in children with NBPP involving a C5-C6 lesion. We investigated a cohort of children with NBPP that included both conservatively treated children and children treated with nerve surgery in early infancy, and compared their results with those of controls.

PATIENT AND METHODS

The study design was a cross-sectional investigation of patients with NBPP. Fifty children with an upper NBPP and 25 healthy children, aged between 7 and 12 years, were recruited for the study. The children with NBPP were patients who were examined during regular follow-up at our tertiary referral clinic (Nerve Centre of the Leiden University Medical Center, The Netherlands). We diagnosed the children originally with NBPP on obstetrical history, physical examination and additionally with EMG when first presentation was between the age of 4 and 6 weeks.

In 30 children (60%), nerve surgery had been performed in early infancy, while 20 had been treated conservatively. In all children, the clinical diagnosis of NBPP was made with involvement of only the C5 and C6 roots. Children who were conservatively treated, showed recovery of elbow flexion with active biceps muscle at 3 to-6 months of age, all had active elbow extension with active triceps muscle and active wrist extension at least against resistance. All children had normal hand function, as judged by neurological examination. The indication for nerve surgery has been extensively described elsewhere.[1] Children who were treated with nerve surgery, underwent CT myelography or MRI to assess root avulsion injury. During the operation, surgical inspection and direct nerve stimulation were performed to assess the diagnosis. The most commonly performed surgical procedure to restore C6 function was grafting from C6 to the anterior division of the superior trunk. Five infants had undergone a transfer of the pectoral nerve to the musculocutaneous nerve, in one patient just accessory tot suprascapular nerve transfer had been performed and one patient had undergone neurolysis. In these seven children, the axonal pathway from C6 to the anterior division had been left intact; this sub-group was compared to the surgical sub-group in which nerve reconstruction had taken place.

The control group was recruited at the Montessori school at Voorburg, the Netherlands, by announcing the study on the school's message board. All children who participated had a normal cognitive function and attended regular schools.[8]

PHYSICAL EXAMINATION

All assessments in both groups were done by the same physical therapist (SB) to avoid confounders. Before starting with the sensibility tests as described in this paper, we did a try-out of the different test methods on a small group of children, which led to adaptations of the test methodology. The tester had more than 37 years of experience with physical assessment and treatment of children in all age groups.

The sensibility of the hands was assessed using two methods. (1) Two-point discrimination (2PD): the minimal distance between two contact points that children recognized as two separate stimuli was investigated using the Mc Kinnon-Dellon Disk-criminator®. We tested the palmar side of the thumb, the index finger and the little finger. (2) The Semmes-Weinstein Monofilament test (SW): nylon filaments of different diameters (D 2.83 mm; F

3.61 mm; J 4.31 mm; K 4.56 mm) were tested, applied twice to each fingertip. The test started with the thinnest filament. For each finger, we noted the number of stimuli with the thinnest filament that were felt, after which thicker filaments were not applied anymore. During both tests, the sensory stimuli were applied to the volar side of the fingertip, while a screen prevented the children from seeing their own hand. For children who had difficulty to maintain presentation of the palmar surface as a result of fatigue or supination weakness, the tester adjusted her position to ensure that the filaments were put perpendicular to the fingertips.

Dexterity was evaluated with a single item from the Movement Assessment Battery for Children-2 (MABC-2), an internationally accepted and validated test for fine motor skills.[9] For children aged 7, 8, 9 or 10, the specific task to perform was to thread a wire through holes in a board. Children aged 11 or 12 years were asked to make a triangle with bolts and nuts. As these specific tasks are bimanual, both the dominant and the assisting hand are tested. Children were not allowed to put either the wire or the triangle on the table, but were required to keep them in both hands. The time they needed to finish the task was noted and converted to a standard score. This score is known to be age-dependent.[9]

In many children with NBPP, the unaffected hand serves as the dominant hand, as hand dominance may have shifted as a result of their lesion. To exclude a potential confounding effect of hand dominance on sensation, we analyzed children whose dominant hand was the unaffected side. We compared the affected side of the NBPP group with the non-dominant hand of the control group. We defined the dominant hand as the hand in which a child holds a pencil to write. A hand preference shift was assumed to have occurred if a child with a right-sided lesion had left-hand dominance.

The study protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center (ABR number 48977) and informed consent was given by the parents.

STATISTICAL ANALYSIS

For continuous outcome variables, we used analysis of variance (one-way ANOVA). Categorical outcome variables were compared between groups using chi-squared tests (exact tests if the expected counts were small). Where appropriate, a Mann-Whitney test

was used instead of a t-test. The Jonckheere-Terpstra test – a rank-based non-parametric trend test similar to the Kruskal-Wallis test – was applied where indicated.[10] The error level was set at p <.0.05. Data were analyzed with SPSS Statistics for Windows, version 22 (IBM Corp.Armonk, NY).

RESULTS

Patient details are presented in Table 1.

Table 1 Patient characteristics

Demographic variables	NBPP	Controls
Total number	50	25
Nerve surgery	30	N/A
Conservatively treated	20	N/A
Mean age (years)	9.8 (SD 1.89)	9.5 (SD 1.46)
Boys/girls	22/28	8/17
Affected side left/right	26/24	N/A

Legend Table 1
SD: standard deviation.

The analysis of the affected non-dominant hand concerned 28/30 surgically treated children and 14/20 conservatively treated children. (Table 2) In the surgically treated group, an assumed hand preference shift was found in 13/15 children, compared to 3/9 children in the conservative group. This difference is statistically significant (p = 0.007).

Table 2 Hand dominance versus affected side

Group				Dominant hand	
				Left	**Right**
Controls				1	24
NBPP	Conservative	Affected side	left	-	11
			right	3#	6*
	Nerve surgery	Affected side	left	-	15
			right	13#	2*

Legend Table 2

Controls: n = 25; NBPP: infants with an NBPP lesion (n = 50), 20 of whom had been treated conservatively and 30 had undergone nerve surgery. A hand preference shift was assumed to have occurred if a child with a right-sided lesion had left-hand dominance.

* Not included in the analysis; # assumed preference shift.

Sensibility with the 2PD

The mean 2PD for the thumb in the control group was 2.12 mm, compared with 2.69 mm in the NBPP group. Similar differences were found for the index finger. The analysis of the mean 2PD showed significant differences in both the thumb and index finger between the affected hand in children with NBPP and the non-dominant hand in the control group. No statistically significant differences were found when comparing the little finger (Table 3 – top). When we compared the affected side with the unaffected side in all infants with NBPP, statistical differences were found for the thumb and index finger, but not for the little finger (Table 3 – bottom). A comparison of the affected and unaffected sides in the NBPP group showed no differences between nerve surgery and conservative therapy. There was no statistical difference within the surgery group, comparing nerve reconstruction with nerve transfer or neurolysis.

Table 3 Mean 2PD in dig 1,2,5

Group	Dig 1 (SD)	Dig 2 (SD)	Dig 5 (SD)
Controls (n = 25)	2.12 (0.33)	2.08 (0.28)	2.48 (0.59)
NBPP (n = 42)	2.69 (0.95)	2.45 (0.71)	2.69 (0.68)
Conservative (n = 14)	2.64 (1.22)	2.43 (0.65)	2.93 (0.83)
Nerve surgery (n = 28)	2.71 (0.81)	2.46 (0.74)	2.57 (0.57)
NBPP – affected side (n = 50)	2.70 (0.88)	2.42 (0.67)	2.70 (0.68)
NBPP – unaffected side (n = 50)	2.28 (0.50)	2.16 (0.37)	2.64 (0.66)

Legend Table 3

The mean 2PD is shown in mm, including Standard Deviation (SD).

Top part of table:

Comparison of the non-dominant side in controls (n = 25) versus affected side in NBPP (n = 42). Differences were calculated as follows:

Digit 1: control vs NBPP p = 0.005; control vs conservative p = 0.051, control vs surgery p = 0.008, conservative vs surgery p = 0.782.

Digit 2: control vs NBPP p = 0.014; control vs conservative p = 0.081; control vs surgery p = 0.021; conservative vs surgery p = 0.854.

Digit 5: No statistically significant differences.

Bottom part of table:

Comparison of the affected and unaffected sides in NBPP. Affected versus unaffected, paired T test: Digit 1: p = 0.001; Digit 2: p = 0.004; Digit 5: p = 0.537.

Sensibility with SW

In the control group, 92% of the children were able to feel the thinnest SW filament (D) on their thumb, compared to 43% in the NBPP group (Table 4 – top). This difference was statistically significant whether we compared the controls with either the total NBPP group ($p<0.001$), the conservatively treated group ($p<0.001$) or the surgically treated group ($p = 0.001$). There was no difference between the surgically treated group and the conservatively treated group ($p = 0.270$ chi-square test). We found similar results for the index finger (data not shown), whereas for digits 3, 4 and 5 we found no statistically significant difference in sensibility. A comparison of the affected and unaffected hands showed a statistically significant difference in the proportion of patients who felt the D filament: 22 versus 42 children ($p<0.001$, McNemar Test), for both the thumb (Table 4 – bottom) and the index

finger (data not shown). There were no statistical differences for digits 3, 4 and 5. There were no statistical differences for the surgical subgroups.

Table 4 Thinnest SW filament that was felt in the thumb.

	Monofilament			
	D	**F**	**J**	**K**
Group	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Controls (n = 25)	23 (92)	2 (8)	0 (0)	0 (0)
NBPP (n = 42)	18 (43)	18 (43)	5 (12)	1 (2)
Conservative (n = 14)	5 (36)	5 (36)	3 (21)	1 (7)
Nerve surgery (n = 28)	13 (46)	13 (46)	2 (7)	0 (0)
NBPP – affected side (n = 50)	22 (44)	22 (44)	5 (10)	1 (2)
NBPP – unaffected side (n = 50)	42 (84)	7 (14)	1 (2)	0 (0)

Legend Table 4

Top part of table:

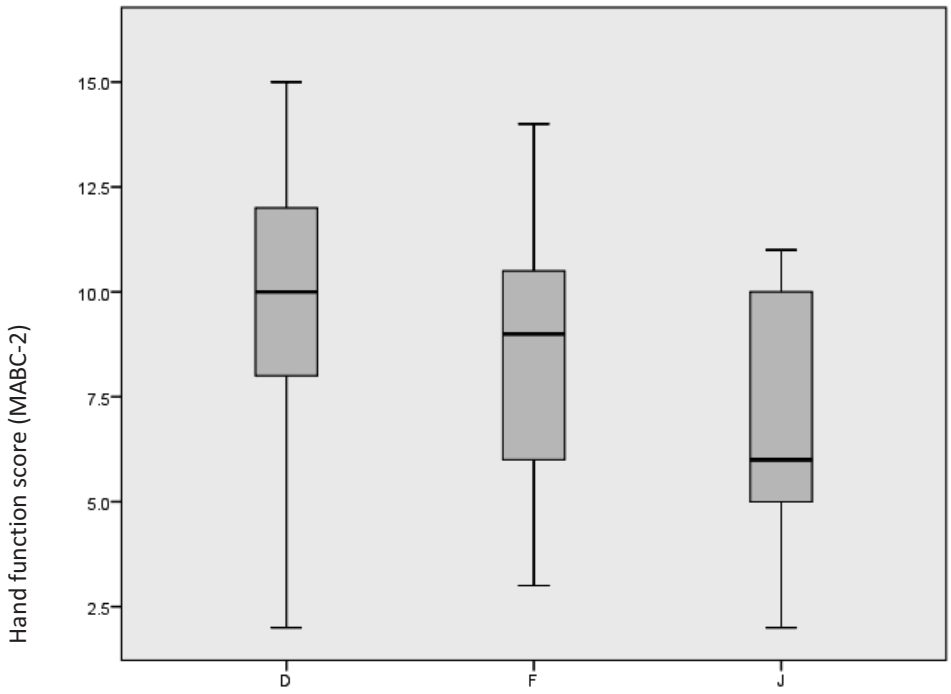
Comparison of the non-dominant unaffected side in controls versus NBPP. The thinnest filament is D (2.83 mm), with increasing thickness in the F (3.61 mm), J (4.31 mm) and K (4.56 mm) filaments. Statistically significant differences were found for controls (n = 25) vs NBPP (n = 42) $p<0.001$; controls (n = 25) vs conservative (n = 14) $p<0.001$; controls (n = 25) vs surgery (n = 28) $p = 0.001$. Difference between conservative (n = 14) and surgery (n = 28) was not significant: $p = 0.270$ (chi-square test)

Bottom part of table:

Comparison of the affected (n = 50) versus unaffected (n = 50) side in NBPP. Difference comparing pairs of those who felt SW filament D and those who did not: $p<0.001$ (McNemar Test).

Hand function according to Movement ABC-2

The children with an upper NBPP had decreased hand function compared with the control group, expressed as the test score (corrected for age) for the single item of the MABC-2 we used ($p = 0.023$, Mann-Whitney test). The median score in the control group was 11.0 (corresponding to a time of 20-21 seconds in a 9-year-old) and that in the NBPP group was 8.0 (26 seconds for the same age). There was a significant difference toward decreasing hand function with increasing SW filament diameter for the thumb ($p = 0.036$). (Figure 1) There was no significant difference for SW digit 2 ($p = 3.33$) or for 2PD ($p = 0.829$).



Thinnest SW filament that was felt in the thumb.

Figure 1 Correlation between SW digit 1 and hand function

Legend Figure 1

Hand function score: standardized value derived from the time it took to complete a single item from the MABC-2. D, F, J: Nylon filaments of different diameters: D = 2.83 mm.; F = 3.61 mm.; J = 4.31 mm. Plot shows median value, 25-75% range (box), 95% range. There was a significant difference toward decreasing hand function with increasing SW filament diameter for the thumb (Jonckheere-Terpstra non-parametric trend test: p = 0.036)

DISCUSSION

In the present study, we found reduced sensibility of the thumb and the index finger in a cohort of 50 children with NBPP with an upper brachial plexus lesion, who had been treated either conservatively or surgically. Scores for the thumb on both the 2PD and SW tests were found to be reduced when comparing infants with NBPP with healthy controls, and also when comparing the affected and unaffected sides in infants with NBPP. Hand function also appeared to be diminished in the NBPP group, based on a single item of the Movement

ABC-2. Together, these findings suggest that decreased sensibility may have a negative impact on hand function.

Our findings contradict previous reports stating that sensory recovery in children with NBPP is generally good,[6, 7, 5] and support others which also found a diminished sensibility.[11, 12, 2] These conflicting data may have resulted from differences in sensory testing methods. Our results support previous results from our group showing that sensibility was affected in adults whose NBPP was conservatively treated.[3]

Decreased hand sensation may contribute to decreased hand function, as normal sensory input to the somatosensory cortex in early life is essential for the development of motor skills.[2, 13, 14] Additionally, the threshold for afferent input to the sensory cortex depends on stored memory and experience, which may be altered in children with NBPP. Another factor that might be related to the clumsiness of the hand may be a reduced proprioceptive sensation. This has been found in the elbow joint,[12] but has not been studied for the hand. Diminished sensibility in one hand may require additional visual control during two-handed activities. Motor control of the thumb and index finger already requires more visual guidance in complex tasks, which may become tiring.[15] The need for additional visual control to properly perform a task should be explained to the caretakers of children with NBPP, and incorporated in physical therapy.

An alternative explanation is that the development of hand function in NBPP infants is impaired due to the diminished range of motion of their shoulder and elbow. Many children are particularly limited in external rotation and supination.[16] This suboptimal positioning of the hand may lead to decreased development of fine motor skills. During the test protocol we choose the described items of the MABC (thread a wire / compose a triangle), as these tests concern a specific bimanual test for which the non-affected hand can adapt to a suboptimal position of the affected hand. Alternative options (e.g. a pegboard task) was considered, but this test requires normal active external rotation, which is usually limited in an upper brachial plexus lesion.

Another factor that influences assessment of motor function is the normal neurological development. In this cohort of children, we did not formally assess possible developmental delays, but in a previous paper we found that developmental delays, including cerebral

palsy, developmental coordination disorder , mental retardation, but also behavioral problems, such as attention deficit hyperactivity disorder, may be present more often in children with NBPP than in the normal population.[17]
Finally, the observed clumsiness could potentially be explained by the fact that lesions that are supposedly limited to the upper trunk may involve subclinical damage to the middle and lower trunks as well. In fact, some authors found electromyographic (EMG) abnormalities in hand muscles of children with normal neurological examination of the hand.[14] We did not examine the intrinsic hand muscles of our children with EMG, and can therefore not exclude this possibility. However, our findings in the sensory examination do not seem to support additional damage apart from C5 and C6. The results of the 2PD test showed a significant difference with healthy controls for the thumb and index finger, but not for the little finger. The same pattern was found in the SW test: there were differences for the first and second fingers, but not for the third to fifth fingers. These findings confirm the anatomical distribution of dermatomes for the thumb and index finger, which are innervated by C6, as well as the involvement of C6 in upper trunk NBPP. The third to fifth fingers were not affected in our patients with NBPP, indicating only C5 and C6 involvement.

A strong point of our study is that we compared the sensibility of infants with NBPP with the sensibility of healthy controls, which has not been done previously. We were therefore able to make a direct correlation with hand function. In order to facilitate the interpretation of our results in the context of those reported in the literature, we also performed a paired comparison of the affected and unaffected sides, as is usually done.

We compared the affected NBPP hand with the non-dominant hand of controls. The reason for this is our assumption that sensation in the unaffected side of the children with NBPP may be better than normal, as a result of more intensive use. The use of the unaffected side as a control may therefore yield differences which cannot be explained only by reduced sensation in the affected hand. A study in our group of healthy children found no difference in sensation between the dominant and non-dominant hands.[8]

A limitation of our study is that no validated and generally accepted measurement tool for sensibility of the hand is available for children. We used existing measurement tools to develop a method that is applicable in children, by adapting this set of methods or tools to

the intended population, and making them suitable for use in practice, in view of the smaller size of children's fingers, their level of understanding and their concentration span. These modifications were tested in a pilot study among healthy children, which led to further adaptations. During the pilot, we found that children below the age of 7 years could not manage sufficient concentration to complete longer sensibility tests. We hope that our protocol may be of value to others in developing a universally accepted way to examine sensibility in children.

In the present analysis, we assessed the non-dominant hand of the control group. In many patients with NBPP, the dominant hand is the unaffected side. A previous paper showed that only 17% of children with a right-sided NBPP were reported to be right-handed.[18] In the general population, it is expected that 90% of children has a right hand preference, so it was hypothesized that in the majority of children with a right sided lesion their hand preference had shifted to the left side. In the present, albeit smaller, series, we found that the left hand was dominant in two-thirds of the patients with right-sided lesions, and hand dominance may have shifted in many of these children. We found a difference between conservatively treated children and those who had undergone nerve surgery. The surgically treated children showed a 'hand preference shift' in 13/15 cases, compared to 3/9 in the conservatively treated group. This finding may reflect the more severe nerve lesions in the surgically treated group as compared to the conservatively treated ones. The groups were too small to compare different surgical strategies, such as proximal reconstruction by nerve grafting and distal nerve transfers. In the latter treatment option, there is no reconstruction of sensory axons. The current study cannot answer the question which of the two is preferred from the perspective of sensibility.

CONCLUSIONS

In conclusion, we found that diminished sensibility in the thumb and index finger correlates with diminished hand function. These findings should contribute to a better understanding and appreciation of the observed clumsiness of the hand in patients with NBPP upper trunk lesions. Giving specific attention to hand function when treating these children might reduce the deleterious effects of diminished sensation. Finally, our test protocol may serve as a step

toward a validated, universally accepted test protocol for sensibility in infants with NBPP and other peripheral nerve lesions.

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Chapter 4

Tactile Perception of the Hand in Children with an upper Neonatal Brachial Plexus Palsy

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Arch Phys Med Rehabil
2022 Dec 16:S0003-9993(22)01763-4

ABSTRACT

Objective

To investigate factors that cause impairment of hand function in children with an upper Neonatal Brachial Plexus Palsy (NBPP), we performed an in-depth analysis of tactile hand sensibility, especially the ability to correctly localise a sensory stimulus on their fingers.

Patients and methods

Tertiary referral centre for nerve lesions in an academic hospital in The Netherlands. The control group was recruited at their school. A cross-sectional investigation of 41 children with NBPP (mean age 10.0 y) and 25 controls (mean age 9.5 y)
The thickest SW monofilament was pressed on the radial or ulnar part of each fingertip (10 regions), while a screen prevented seeing the hand. Correct localization of the applied stimuli was evaluated, per region, per finger and per dermatome with a test score. The affected side of the NBPP group was compared with the non-dominant hand of the controls.

Results

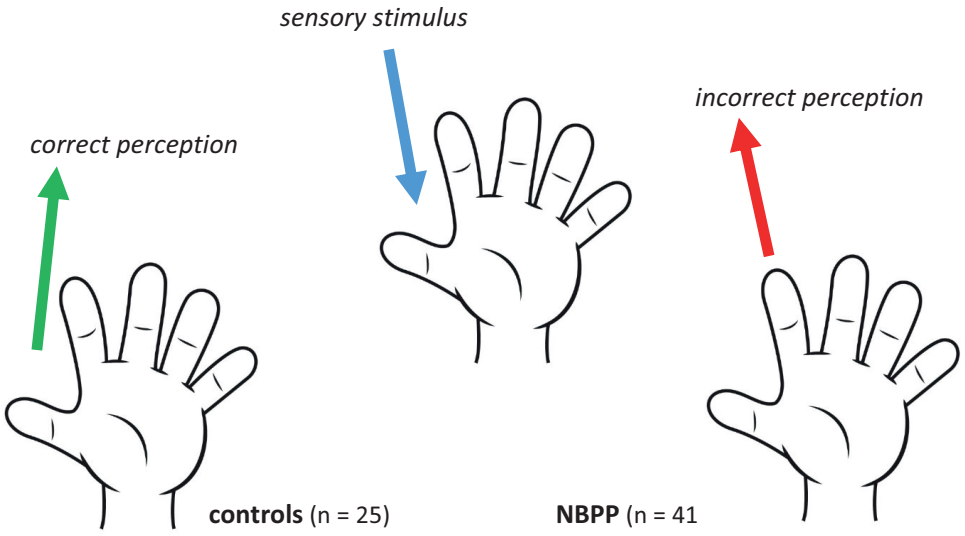
The ability to localize stimuli on the tips of the fingers in children with an upper NBPP was significantly diminished in all fingers, except for the little finger, as compared to healthy controls. Mean localization scores were 6.6 (thumb) and 6.3 (index finger) in the NBPP group and 7.6 in both fingers for controls (maximum scores 8.0). Localization scores were lower in regions attributed to dermatomes C6 and C7, but not to C8,

Conclusion

Children with an upper NBPP showed a diminished and incorrect ability to localize sensory stimuli to their fingers. This finding is likely one of the factors underlying the impairment of hand function and should be addressed with sensory focused therapy.

GRAPHICAL ABSTRACT

Sensory Localization in children witch C5-C6 Neonatal Brachial Plexus Palsy



Clinical impact: incorrect perception of sensory stimuli may contribute to diminished hand function.

NerveCenter Leiden

INTRODUCTION

The neonatal brachial plexus palsy (NBPP) is a nerve traction injury that occurs during birth. The most common type involves spinal nerves C5 and C6. In more severe cases, the C7, C8 and T1 spinal nerves are damaged as well.[1]

An upper NBPP results in impaired or loss of force in the supraspinatus, infraspinatus, deltoid, biceps and brachioradialis muscles and thereby affects the movement of the shoulder and elbow. The involved spinal nerve C6 provides important sensory input to the hand, but the level and quality of sensation in the fingers is routinely not well documented. Treatment outcome analysis generally focusses on the amount of motor recovery of the C5, C6 deficits. In one of the rare reports where sensory recovery of the hand was studied, it appeared to be excellent.[2] In contrast we showed that two-point discrimination (2PD) and touch-pressure testing with Semmes-Weinstein Monofilaments (SW) of the thumb and index finger was diminished in children with an upper NBPP.[3] Moreover, we showed that there was a reduction of gripforce[4], and diminished dexterity[3]. Thus, children with an upper NBPP not only have impaired shoulder and elbow function, but impairment of hand function as well.

The identification of factors that cause the clumsiness of the hand is not complete which is why it is difficult to provide effective treatment. Finger sensation also includes the ability to localize a stimulus, next to 2PD and pressure. Therefore, we assessed in detail the ability to localize applied sensory stimuli at the fingertips in children with an upper NBPP.

PARTICIPANTS AND METHODS

The study design was a cross-sectional investigation of patients with NBPP between 7 and 12 years of age who were compared to controls. Fifty children with an upper NBPP (22 boys, 28 girls, mean age 9.8 years (range 7.0 -12.8 years) and 25 healthy children (8 boys, 17 girls, mean age 9.6 years (range 7.2- 11.8 years) were recruited for this study. One child could not complete the localization test, leaving 49 children with NBPP for initial analysis. In the final analysis we only included children whose dominant hand was the unaffected side (n = 41) Patient details are presented in Table 1.

Table 1 Patient characteristics

Demographic variables	NBPP		Controls
	Enrolled	Final analysis	
Total number	49	41	25
Nerve surgery	30	28	N/A
Conservatively treated	19	13	N/A
Mean age (years)	9.8 (SD 1.89)	10.0 (SD 1.90)	9.5 (SD 1.46)
Range (years)	7.0 - 12.8	7.0 - 12.8	7.2 - 11.8
Boys/girls	22/28	19/22*	8/17
Affected side left/right	26/24	25/16*	N/A

Table 1 Legend

NBPP: Neonatal Brachial Plexus Palsy;

* The number of children with NBPP.

The children with NBPP were examined during regular follow-up at our tertiary referral clinic The NBPP diagnosis was based on the obstetrical history, neurological examination and was confirmed with additional EMG studies if the patient was seen before 6 weeks of age.
The included children with NBPP showed paralysis or paresis of muscles related to the C5 and C6 spinal nerves at the age of three months. They showed absent or weak shoulder abduction, shoulder external rotation, and lack of elbow flexion against gravity with the arm brought in 90 degrees of abduction, which was tested in the supine position. The biceps muscle was palpated to assess contraction of the biceps muscle. They had active elbow extension with active triceps muscle and active wrist extension which was at least strong enough to overcome resistance. All children had normal motor hand function, evaluated by routine clinical examination. The indication for nerve reconstructive surgery was extensively described previously.[1] In short, children who lacked recovery of elbow flexion executed by the biceps muscle, gleno-humeral external rotation and abduction at the age of 3 to 6 months were selected for nerve surgery. Children who were conservatively treated showed recovery of elbow flexion with active biceps muscle at 3 to 6 months of age.
In 30 children with NBPP (61%), nerve surgery was performed in early infancy, while the remaining 19 were treated conservatively. Children who were selected for nerve surgery first underwent MRI or CT myelography to assess root avulsion injury. During the operation, surgical inspection and direct nerve stimulation were performed to assess the severity of the

nerve lesion. In 23 infants, the C6 function was restored by grafting from C6 to the anterior division of the superior trunk. Of the remaining seven infants, five underwent transfer of the pectoral nerve to the musculocutaneous nerve, in one patient the accessory nerve was transferred to the suprascapular nerve and in one patient neurolysis was done. In these seven children, the neural pathway from C6 to the anterior division had been left intact. Depending on the extent of the lesion, C5 was grafted to the posterior and/or anterior divisions of the superior trunk and to the suprascapular nerve. To document recovery, shoulder function was assessed using the Mallet score,[5] and the Medical Research Council (MRC) grade of biceps force was documented.

The control group was recruited at the Montessori school in Voorburg, The Netherlands (a regular primary school), by announcing the study on the school's message board. All children who participated had a normal cognitive function and attended regular schools.[6] All children were assessed in their native language (Dutch).

In 83 % of the children with NBPP on the right side, the unaffected hand served as the dominant hand, as hand dominance may have shifted due to the lesion.[7] To exclude a potential confounding effect of hand dominance on sensation, we only analysed children whose dominant hand was the unaffected side. We compared the affected side of the NBPP group with the non-dominant hand of the control group (n = 41). We defined the dominant hand as the hand in which a child would hold a pencil to write. A hand preference shift was assumed to have occurred if a child with a right-sided lesion had left-hand dominance, see Table 2.

Sensory localization test of the fingers

The assessment of the ability to localize applied sensory stimuli applied at the fingertips was performed by a single pediatric physiotherapist (SB) to avoid confounding in both groups. The tester has more than 41 years of experience with physical assessment and treatment of children in all age groups.

The protocol to test localization was adapted from Jerosch-Herold[8] and Anguelova.[9] The child was sitting and the elbow and supinated forearm were resting on a table. The shoulder was positioned in 0^{o} anteflexion, 0^{o} abduction and 0^{o} external rotation. If this position was not possible due to lack of external rotation, the upper arm was held in a resting position in internal rotation. The dominant hand was tested first. Each fingertip was divided in two

Table 2 Hand dominance versus affected side

Group				Dominant hand	
				Left	**Right**
Controls				1	24
NBPP	Conservative	Affected side	left	-	10
			right	3#	6*
	Nerve surgery	Affected side	left	-	15
			right	13#	2*

Table 2 Legend

NBPP: Neonatal Brachial Plexus Palsy;
The number defines the number of children within each group.
Included in the analysis where children in whom the affected side was the non-dominant hand: a hand preference shift was assumed to have occurred in these children;
* Not included in the analysis.

regions, radial and ulnar of the midline. The thickest SW monofilament was pressed at the radial or ulnar half for 2 seconds. The children were asked to indicate in which finger and which region they felt pressure, while a screen prevented them from seeing their own hand. During the test no feedback to the child was provided whether the correct region had been identified. The child was shown a drawing of the hand with numbered regions of the fingertips in order to facilitate the specification of the region. (Figure 1).

Regions were tested in a quasi-random order: each region was tested two times with at least one test of another finger in between. The order of the tested regions had been determined beforehand in a quasi-random order. Each correctly identified region scored two points. When the pressure was localized in the correct half of an adjacent finger, or in the wrong half of the correct finger, one point was awarded. The scores were added up to form a sum score. For each finger a maximum score of 8 points could be reached, 4 points for each of the two regions. In this way the maximum score for each hand was 40 points (5 fingers x 2 regions x 2 test rounds x 2 points). We defined the dermatomes C6, C7 and C8 in two ways, which differed in whether area 4 (ulnar side of index finger) was attributed to C6 or to C7. We analysed the differences between the mean for each region, finger and cluster of points:

C6 (1+2+3), C7 (4+5+6+7) and C8 (8+9+10), and as C6 (1+2+3+4), C7 (5+6+7), and C8 (8+9+10).

The study protocol was approved by the Medical Ethics Committee of the Leiden University Medical Centre (ABR number 48977) and informed consent was given by the parents.

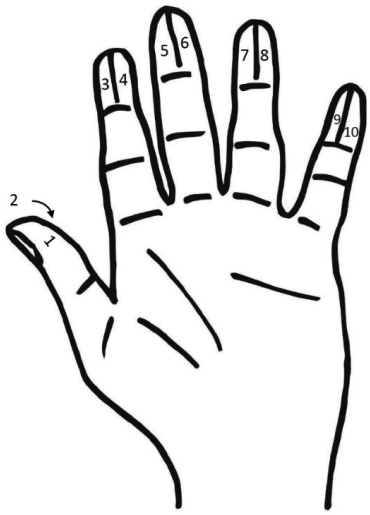


Figure 1 Drawing of the numbered regions of the hand

STATISTICAL ANALYSIS

Data were analysed with SPSS Statistics for Windows, version 26 (IBM Corp.Armonk, NY). The error level was set at $p < 0.05$. We used the two-sample t test to compare mean localization test scores between children with NBPP and children without NBPP for individual finger regions (radial or ulnar finger side), each finger (combined radial/ulnar sides), and groups of regions (finger scores combined, corresponding to the dermatomes of the C6-8 levels).

RESULTS

In the NBPP group, 96% of the children reached Mallet score 3 or 4 regarding hand to mouth function and hand to head function. Shoulder abduction recovered to Mallet 3 or 4 in 98%.

External rotation recovered to Mallet 3 or 4 in only 32% of the children. The MRC muscle force of the biceps was 4 or 5 in 98% of the children.

The NBPP group showed a larger variety in the regions where the tactile stimulus were perceived as compared to controls. The responses are presented in Table 3a and b.

Table 3a Comparison of region touched vs region participants felt in the non-dominant hand of the control group

		Touched									
		Thumb		Index		Middle		Ring		Little	
	Region	1	2	3	4	5	6	7	8	9	10
Felt	1	88%	8%								
	2	10%	92%								
	3	2%		90%	8%	6%					
	4			4%	90%		10%		2%		
	5			4%		76%	2%	8%			
	6			2%	2%	6%	84%	4%	16%		
	7					10%	2%	84%	0%	4%	
	8					2%	2%	4%	82%	2%	
	9									92%	2%
	10									2%	98%

Table 3b Comparison of region touched vs region participant felt in the affected non-dominant hand in the NBPP group

		Touched									
		Thumb		Index		Middle		Ring		Little	
	Region	1	2	3	4	5	6	7	8	9	10
Felt	1	70%	33%		1%						
	2	27%	66%	1%	4%						
	3	2%	1%	71%	4%	5%		1%			
	4			6%	67%	1%	5%	0%	5%		
	5			13%	6%	56%	7%	15%	1%		
	6			5%	11%	12%	68%	7%	10%		
	7			4%	5%	17%	4%	62%	9%	1%	
	8				2%	9%	15%	15%	74%	0%	
	9	1%								85%	9%
	10						1%		1%	13%	91%

Table 3 Legend

Percentage of responses in which region the child felt the touch region. Cells are shaded darker depending on their value (<10% white, 40%-60% darkest, >90% white)

The sum of the test score per region is presented in Table 4. The test scores for regions 1 through 7 differed significantly between patients and controls, but not for regions 8 through 10.

When comparing localization per finger, which consisted of the sum of its two contributing regions, we found a significant difference for the thumb, index finger, middle finger, ring finger, but not for the little finger, see Table 5.

The comparison of the localization test score per dermatome revealed a significant difference for the C6 and C7 dermatome, but not for C8. Because regions are attributed differently to dermatomes, we performed two different analyses: 1) C6: regions 1/2/3 and C7: 4/5/6/7 and 2) C6: 1/2/3/4 and C7:5/6/7. C8 consisted of regions 8+9+10.[10, 11] The results of these two analyses did not differ.(Table 6) There was a statistical difference when comparing the sum score for the whole hand ($p = 0.001$).

Analysis of the localization test score between the conservatively treated group ($n = 13$) and the surgically treated group ($n = 28$) showed a significant difference for region 2 ($p = 0.013$). The mean score for region 2 was 3.5 (SD 0.75) for the surgically treated group and 2.77 (SD 1.01) for the conservatively treated group. The entire thumb consisting of regions 1 and 2 also scored better in the surgically treated group ($p = 0.030$). We found no significant differences for other regions or fingers. There were no differences regarding the dermatomes C6 ($p = 0.40$) and C7 ($p = 0.55$).

Table 4 Localization test score per region

	n	Thumb		Index		Middle		Ring		Little	
Tested Region		1	2	3	4	5	6	7	8	9	10
Controls	25	3.8(0.60)	3.8(0.50)	3.8(0.66)	3.8(0.50)	3.4(0.77)	3.7(0.63)	3.6(0.76)	3.6(0.70)	3.8(0.66)	4.0(0.20)
NBPP	41	3.3(0.82)	3.3(0.90)	3.2(1.13)	3.1(1.08)	2.9(1.21)	3.2(0.97)	3.1(1.00)	3.4(0.86)	3.7(0.46)	3.8(0.44)
p (*t*-test)		0.020*	0.003*	0.017*	<0.001*	0.027*	0.030*	0.045*	0.183	0.705	0.106

Table 4 Legend

NBPP: Neonatal Brachial Plexus Palsy

Results presented as mean of the sum test score per region, the maximum score per region is 4; (Standard Deviation);

* Significant at 5% for the 2–sample t-test.

Table 5 Localization test score per finger

	n	Fingers				
		Thumb	**Index**	**Middle**	**Ring**	**Little**
Tested regions		1+2	3+4	5+6	7+8	9+10
Controls	25	7.6(0.87)	7.6(0.77)	7.2(1.18)	7.2(1.27)	7.7(0.68)
NBPP	41	6.6(1.39)	6.3(1.69)	6.2(1.77)	6.5(1.63)	7.5(0.67)
p (t-test)		0.001*	<0.001*	0.008*	0.040*	0.289

Legend Table 5

NBPP: Neonatal Brachial Plexus Palsy

Results presented as mean of the sum test score per finger, the maximum score is 8 per finger; (Standard deviation);

* Significant at 5% for the two-sample t-test

Table 6 Localization test score per dermatome

	n	Nerves					
		C6	**C7**	**C6-alt***	**C7-alt***	**C8**	**hand**
Tested regions		1+2+3	4+5+6+7	1+2+3+4	5+6+7	8+9+10	Σ 1 to 10
Controls	25	11.3 (1.11)	14.6 (1.94)	15.1 (1.24)	10.8 (1.64)	11.4 (1.25)	37.2 (3.61)
NBPP	41	9.8 (1.87)	12.4 (3.13)	12.9 (2.42)	9.3 (2.38)	10.9 (1.04)	33.1 (4.97)
p (t-test)**		<0.001*	0.001*	<0.001*	0.004*	0.115	0.001*

Legend Table 6

NBPP: Neonatal Brachial Plexus Palsy

Results presented as mean of the sum score (Standard Deviation);

* alt: alternative dermatome definition (as described in the text);

** Significant at 5% for the two-sample t-test

DISCUSSION

Sensory input from the fingers is of eminent importance for proper cerebral control of hand function. Finger sensation contains different qualities, such as pressure threshold, two-point discrimination and localization. All sensory qualities together are processed in the cerebral cortex to enable delicate finger movements.[12] Previously, we showed that 2PD and the SW

monofilament pressure testing in the thumb and index finger was significantly lower in children with NBPP compared to controls.[3] In upper NBPP lesions with clinical involvement of C5 and C6 roots, in-depth analysis of the localizing quality of the fingers has not been done so far. The present study shows that the ability to localize stimuli on the tips of the fingers in children with an upper NBPP is significantly diminished in all except for the little finger as compared to healthy controls. We found statistically significant differences per region of the fingers. Furthermore, the tactile localization was significantly diminished in dermatome C6 and C7, but not in C8.

Our findings should create awareness amongst therapists regarding the reduced sensory qualities of the hand in children with an upper NBPP. Moreover, it should encourage therapists to address hand sensation in rehabilitation programs on a regular basis. Especially traditional sensory re-eduction and activity-based sensory re-eduction have been supported as rehabilitative interventions aiming to improve cortical plasticity and improve functioning after nerve repair.[13, 12] Frequent application of different types of sensory stimuli to the fingers from early infancy onwards potentially stimulates central synaptogenesis and dendritic sprouting in a learning process which should ultimately lead to improvement of interpretation and appreciation of sensory input, and thereby hand function.

No differences were found between the children with NBPP who were treated conservatively or surgically, except for the thumb and region 2 of the thumb, which scored slightly better in the surgically treated group. This signifies that following nerve reconstruction, nerve regeneration provides levels of localizing ability which is at least comparable to those children with NBPP whose nerve injury was milder and therefore were not operated. In other words, the performed nerve surgery improves the level of sensibility befitting a very severe nerve injury (i.e. neurotmesis) to that of a less severe injury (i.e. axonotmesis).

This study provides detailed information of the diminished and incorrect feedback of localization stimuli. Profusely disturbed sensation of the fingers was also found after surgical repair of the median nerve in adults.[14] Absence of or incorrect sensory feedback results in the so called “blind” hand. Specific tasks with a blind hand can only be performed under visual control, but not without. Having a blind hand affects patient’s daily activities, for example holding a pen, searching for a key in a pocket, closing a top button or typing. Specific sensory re-education programs have been applied in adults to facilitate

understanding of the new sensory patterns provided by the hand and the rehabilitation focus is on modulation of central nervous processes rather than peripheral factors.[14]

Our findings showed that the localizing quality of sensory stimuli in four fingers was diminished. This can be explained by misrouting of axons during regrowth.[15] This factor that contributed to the mismatch in afferent feedback.[9] Because the NBPP lesion occurs when the brain is still developing, the impact have on motor program development is profound. It was previously hypothesized that a diminished tactile input to the brain could explain diminished embedding of movement of the affected arm, which was coined 'developmental apraxia'.[16] The reduced hand grip-force and dexterity may also be caused by disturbances in cerebral control development.[3, 4] It was found in a MRI study that there was more asymmetry in both supplementary motor area and primary somatosensory areas in children with NBPP.[17]

A normal sensory input to the somatosensory cortex in early life is essential for the development of motor skills.[16, 18, 19] The nerves in the arm contain 90% sensory axons, and only 10% are motor.[20] This may imply that upper limb motor execution, and particularly dexterous coordination of hand movement, requires a large convergence of afferent input for feedback control. The threshold for afferent input to the sensory cortex depends on stored memory and experience, which may be altered in children with NBPP.[3] Another factor which may contribute to diminished hand function in upper NBPP is reduction of proprioceptive sensation. This has been shown to be reduced in the elbow joint,[21] but has not yet been studied in the finger joints. Interestingly, both in the control group and the NBPP group, children often asked whether they were allowed to move their fingers during testing. The children explained that they could then localise the stimulus.[6] This phenomenon might point to an additive effect of proprioceptive input, normal or abnormal, to correctly localize a stimulus.

An unexpected finding was that sensibility was diminished in the C7 dermatome in children who were clinically diagnosed with a nerve lesion confined to C5 and C6. Cervical dermatomes C6 and C7 are defined differently. Therefore, two different analyses were performed in which the ulnar area of the index finger was attributed either to C6 or to C7.[10, 11] The result of these additional analyses did not differ. Our findings imply that in children in which the motor function deficit is clinically confined to C5 and C6 only, the C7 root may be affected sub-clinically as well. In a previous motor evaluation of axonal

misrouting in adult patients with clinically an upper NBPP, it was found that misrouting was present in the triceps muscle in more than 50 %.[22] Alternatively, sensory overlap between the C6 and C7 dermatomes may explain this finding. A systematic review of contralateral C7 transfer revealed that sensory abnormalities after dividing the C7 root were found in the thumb, the index finger and the middle finger.[7]

The same localization test as we have used here, has been done previously in adults with an upper NBPP who were treated conservatively and compared to controls.[9] The scores in adults did not differ significantly which does not fit with our present findings in the young. The discrepancy might be caused by differences in lesion severity, or it might indicate that sensation qualities in NBPP may still improve over a long period of time.

Future studies should include in depth hand function assessment and patient-reported outcome scores which should also include sensibility. The strength of our study is that a relatively large group of upper children with NBPP were analysed in depth covering all fingers of both hands and compared to a control group.

Our finding that the tactile perception of the fingers in children with NBPP is disturbed emphasizes the need for dedicated and focused therapy. This might imply using visual feedback of the affected hand and stimulating both hands together in exercises.

STUDY LIMITATION

A drawback of the localization test is that it required a lot of concentration from the children. As the control group were of the same age, it is unlikely that this factor affected the outcome in the NBPP group to such an extent that it explains the differences we found. Another drawback is that we did not correlate the results of the localization test with daily activities.

A weakness of our study is that the participating children were selected from our tertiary referral clinic at the age of 7-12 years. As a consequence, surgically treated children were over-represented in the presented series. Children with a very good recovery may have been discharged from further follow-up at younger ages. Thus, we could not systematically document decreased sensibility and clumsiness of the hand in all our patients.

CONCLUSION

Children with an upper NBPP are not only affected by the impaired motor function of the shoulder and elbow, but also by a diminished and incorrect ability to localize stimuli to the fingers. This finding may be one of the contributing factors that lead to clumsiness of the hand. Addressing tactile perception with occupational treatment may reduce these deleterious effects on hand function of these children.

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Chapter 5

Children with an upper Neonatal Brachial Plexus Palsy: Awareness of Diminished Sensibility and Pain in the Hand

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Submitted

Abstract

Objective

In previous research, we found that objective outcomes such as two-point discrimination, Semmes- Weinstein monofilament testing, and localization ability of the thumb and index finger were diminished in children with a C5-C6 Neonatal Brachial Plexus Palsy (NBPP). We performed the present study to investigate whether these children report a diminished subjective sensation and/or pain in their hand, and to assess whether their parents are aware of these features.

Patients and Methods

During regular outpatient clinic visit 45 children (mean age 10 years) and their parents answered two simple questions concerning altered sensation and pain in the affected hand. The answers of the children were compared with those of the parents. We additionally analyzed the answers of the children in relation to two-point discrimination and Semmes-Weinstein monofilament tests.

Results

We found that 13/45 children (29%) reported a different sensation in the affected hand as compared to the unaffected side. Nine parents of these 13 children (64%) were not aware of the diminished sensation. Pain in the hand was reported by 14/45 children (31%), while the parents of only one child (9%) were aware of the pain. There was no correlation between the responses to the questions and the results of two-point discrimination and Semmes Weinstein testing.

Conclusion

Children with a C5-C6 NBPP have a diminished sensibility of their affected hand, but they are often not aware of this reduced sensation. Altered sensation and pain in the hand are often overlooked aspects of NBPP, but form relevant features.

INTRODUCTION

The neonatal brachial plexus palsy (NBPP) is a nerve traction injury that occurs during birth. Most commonly, the spinal nerves C5 and C6 are affected. In more severe cases, C7, C8 and T1 are involved as well.[1]

Previously, we reported results from an in-depth study of sensation of the hand in a cohort of fifty children with a C5 and C6 NBPP. Both conservatively and nerve surgically treated children were included. We found that two-point discrimination, Semmes- Weinstein monofilament testing, and localization ability of the thumb and index finger were diminished. The impeded sensibility had a negative impact on hand function.[2, 3] Additionally, we showed that both gripforce and dexterity of the affected hand of infants with C5 and C6 NBPP were reduced.[4] The literature on sensibility of the hand after NBPP is conflicting: some papers report findings in line with our previous findings[5, 6], while other papers have reported that sensory recovery after NBPP was good.[7-10]

The subjective experience of touch has been assessed only very rarely. From a cohort of 65 surgically treated children from The Hospital of Sick Children in Toronto, seventy percent described, when asked, that the affected limb "felt different", every day or at least once a week.[11] This was surprising, as during regular follow-up in our outpatient clinic, neither the children nor their parents spontaneously bring up sensory disturbances. We, therefore, chose to include a short and simple questionnaire in our research protocol to systematically assess subjective sensory disturbances and pain in these children. Additionally, we assessed whether parents were aware of a diminished sensation or pain in the hand of their child. This short questionnaire was delivered to children and their parents, just prior to a detailed analysis of hand sensation.

PATIENTS AND METHODS

During their regular follow-up visit at our tertiary referral clinic (Nerve Centre of the Leiden University Medical Center, The Netherlands), fifty children with C5, C6 NBPP between 7 and 12 years of age were included. In 30 children nerve surgery had been performed in early infancy, while 20 had been treated conservatively.

A simple questionnaire on paper was handed out, one to the child and one to the parents. (Table 1).

Table 1 Questionnaire (English translation)

For	Question
Children	1) Do you feel a difference in sensation in your affected hand when you compare it to the unaffected side?
	2) Do you feel pain in your affected hand?
Parents	1) Does your child sometimes indicate that feeling in the affected hand is different from the unaffected side?
	2) Does your child sometimes indicate that he/she has pain in the affected hand?

Both the children and their parents had to answer the questions separately by simply choosing 'yes' or no'' to the questions posed. Occasionally, the child was helped to read the questionnaire, but never helped while giving the answer. The researcher was in the same room to prevent the parents to help or influence the answers of their child. Analysis of the questionnaire was performed only when all questions were completed by both the children and their parents.

After answering the questions, the sensibility of the hand was analyzed in detail according to our research protocol which we previously described in detail. Briefly, two methods were used namely 1) two-point discrimination (2PD) and 2) the Semmes-Weinstein (SW) monofilament test.[2]

The study protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center (ABR number 48977) and informed consent was given by the parents.

STATISTICAL ANALYSIS

We used Pearson's or Spearman's correlation coefficients, depending on the type of variable, Pearson chi-square test and the Mc Nemar-test. The error level was set at $p < 0,05$. Data were analyzed with SPSS Statistics for Windows, version 28 (IBM Corp. Armonk, NY).

RESULTS

The questions were completed 45 times out of 50 by both children and parents. The mean age of the children was 10 years (SD 1.83).

Thirteen of 45 children (29%) reported that sensation in the affected hand differed from the unaffected side, 8 of whom had been treated conservatively, 5 were operated. The

remaining 32 children (71%) did not experience a different sensibility (11 conservatively, 21 surgically treated).

Four parents of the 13 children who reported a difference in hand sensation indicated that their child had mentioned it. The remaining 9 parents answered that they were unaware of any sensation differences. Of the 32 children who did not report a different sensibility, 2 of the parents stated that their child had mentioned a difference in sensation (see. Table 2).

Table 2. Sensibility of the hand: comparison of answers to the questions regarding sensation in the hand provided by both the children with a C5, C6 neonatal brachial plexus injury and their parents (n = 45)

		Different according to children		Total
	Answers	**Yes**	**No**	
Different according to parents	**Yes**	4	2	6
	No	9	30	39
Total		13*	32**	45

Table 2 Legend

* 8 conservative, 5 nerve surgery

** 11 conservative, 21 nerve surgery

The sensibility of the hand as analyzed with two-point discrimination (2PD) and Semmes Weinstein (SW) monofilaments was compared with the unaffected side.[2] The differences of the 2PD were statistically significant for the thumb (paired t-test $p = 0.001$) and index ($p = 0.004$). The thinnest SW filament was often not recognized in the affected thumb and index finger ($p < 0.001$; McNemar Test).[2]

We analyzed the relationship between the answers of the children to the questionnaire with the results of the 2PD for thumb and index. The Pearson correlation coefficient was -0.11 ($p = 0,48$) and -0.14 ($p = 0.36$) respectively. Additionally, we analyzed the relationship of the responses to the questionnaire with SW testing, which resulted in a Spearman correlation of 0.01 for the thumb ($p = 0.93$) and -0.09 for the index ($p = 0.56$), see Table 3. We repeated these analyses in two age groups: children younger than 10 years ($n = 23$) and older than 10 years ($n = 22$). The results were similar: no correlations were found (data not shown).

There was no correlation between subjective sensation and whether primary nerve surgery had been performed or conservative therapy was provided (Pearson Chi-Square Test: 0.037, p = 0.848).

Table 3 Correlation coefficients between the answers from the children regarding the questions about differences in sensation in the affected and unaffected hand (yes/no) and the sensibility tests 2PD, SW

	2PD		SW	
	Dig 1	**Dig 2**	**Dig 1**	**Dig 2**
Statistical test	Pearson	Pearson	Spearman	Spearman
Correlation coefficient	-0.11	-0,14	0.01	-0.09
p	0.48	0.36	0.93	0.56

Table 3 Legend

2PD: Two-point discrimination test; SW :Semmens Weinstein test.
Pearson: Pearson Chi-Square Test; Spearman: Spearman correlation

The question about pain was completed by both children and parents 45 out 50 times. The mean age of these children was 9.9 years (SD 1.86).

Thirty-one of the 45 children (69%) reported that they did not experience pain (12 conservatively, 19 surgically treated). The parents of these children consistently reported that their child had no pain. The remaining 14 children (31%) reported that they experienced pain in the affected hand (5 were conservatively treated, 9 surgically were treated). Only one parent of these 14 children was aware of the pain of their child (see Table 4).

Table 4 Answers to the questions about pain in the hand of both the children with a C5, C6 neonatal brachial plexus injury and their parents (n = 45)

		Pain according to children		**Total**
		Yes	**No**	
Pain according to parents	**Yes**	1	0	1
	No	13	31	44
Total		14*	31**	45

Table 4 Legend

* 5 conservative, 9 nerve surgery
** 12 conservative, 19 nerve surgery

There was no correlation between the presence / absence of pain and whether primary surgery had been performed (Pearson Chi-Square Test: 2.461, p = 0.117). We tested the correlation between the presence or absence of pain and the outcome of sensory testing, in the same way as we analyzed subjective sensory differences described above, and found no correlations (data not shown).

DISCUSSION

In a previous study we showed that children with a C5, C6 NBPP lesion have a decreased sensibility in the thumb and index finger, which was assessed with 2PD and SW filaments testing. In the current paper, we analyzed whether children and their parents were aware of the impaired sensation. We found that 13/45 children (29%) of children with an NBPP expressed, when asked, that they had a different sensation in the affected hand as compared to the unaffected side. The vast majority of the parents was not aware of these differences. As regard to pain, 14/45 (31%)of the infants mentioned that they experienced pain in the hand, while the parents of only one child (9%) were aware of the pain.

The major finding of this study is that we did not find a correlation between the responses of the children to the questions and the outcome of two-point discrimination and Semmes Weinstein testing (Table 3), regardless of their age group. While the objective testing results indicated that the children had a different sensation in the affected hand as compared to the un-affected hand, less than one third also indicated to experience a different sensation. From these results we conclude that in this series the majority of children with an upper NBPP have a diminished sensibility of their affected hand, but that these children are not aware of this reduced sensation.

We hypothesize that this lack of awareness results from the early lack of sensory input to the brain resulting in habituation: they simply don't know otherwise. Only occasionally, children spontaneously mentioned difficulties they experienced in daily life which we could link to a reduced sensibility of the affected hand, whereas the children themselves did not connect their limitations to the underlying sensory loss. To provide insight into the significance of our findings for daily practice, we give some examples. One child mentioned difficulties to switch gears of his race bike which were to diminished sensitivity of his thumb. Another child described how she tested whether a pan is hot or not. She touched the pan with the thumb and index finger of the affected side, because as it would be hot, it would be too painful to

touch it with the non-affected hand. Lastly, we found inflammation of the cuticle due to biting the thumb and index finger of the affected side, which could be tolerated only because of a diminished pain sensation. Although the sensation loss in children with upper NBPP is not complete, it may still effects daily life activities.

Another aspect that needs to be addressed is the current lack of awareness amongst treating occupational or physical therapists of any sensibility disturbances in the hand of children with NBPP. As sensibility provides input for the brain to execute fine motor tasks and complex hand function, these disturbances should be taken into account while developing and executing training programs. Previously, we showed that children with an upper NBPP do not only have an impaired sensibility, but a reduction of gripforce[4] and dexterity[2] underlying a diminished hand function.

Parents were often surprised to learn that the sensory testing of their child showed a diminished sensibility in the affected hand. They apparently assumed that the sensibility was not affected because their child never mentioned it spontaneously.

Besides the subjective awareness of diminished sensibility, we posed a question on pain. In the present series around 30% of the children reported to have pain in the hand of the affected arm. This percentage is much lower as compared to the 70% previously reported by the Toronto group.[11] The reason for this discrepancy might be that in the current series only patients with NBPP lesions limited to the C5, C6 spinal nerves were studied, whereas more extended lesions affecting the C7, C8 and /or T1 roots were included in the Toronto series as well. In addition, the Toronto series comprised only children who were operated, while in the present series also conservative treated children were included. Another difference was the way the pain was assessed, namely with the Faces Pain scale and / or the Adolescent Pediatric Pain Tool and not a dichotomous questionnaire.

Another paper reported pain prevalence around 78% (29 children out of 37). The pain had been spread out throughout the whole arm, irrespective of severity and was episodic in nature. The type of pain was described as musculoskeletal and nociceptive.[12]

Surprisingly, only one of the parents was aware of the pain in the hand of their child. The parents of those children who mentioned to have pain supposed that their child mistakenly answered the questions the wrong way around, because they had never heard them complain. Another factor that might also have played a role is a difference in phrasing or

interpretation of pain. Some children, for instance, said: “It does not feel nice when you touch the top of my finger”. Children may not only experience pain in a different way, but they may also use other words to describe pain.[11] For children, pain can be expressed as ‘pain’, but also as an ‘unpleasant feeling’.

The questions were given to the parents and children separately before starting the sensibility testing. We did not find a correlation between the answers of the children and the sensibility tests, signifying that most children were not aware of their sensory deficit. Regularly during testing, both the child and the parents were surprised when the sensation appeared to be diminished. The following striking reaction of a child was noted: “Now it became clear to me why, during typing or playing the piano, I always need to visually control my affected hand”.

The number of reports dealing with sensibility of the hand in children with NBPP is limited, and conclusions are conflicting.[13] Some papers reported normal sensory findings[7-10], whereas others reported that sensibility was affected.[5, 6] These conflicting data may be the result of different methods how sensation was tested and difference in the interpretation of the results.[14] Anand and Birch, for example, tested the sensibility with six sensory modalities: monofilaments, cotton wool, pinprick, warm/cool sensation, joint position sense and vibration. Their definition of ‘excellent restoration’ of sensory function was recovery to normal limits in all dermatomes ‘for at least one modality’. In their series only 6 / 20 operated patients recovered to normal SW testing results, so we feel that the often-cited excellent recovery in their paper may be partly due to their optimistic definition of good recovery.[7]

The strength of the present study is that we posed our questions prior to examining hand sensation. A second strength is that we also asked the parents. A weakness of the study is that we did not assess whether the children are so used to the impaired sensory input that they, therefore, do not mention it. Additionally, we did not assess whether parents may have misinterpreted complaints that were actually expressed by their child or even have unconsciously denied them. It should thereby be considered that an important part of the daily focus of the parents in relation to the NBPP is whether tasks can be executed which involve motor function and sensory perception might thereby be pushed to the background. Another drawback of this study is that the questions we used were not validated. Unfortunately, a validated questionnaire was not available. The youngest children in our

cohort were 7 years old. Especially the young ones asked support from their parents to help them understand the questions. Although we strived to minimize such interaction, we cannot completely exclude whether parents exerted some influence on how their child answered the questions. We feel, however, that this cannot have been to such an extent that this may have affected the outcome of the study.

CONCLUSION

Children with a C5, C6 NBPP lesion have sensory loss in the hand, next to shoulder and elbow motor function limitations. Both children and parents are frequently not aware of the sensory impairment of the hand. One third of the children expressed pain in the hand, which was hardly recognized by their parents. Both loss of sensation in the hand and pain in children with C5, C6 NBPP are factors that deserve attention, not only of the parents, but also of therapists to optimize treatment.

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Chapter 6

Gripforce Reduction in Children with an Upper Neonatal Brachial Plexus Palsy

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J Rehabil Med. 2021 Aug 7;53(8):jrm00219

Abstract

Objective

The aim of this study was to assess gripforce in children with a C5 and C6 neonatal brachial plexus palsy (NBPP) as it may affect hand use. Applying classic innervation patterns, gripforce should not be affected as hand function is not innervated by C5 or C6. Here we compare gripforce in NBPP with a healthy control group and assessed correlations with hand sensibility, bimanual use and external rotation.

Patients and Methods

50 Children with NBPP (mean age 9.8 y) and 25 controls (mean age 9.6 y) were investigated. Nerve surgery had been performed in 30 children and 20 children had been treated conservatively. Gripforce of both hands was assessed with the Jamar dynamometer. Sensibility of the hands was assessed with two-point discrimination and Semmes-Weinstein Monofilaments. External rotation was assessed using the Mallet score. Bimanual use was measured by using one of three dexterity items of the Movement Assessment Battery for Children-2. The affected side of the NBPP group was compared with the non-dominant hand of the control group using one-way ANOVA, chi-squared and Mann-Whitney tests.

Results

The mean gripforce of the affected non-dominant hand of children with NBPP was diminished as compared to healthy controls (95 N and 123 N, respectively, with $p = 0.001$). The mean gripforce of the non-dominant hand in the control group was 92% of that of the dominant hand, while it was only 76% in the NBPP group ($p = 0.04$). There was no relationship between gripforce reduction and sensibility, bimanual use or shoulder external rotation.

Conclusions

The gripforce in NBPP infants with a C5 and C6 lesion is lower than that of healthy controls although classic interpretation of upper limb innervation excludes this finding. The reduction of gripforce in upper NBPP lesions is not widely appreciated as a factor inherently compromising hand use. The reduction of gripforce should be taken into consideration in planning the type of rehabilitation and future activities.

INTRODUCTION

Neonatal brachial plexus palsy (NBPP) is a nerve traction injury that occurs during birth. The most common type involves a lesion of the two upper spinal nerves C5 and C6. In more severe cases, spinal nerves C7, C8 and T1 are involved as well, see Malessy & Pondaag.[1] Classic anatomical innervation schemes indicate that C5 mainly innervates the deltoid, supraspinatus and infraspinatus muscles, whereas the biceps, brachialis and brachioradialis muscles are mainly innervated by C6, see Merle d'Aubigné & Deburge.[2] An upper lesion should, therefore, only affect shoulder functions and elbow flexion. Our clinical observation is, however, that children with an upper NBPP employ their hand less often and the dexterity of the hand seems diminished. Anecdotally parents affirm this observation. A satisfactory explanation for these phenomena are difficult to provide. After all, hand function in itself should not be affected in upper plexus injuries because the muscles of the hand are innervated by the lower nerves of the brachial plexus, C8 and T1.Three factors could theoretically affect hand use: 1) a diminished positioning of the hand in space, 2) a diminished sensibility and 3) gripforce reduction. Research has shown that recovery of glenohumeral external rotation is limited after conservative management or nerve surgery reaching beyond the sagittal plane in only 20% of patients, see Pondaag et al.[3] Limitations in external positioning may affect the development of the preferred hand for writing and playing, see Krumlinde-Sundholm et al.[4] Sensibility of the thumb and index finger in children with an upper plexus lesion (whether treated surgically or conservatively) is also diminished, see Buitenhuis et al[5] and Anguelova et al[6] which is correlated with diminished dexterity see Buitenhuis et al.[5] Some studies have been performed in children with an upper palsy to explore whether the use of the hand is reduced because of a reduction of gripforce. The applied methodologies in these studies, however, leave doubts as to the value of the results. Namely, the affected side was compared to the non-affected side of the individual child, see Krumlinde-Sundholm et al[4], Strombeck et al[7] and Kirjavainen et al[8]. Regardless of the outcome, this type of comparison does not discriminate whether findings are caused by a relative increase of gripforce in the non-affected side, by hand dominance or by an actual reduction of intrinsic gripforce of the affected hand. In addition, the criteria used to define a reduction of gripforce were chosen quite arbitrary and were based on measurements in

adults. To overcome these issues, potential gripforce differences can only be addressed in the setting of a comparison with a healthy control group of the same age.
In the present study we compared the gripforce of the hand in children with an upper NBPP with healthy controls. In addition, we correlated gripforce with hand sensibility, dexterity/bimanual use and glenohumeral external rotation, in order to gain a better understanding of the bimanual use of the hand.

PATIENTS AND METHODS

We used a cross-sectional investigation design of patients with NBPP. Fifty children with an upper NBPP and 25 healthy children were recruited for the study. Ages of both groups ranged between 7 and 12 years. The children with NBPP had been examined on a regular basis from an early age at our tertiary referral clinic (Nerve Center of the Leiden University Medical Center, The Netherlands). The diagnosis of NBPP was based on the obstetrical history and the neurological examination and additional electromyography examination performed between the ages of 4 and 6 weeks, see Malessy et al.[9] Nerve surgery was performed in 30 children (60%) in early infancy, while 20 had been treated conservatively. Based on the neurological examination, all children only had a lesion of the C5 and C6 spinal nerves. At the first visit to our clinic, all participants had a normal hand function, normal elbow extension based on active triceps muscle and active wrist extension at least against resistance. Hence, these children were diagnosed with a C5-C6 lesion, with intact C7-C8-T1 functions. The children who were conservatively treated showed recovery of elbow flexion with active biceps muscles at 3 to 6 months of age.
The indication for nerve surgery has been extensively described by Malessy & Pondaag.[1] Children who were operated upon underwent MRI myelography to assess root avulsion injuries. During the operation, surgical inspection and direct nerve stimulation were performed to confirm the clinical diagnosis. To restore C6 function, grafting from C6 to the anterior division of the superior trunk (ADST) was performed in 23 of the 30 infants. Of the remaining seven patients, five had a medial pectoral nerve to musculocutaneous nerve transfer. In one surgically treated patient, accessory to suprascapular nerve transfer was the sole procedure, and in one other patient surgery was limited to neurolysis. In these seven children, the nerve pathway from C6 to the ADST (containing the sensory fibres of the C6

dermatome) was in continuity. This sub-group of seven patients was additionally compared to the 23 infants in which C6 was grafted to the ADST.
The control group was recruited at the Montessori school at Voorburg, the Netherlands, by announcing the study on the school's message board. All children who participated had a normal cognitive function and attended regular school, see Buitenhuis et al.[10]

Physical examination

The physical examination of all participants was performed by one physical therapist (SB). with a huge experience of physical assessment and treatment of children in all age groups. The gripforce of both hands was assessed with the Jamar dynamometer, according to a standard protocol, see Molenaar et al.[11] The child was sitting with the elbow and forearm resting on a table, with the wrist in a neutral position between pronation and supination. The shoulder was positioned in 0° anteflexion, 0° abduction and 0° external rotation. If this position was not possible due to lack of external rotation, the upper arm was held in a resting position in internal rotation. The dominant hand was tested first. The child was asked to squeeze the handles of the Jamar dynamometer as forcefully as possible. Three attempts at maximum force were recorded, and the mean of the three values was calculated. Before the three measurements were done, we instructed the children very well to do their utmost best to perform as well as they could. Also, during the testing we encouraged them to use the maximum of their abilities. The affected side was compared with the non-affected side within the NBPP group. Additionally, we compared the non-dominant affected side of the NBPP group with the non-dominant hand of the control group.
The dominant hand was defined as the hand in which a child holds a pencil to write. A hand preference shift in the NBPP group was presumed to have occurred if a child with a right-sided lesion had left-hand dominance, see Yang et al.[12] When the dominant side was the affected side, children were excluded from analysis.

The sensibility of the hands was assessed with two-point discrimination (2PD) (Bell-Krotoski et al[13] of the index finger and the Semmes-Weinstein Monofilament test (SW) (Weinstein[14]) of the thumb of the non-dominant side in the NBPP group. External rotation was assessed using the relevant Mallet sub-score, see Mallet.[15] A score of Mallet I signifies no active

external rotation. Mallet II indicates < 0° active external rotation. Mallet III represents active external rotation between 0–20°. Mallet IV means >20° active external rotation.
The combined use of both hands was measured by a single item from the three dexterity items of the Movement Assessment Battery for Children-2 (MABC-2), an internationally accepted and validated test for fine motor skills by Schulz et al.[16] For children aged 7, 8, 9 or 10 the specific bimanual task consisted of threading a wire through holes in a board. Children aged 11 or 12 years were instructed to construct a triangle with nuts and bolts in correspondence with MABC-2. We selected this bimanual task because it requires employment of the affected hand. Children were not allowed to put either the wire or the triangle on the table, but were instructed to keep them in both hands. The time needed to finish the task was noted and converted to a standard score, and corrected for age using the MABC-2 manual. We have reported the sensibility and the dexterity results of the NBPP and control groups in a previous paper, see Buitenhuis et al.[5]

The study protocol was approved by the Medical Ethics Committee of the Leiden University Medical Centre (ABR No. 48977) and informed consent was given by the parents.

Statistical analysis

We used analysis of variance (one-way ANOVA) for continuous outcome variables. Categorical outcome variables were compared between groups using chi-squared tests (exact tests if the expected counts were small). Where appropriate, a Mann-Whitney test was used instead of a t-test. The error level was set at $p < 0.05$. Data were analysed with SPSS Statistics for Windows, version 23 (IBM Corp. Armonk, NY).

RESULTS

Patient details are presented in Table 1.
We compared the affected (non-dominant) side in the NBPP group with the non-dominant side of the control group and we compared the difference in gripforce between the dominant and non-dominant hand within the NBPP group, respectively, within the control group. This analysis of the 'affected non-dominant hand' concerned 28/30 surgically treated children and 14/20 conservatively treated children, see Table 2.

Table 1 Patient characteristics

Demographic variables	NBPP group	Control group
Total number	50	25
Nerve surgery	30	NA
Conservatively treated	20	NA
Mean age (years)	9.8 (SD 1.89)	9.5 (SD 1.46)
Boys/girls	22/28	8/17
Affected side left/right	26/24	NA

Table 1 Legend

NBPP: Neonatal Brachial Plexus Palsy; NA: Not Applicable; SD: Standard Deviation.

Table 2 Hand dominance versus affected side

				Dominant hand	
Group				**Left**	**Right**
Controls				1	24
NBPP	Conservative	Affected side	left	-	11
			right	3#	6*
	Nerve surgery	Affected side	left	-	15
			right	13#	2*

Legend Table 2

NBPP: Neonatal Brachial Plexus Palsy.

presumed preference shift: a hand preference shift was presumed to have occurred if a child with a right-sided lesion had left-hand dominance; * lesion on dominant side: not included in the analysis.

In the surgically treated group, a hand preference shift was found in 13/15 children (87%), while in the conservatively treated patients, a hand preference shift was found in 3/9 children (33%). This difference was statistically significant ($p = 0.007$). We cross-checked for gender or age as a confounder, as gripforce was shown to increase with age, and boys are usually stronger than girls, see Molenaar et al.[17] Our NBPP group was 0.3 years older than the control group, and gender did not influence the results, thereby ruling out these confounders.

The mean gripforce of the non-dominant affected hand was statistically significant reduced in the NBPP group as compared to the non-dominant hand of the controls (95 N and 123 N, respectively, with p = 0.001). The mean gripforce of the non-dominant hand in the control group was 92% of that of the dominant hand. The gripforce of the non-dominant hand of NBPP group was 76% of that of the dominant hand (p = 0.04). (Figure 1 and Table 3**I**)
Gripforce did not differ statistically between the conservatively and surgically treated subgroups. The mean gripforce was 75% of the unaffected side after nerve grafting (n = 22); 81% after nerve transfer (n = 5), and 78% after conservative treatment (n = 14).
The gripforce of the non-injured dominant hand was diminished 10% in children who had undergone nerve surgery compared to controls (121 N versus 134 N; p = 0.20), and 15% in children who shifted dominance (114 N versus 134 N; p = 0.13), see Table 3.

Table 3 Gripforce of the hand (Newton)

		Mean* (SD)	
Group		**Dominant**	**Non-dominant**
Controls	(n = 25)	134 (42)	123 (42)
NBPP	All (n = 41)	125 (45)	95 (38)
	Conservative (n = 14)	132 (41)	100 (30)
	Nerve surgery (n = 27)	121 (48)	92 (42)
	Presumed preference shift (n = 16)	114 (42)	92 (45)
	No presumed preference shift (n = 25)	128 (47)	94 (33)

Legend Table 3

NBPP: Neonatal Brachial Plexus Palsy; SD: Standard Deviation; n = sample size.
* The mean gripforce of the non-dominant affected hand in the NBPP group differs significantly from the non-dominant hand of the control group (p = 0.001, t-test); there was no significant difference between conservative treatment and nerve surgery in the NBPP group for both the non-dominant affected hand (p = 0.34) and for the dominant non-affected hand (p = 0.42). The difference between the children with and without a presumed preference shift was not significant for the non-dominant affected hand (p = 0.92) and for the dominant non-affected hand (p = 0.32). The difference between the dominant hand after a presumed preference shift and the dominant hand of the control was not significant (p = 0.14).

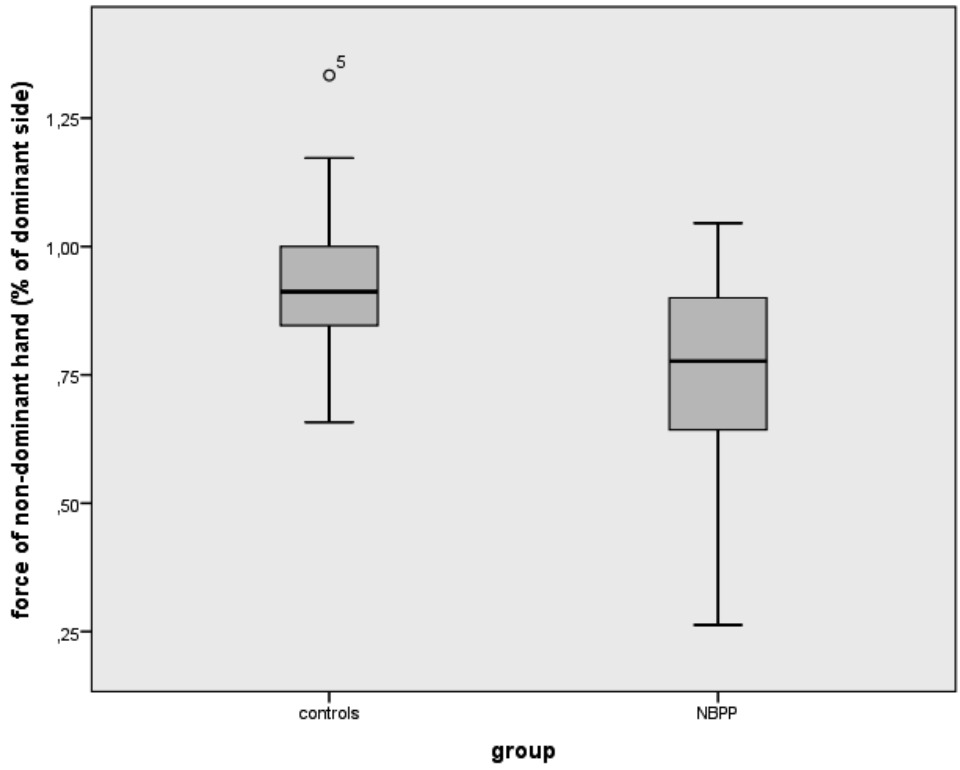

Figure 1 Gripforce of the non-dominant hand as a percentage of the dominant side

Legend Figure 1

Controls: mean gripforce of the non-dominant hand was 92% of that of the dominant hand; NBPP (neonatal brachial plexus palsy)-group: mean gripforce of the non-dominant hand was 76% of that of the dominant hand.

In the MABC2 bimanual use test, the children in the control group (n = 22) had a mean test score of 11.0, compared with a mean test score of 8.0 in the NBPP group (n = 50). The higher test score signifies that the controls perform the bimanual use test faster than the children with NBPP, which was statistically significant (p = 0.036). Due to a slight age difference between patients and controls, 31/50 (62%) of the children with NBPP performed the wire thread test compared with 20/22 (91%) of the controls. We additionally analysed the wire thread test only to rule out different outcomes due to the difference between the wire thread test and triangle construction test. The time to thread the wire through holes in a board, was 29.9 seconds in the NBPP group (mean age 10.1 year) compared with 23.9

seconds in the control group (mean age 9.1 year). This difference in time was also significant ($p = 0.01$).

Shoulder external rotation scores were Mallet grade I in 16 children with NBPP; Mallet II in 18; Mallet III in 12; and Mallet IV in 4.
We found no correlation between sensibility and gripforce. Nor did we find a correlation between gripforce and the bimanual use test (Pearson Correlation coefficient: 0.092, $p = 0.47$). We found no correlation either between gripforce (corrected for age) and the Mallet subscore for external rotation ($p = 0.57$).

DISCUSSION

This study was performed to analyse whether gripforce is reduced in children with an upper NBPP lesion following the clinical observation that the affected hand is used less. This research question was supported by the observation of others that a shift of hand preference occurs in many children with NBPP, see Yang et al.[12]
In the present study, we found a reduced gripforce of the affected side which was 76% of the unaffected side. In the healthy control group, the mean gripforce of the non-dominant side was 92% of that of the dominant hand. The findings in the control group matches those of a previous report in which a 94% ratio was found by Molenaar et al.[11]
Our findings take away the doubts that still existed as regard to gripforce levels in upper NBPP lesions. Previously, it was stated that 50% of children with C5–C6 lesions have a reduced gripforce, see Krumlinde-Sundholm et al[4] and Strombeck et al[7]. A Martin Vigori meter consisting of a rubber bulb connected to a manometer was used. The bulb had to be squeezed 3 times and the highest value for each hand was recorded. Gripforce was regarded as reduced when it was 20% less than the strength in the unaffected hand. The cut-off point of 20% was chosen based on gripforce measurements with a dynamometer in adults, see Petersen at al[18], Strombeck et al[19] and Bechtol[20], which is, in the setting of children, quite arbitrary. In another study another cut-off point was applied, namely more than 89% of the unaffected hand. It was found that only 18% of children with NBPP with a C5-C6 injury had a normal gripforce ratio, see Kirjavainen et al.[8] The discrepancies between the studies of Kirjavainen et al[8], Petersen at al[18] and Bechtol[20], illustrate the effect of choosing different criteria on outcome, and create doubts as to its value.

The factors that cause a decrease of hand gripforce in NBPP with C5-C6 lesions need still to be determined.

A neuroanatomical explanation for the innervation of gripforce seems unlikely, as the long flexors of the fingers are innervated by C8 and T1, which should be normal in children with an upper trunk lesion. Indirectly, the innervation of wrist extension might play a role, as stable wrist extension is essential for a strong hand grip. Electrophysiological studies have shown that the nerve fibers innervating the extensor carpi radialis muscle arise from C5 and C6, see Zhang et al.[21] A reduced innervation of wrist extension could therefore contribute to a decrease of gripforce. In our experience, however, in lesions limited to the C5-C6 spinal nerves we never observe prominent reduction of wrist extension when we resect a neuroma of the superior trunk followed by nerve grafting. This implies that there is sufficient innervation from C7 and C8 to maintain a proper wrist extension with the extensor carpi radialis and ulnaris muscles, see Zhang et al.[21] All in all, it seems therefore unlikely that neuroanatomical factors are involved in the reduction of gripforce in C5-C6 NBPP lesions.

An indirect explanation of the reduced gripforce of the hand on the affected side in children with NBPP might be the reduced use the affected side less often, and this in turn may lead to a decreased force. The factors causing less use of the hand caused by impaired spatial positioning due to a limited shoulder function, and diminished dexterity due to reduced sensibility. These factors have been investigated and it has been shown that the ability to incorporate the affected arm and hand in a co-ordinated movement pattern correlated with sensation and prehension of the hand, but not with shoulder and elbow function, see Dumont et al.[22]

We found no statistical correlation between gripforce and sensibility, between gripforce and external rotation, or between gripforce and bimanual use. Because of the absence of such correlations, a direct relationship seems unlikely. One might cautiously conclude that other factors, which have so far not been defined or measured, play a causative role. One of these might be cerebral control which is potentially disturbed in the development of central motor programs. In clinical observations and fMRI data, we found evidence of changes in central control see Anguelova et al.[23 24] It was previously hypothesized that a diminished tactile input to the brain could explain diminished embedding of movement of the affected arm, which was coined ‘developmental apraxia’, see Brown et al.[25] Strombeck et al[26]

concluded considerable EMG changes observed in NBPP, even within fully recovered children. We previously assessed sensibility with 2PD and SW filaments, and found that the index finger is the most sensitive finger tested with the 2PD test, and the thumb with the SW, see Buitenhuis et al.[10] Sensibility of thumb and index finger are essential to perform fine motor tasks, and it proved to be these fingers that showed diminished sensibility in the children with an upper trunk lesion. The absence of a correlation between gripforce and sensation in this study, does not exclude a role of sensation. Disruption of proprioception might be of more relevance, rather than the tactile sensation we tested, see Figure 2.

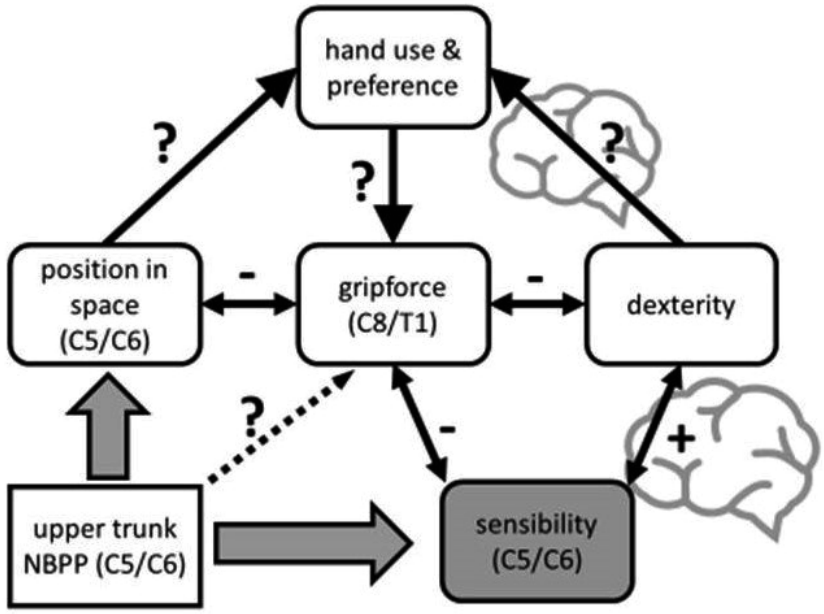

Figure 2 Potential correlations between sensibility, gripforce and dexterity to explain diminished hand use in children with NBPP

Legend Figure 2

– no correlation (current paper); **+** correlation according to Buitenhuis et al[5]

An attempt to explain diminished hand use in children with an upper trunk NBPP lesion. Diminished upper trunk function results in diminished sensibility of the hand and diminished shoulder function, but cannot anatomically explain diminished gripforce. Cerebral control may play a role to connect sensibility and hand use.

For the execution of a fine coordinative movement, such as threading a wire through holes in a board or constructing a triangle with nuts and bolts, both proprioceptive and tactile sensibility are more important than force.

In this series, the non-injured dominant hand had a 10-15% decreased gripforce compared to the dominant hand in controls both in children who had undergone nerve surgery as well as in children who had a presumed dominance shift. These differences were not statistically significant, and may be a result of chance. However, we feel that this observation deserves further study as the absence of statistical significance can also be caused by the relatively limited size of our cohort. Not surprisingly, a dominance shift occurred frequently in surgically treated children who suffered a more severe nerve lesion than conservatively treated children. We hypothesize that a shift of hand dominance affects the dominant non-injured side at the cerebral levels of movement control, causing an additional disadvantage for learning bimanual activities. A cortical dominance shift has been described earlier in relation to speech development, see Auer et al.[27]

Finally, our findings may be relevant for strategic choices in brachial plexus repair. Fascicles from the ulnar and median nerves are used as donors in transfers to the biceps and brachialis motor branch to reanimate elbow flexion in case of root avulsion in NBPP. Although the use of these fascicles might jeopardize hand function development, hand dysfunction was not found following the use of either the ulnar or median fascicle in a small series of 8 patients, see Siqueira et al.[28] In this series, however, only the affected hand was examined, and findings were not related to the non-affected side or healthy controls. Since we show that gripforce is reduced even in upper lesions, it might actually be the case that more hand function is lost due to the application of this technique than is currently appreciated.

One limitation of our study is that the participating children were followed at our tertiary referral clinic, and as a result, surgically treated children were overrepresented in our sample. Surgical procedures were diverse, but gripforce did not statistically differ in different surgical groups. Additionally, children with a good clinical recovery after surgery or conservative treatment usually do not have a long follow-up and are, therefore, underrepresented in the current study. Another limitation of our study is that we did not systematically document whether the use of the hand was diminished, but rather documented it anecdotally when parents reported it during visits of our clinic. Future

studies should include patient reported outcome measures for example the Hand-Use-at-Home questionnaire to document the frequency of hand employment, see Van der Holst et al.[29]

In summary, various explanations have been offered for the diminished hand use in children with NBPP with an upper palsy. (Figure 2) In the current study, children appeared to have a diminished gripforce. This finding was not directly correlated to diminished sensibility or other factors.
More research is needed to fully understand the diminished hand usage and gripforce in upper trunk NBPP. It is advised to assess the dominant non-injured hand in future cohorts, and its role in dexterity and bimanual activities. This may ultimately provide clues for designing tailored physical or occupational therapy to improve hand usage.

CONCLUSION

We found a reduced gripforce of the hand in children with an upper neonatal brachial plexus lesion, which we hypothesize to be caused by diminished use of the hand, and diminished cerebral control. Additionally, the non-injured hand had diminished grip force, especially in children with a presumed dominance shift, which may further impair their bimanual ability.
We did not find a relationship between gripforce and sensibility, bimanual use or shoulder external rotation function.

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Chapter 7

Neonatal Brachial Plexus Palsy and Central Developmental Disability

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Early Hum Dev. 2012 Sep;88(9):731-4

Abstract

Objective

First, to assess whether children with an neonatal brachial plexus palsy (NBPP) have a higher incidence of Central Developmental Disability (CDD) compared to the general population. Second, to test the ability of fidgety General Movements (GMs) to identify CDD children already at three months of age.

Patients and Method

From a prospective cohort study of 48 infants with NBPP, for 38 children videos were available to assess GMs at the age of 3 months. Demographic data and severity of the brachial plexus lesion were additionally scored. At a mean age of 4.8 years the children were evaluated for the presence or absence of CDD.

Results

Five patients (13%) had CDD. One patient had a cerebral palsy and four showed definite other motor and/or mental problems. There was no correlation between the quality of the GMs at three months and CDD. There was no correlation between the severity of the nerve lesion and CDD. We found a correlation between quality of the GMs and severity of the nerve lesion.

Conclusions

Children with NBPP have a high incidence of CDD. In our cohort fidgety GMs had no predictive value for CDD at a later age.

INTRODUCTION

Neonatal brachial plexus palsy (NBPP) are caused by traction during delivery.[1, 2] The resulting nerve injury may vary from neurapraxia or axonotmesis to neurotmesis and avulsion of rootlets from the spinal cord. The degree of spontaneous recovery correlates inversely with the severity of the nerve lesion.

The upper part of the brachial plexus is most commonly affected, resulting in paresis of shoulder abduction, external rotation and elbow flexion. In more severe cases, the remaining parts of the plexus are also involved.

Fortunately, most children show good spontaneous recovery. Despite important flaws in methodology of natural history studies, it may be concluded that the percentage of children with residual deficits probably ranges between 20 and 30 %.[3]

NBPP is a disorder of the peripheral nervous system. In our tertiary NBPP referral center, we are regularly confronted with infants with coinciding developmental problems or neurological disorders of the central nervous system. For instance, we saw children with NBPP and cerebral palsy (CP), developmental coordination disorder or mental retardation, but also behavioural problems, such as Attention Deficit Hyperactivity Disorder (ADHD). For the purpose of this study, all of these entities are grouped and referred to as Central Developmental Disability (CDD). It appeared that such problems occur more frequently in children with NBPP than in the normal population; to our knowledge, however, systematic research on the presence of coinciding CDD in children with NBPP has not been performed so far. Only one previous publication described a high incidence of developmental and behavioural problems in surgically treated NBPP infants.[4]

A correlation between the occurrence of NBPP and CDD seems logical. Children with NBPP usually have a history of a difficult delivery. Such a frustrated delivery is correlated with a higher incidence of performing multiple obstetric manoeuvres and prolonged second stage of labour.[5, 6] An additional consequence of a traumatic delivery could potentially be damage to the central nervous system, which in turn might lead to developmental delay or neurological disorder.

CDD can be predicted by scoring General Movements (GMs) in children of 3 months of age. These GMs are spontaneous movements of all body parts. GMs have shown to be a reliable tool for the prediction of central neurological problems; especially the quality of fidgety GMs

at the age of three months has a high predictive value for developmental outcome at later age.[7] Abnormal GMs have an incidence of 5% in the general population.[8] The incidence in the Dutch population of developmental problems is around 4%[9], of cerebral palsy 0.1-0.2%[10] and of ADHD 3-5%.[11]

We studied whether our population of children with NBPP have a higher incidence of CDD as compared to the general population. In addition, we examined whether the GM score can predict which children with NBPP are at risk of CDD. Finally, we looked at correlations between the severity of the nerve lesion, the quality of the fidgety GMs and the presence of CDD.

PATIENTS AND METHODS

The present study was part of a larger project on the value of early electromyography (EMG) to predict outcome in NBPP.[12] The study protocol was approved by the Medical Ethics Committee of the LUMC. Patients were actively and prospectively recruited by announcing the study to appropriate medical specialists in the Netherlands. After informed consent, three visits were scheduled around 1 week, 1 month and 3 months of age. Infants who could not be seen before 2 months of age were excluded. In total 48 infants were included. The infants were filmed at the age of 3 months (mean 87 days, median 87, range 29) in a supine position during 10 minutes without interruption. The recordings were independently scored according to a standardized protocol[9] by two experienced investigators (SB and MSvW). The fidgety GMs are usually scored in all limbs; in this study the paretic arm was not included. The complexity, fluency and variety of fidgety movements were classified as normal-optimal, normal-suboptimal, mildly abnormal and definitely abnormal. (Table 1)

Table 1 Classification of quality of general movements[7]

Classification		Complexity	Variation	Fluency
Normal	Normal-optimal	+++	+++	+
	Normal-suboptimal	++	++	-
Abnormal	Mildly abnormal	+	+	-
	Definitely abnormal	-	-	-

Fidgety GMs can only be reliably scored in the appropriate behavioural states (not crying, awake).[7] Whenever the patient was not in the appropriate behavioural state the GMs were not scored.

Demographic data and severity of the brachial plexus lesion were additionally scored. The severity of the NBPP was qualified as either severe or mild.[12] A severe nerve lesion was defined as neurotmesis or avulsion of the roots C5 and C6 (irrespective of the function of the roots C7-C8-T1). A mild lesion was defined as an axonotmesis lesion of C5 and C6 with spontaneous recovery after two years of follow-up of a full range of active elbow flexion, a normal or subtotal range of supination and a normal or nearly normal shoulder function without prominent secondary abnormalities.

Central developmental disability (CDD) was defined in the current analysis as any mental and/or neurological impairment, which was diagnosed or confirmed by an independent specialist, such as the referring paediatric neurologist or paediatric rehabilitation specialist. The final chart review for CDD took place when the infants had a mean age of 4.8 years (range 4.1-5.6).

Statistical analysis

The statistical analysis was performed with the SPSS statistical package 17 (© SPSS Inc). For correlation of the GMs and the severity of the nerve lesion or presence of developmental impairment we applied the chi-square test and the Mann-Whitney test. A p-value of < 0.05 was considered statistically significant.

RESULTS

Of the initial 48 infants, two parents decided to abort the study before the third month, because good spontaneous recovery occurred before that time. A video film could not be made due to technical problems in three infants and it was not possible to score the GMs due to an inappropriate behavioral state of five patients. Eventually, 38 recordings could be scored and were further analyzed. (Figure 1)

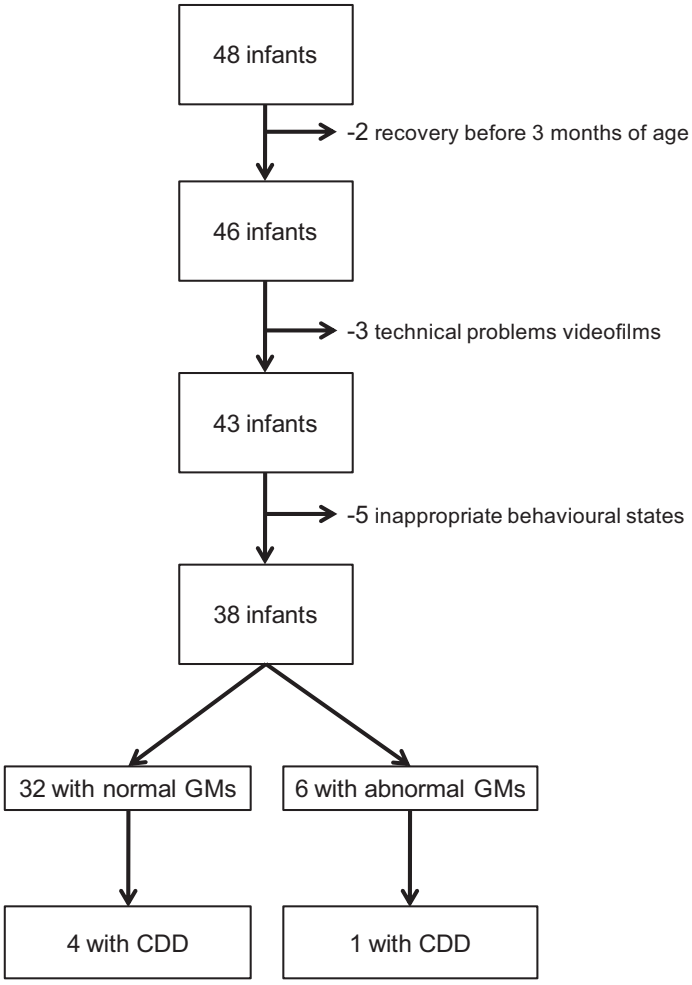

Figure 1 Inclusion and results.

The results of the analysis of the video recordings are presented in Table 2, the inter-observer agreement was 100% (kappa = 1).

A total of five patients had CDD. One patient had a cerebral palsy, and four showed definite other motor or mental problems. The percentage of patients with CDD was 13% (95% confidence interval 2.4-24%). (Table 3) The patient with a cerebral palsy showed normal GMs. The other four showed abnormal GMs in one patient and normal GMs in three patients. (Figure 1, Table 3)

There was no correlation between the quality of fidgety GMs and the presence of CDD.

Table 2 Fidgety GMs, classified by nerve lesion (n = 38)

Fidgety GMs	Severity of NBPP		Total
	Mild	Severe	
Normal-optimal	18	3	21
Normal-suboptimal	5	6	11
Mildly abnormal	1	4	5
Definitely abnormal		1	1
Total	24	14	38

Table 3 Details of five patients with CDD

Condition	GMs score	Nerve lesion
CP: Spastic paresis of both legs	o	Severe
Suspect for developmental coordination disorder and currently examined for epilepsy	so	Mild
Generalised hypotonia and concentration difficulties	a	Severe
ADHD, Motor clumsiness	o	Mild
Clumsy motor behavior, developmental coordination disorder	o	Mild

Legend Table 3
o = optimal; so = suboptimal; a = abnormal

Fourteen children had a severe nerve lesion and the remaining 24 children had a mild nerve lesion. In the group of infants with a severe nerve lesion, four infants had mildly abnormal GMs and one had definitely abnormal GMs.(Table 2) Of five patients with CDD, two had a severe nerve lesion and three a mild nerve lesion.

A statistically significant different distribution was found for GM quality and nerve lesion severity (chi-square = 11.790, with 3 degrees of freedom, p = 0.008). Infants with a severe lesion had worse GM scores. (Figure 2) The Mann-Whitney test confirmed statistically significance between the two groups (p = 0.001, two-tailed test).

There was no statistical difference for distribution of CDD and nerve lesion severity.

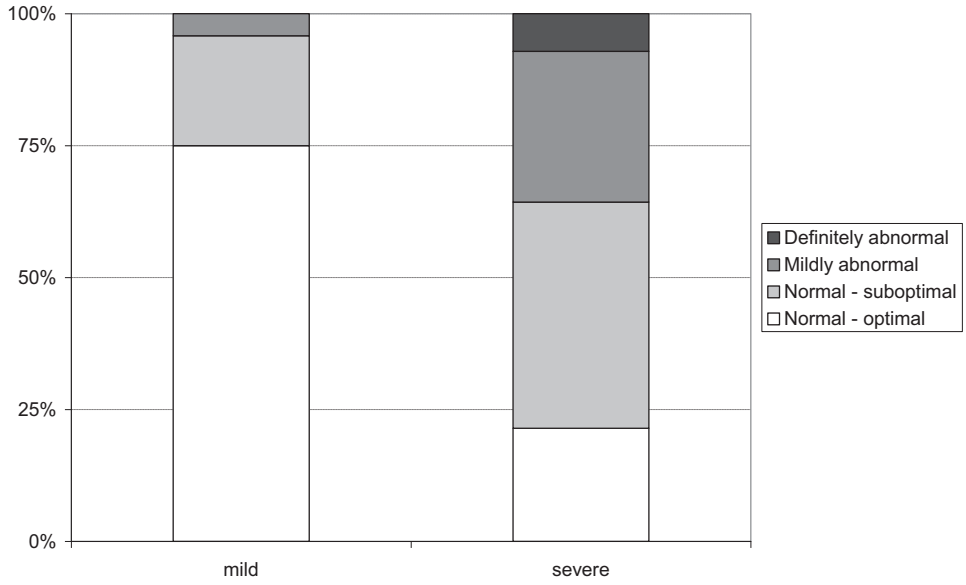

Figure 2 Stacked column chart showing the distribution of the quality of GMs in severe (n = 24) and mild nerve lesions (n = 14).
p = 0.008 (chi-square = 11.790, with 3 degrees of freedom)

DISCUSSION

The first aim of our study was to investigate the incidence of CDD in NBPP infants. (Figure 3) We found that 5 of 38 (13%) of the study group had a motor or developmental impairment in some way. This is higher as compared to the general population. The exact percentage may, however, not be accurate (95% confidence interval 2.4-24%) as our sample population was small. In the Netherlands, CP has an incidence of 0.15 %[10], and CDD / ADHD has an incidence of 5%.[13]

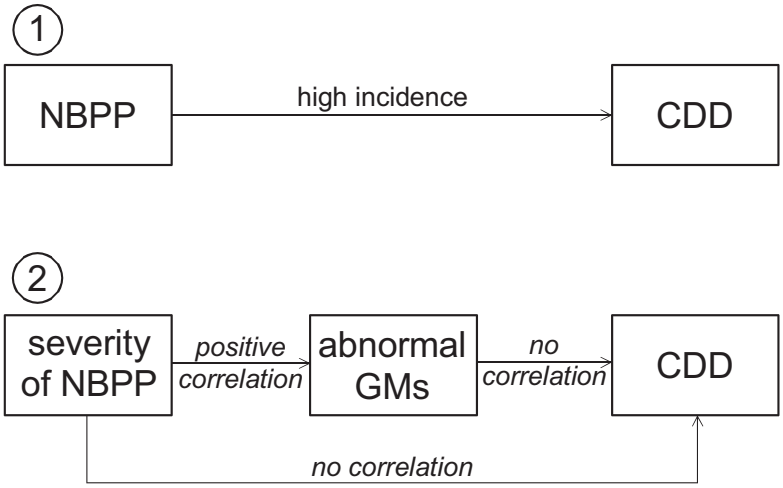

Figure 3 Results: relationships between NBPP, abnormal GMs and CDD

It remains speculative how to explain this apparent higher incidence of coinciding CDD in case of NBPP. One hypothesis is that shoulder dystocia is a risk factor for NBPP. During shoulder dystocia, the risk of hypoxic ischaemic encephalopathy increases with prolonged head-to-body interval.[14] Hypoxic ischaemic encephalopathy may result in cerebral palsy.[15] More recently it was described, that mild or moderate asphyxia is also a risk factor for the development of cognitive/executive dysfunction or memory and/or attention problems, such as we found in our patient cohort.[16, 17]

Our finding of a high incidence of coinciding CDD in NBPP infants, is in accordance with one previous report. Around half of twenty-three nerve surgically treated NBPP infants scored at or above the cut-off score of twelve of the Pre-School Behaviour Checklist.[4] The effects in this cohort were independent of the general condition of the child at birth, as indicated by their Apgar scores.

Our second aim was to test correlations between CDD, quality of GMs and severity of the nerve lesion. In the general population abnormal GMs have an incidence of 4%.[8] In our population, we found that 6 of the 38 children (16%) had a diminished quality of fidgety GMs (5 mildly abnormal, 1 definitely abnormal). This high prevalence could be indicative for a higher risk of these 6 patients for developmental disability at a later age. At follow-up the diminished quality of the GMs could not be correlated to the presence of CDD. There was,

however, a correlation between the severity of the nerve lesion and the quality of the GMs: in patients with a severe nerve lesion, an increase in abnormal and suboptimal GMs was found. (Figure 3)

There was no correlation between the severity of the nerve lesion and presence of CDD. In an earlier study, we studied children with a NBPP and the age of independent walking.[18] We found that 80% of children could walk independently at a normal age of 12.1 months (SD 1,8 months, P1: 8,2 months, P99 17.6 months).[19] There seemed to be a delay in about 20% of children, which did not correlate with the severity of the nerve lesion.

We tried to predict the occurrence of CDD at a later age using GMs at the age of three months. GMs are spontaneous movements of all body parts which can be observed during pregnancy and early childhood. The quality of the fidgety GMs at the age of three months has a high predictive value for development disorders at later age. Especially the presence of *definitely abnormal* GMs at fidgety age, which implies a total absence of the elegant, dancing complexity of fidgety movements, has a claimed accuracy of predicting cerebral palsy of 85% to 98% in high-risk populations.[7] The remaining 2-15% of infants with definitely abnormal GMs show other developmental problems, such as minor neurological dysfunction, attention deficit hyperactivity disorder or cognitive problems. *Mildly abnormal* GMs at fidgety age are related to the development of minor neurological dysfunction, attention deficit hyperactivity disorder and aggressive behaviour, but the accuracy to predict these problems is modest due to relatively many false positives, resulting in a small positive predictive value.[7, 20]

In our present patient series only one child was scored as having definitely abnormal GMs. This patient developed a generalized hypotonia and concentration problems. The remaining four children that showed CDD during follow-up scored normal or suboptimal GMs. From the one patient that proved to develop a spastic paresis of both legs, the fidgety GMs were scored as normal.

The reasons why prediction of CDD on the basis of the GMs in our patient group was not possible, remains speculative. As we found CDD in 13% of our cohort, NBPP infants may be considered a high-risk group. Two hypothesis will be discussed.

First, fidgety GMs may not be reliably scored in the presence of an NBPP, due to the presence of upper limb paresis on one side. The diminished quality of fidgety GMs might be the result of the paresis. However, 3-month-old infants were investigated with one or more fixed or immobilized arm.[21] Immobilization can be considered to result in a comparable to that in NBPP. It was found that immobilization did not influence the quality of fidgety GMs[21]. The evaluation of GMs in children with an NBPP should therefore, theoretically, not be hindered by the presence of the paresis.

A second reason for the present results could be that the applied methodology to assess developmental disorders was inappropriate. The mean follow-up time of 4.8 years might have been too short. Minor developmental problems are usually only diagnosed in children beyond the age of eight years. In addition, a validated method to assess motor development in children with NBPP does not exist. The available scoring methods, like the Bayley Scales of Infant Development[22] and the Movement Assessment Battery for Children[23], depend on bimanual activity of the examined child. It is intuitive that these scoring methods cannot be applied to infants that have an NBPP.

Weaknesses of our study consist firstly of an inclusion bias. The investigated patients were actively recruited for enrolment in the EMG-study and seen at our tertiary referral centre. This may lead to an overestimation of the part of patient with a severe nerve lesion. However, as the present study has a descriptive nature, this should not influence our results. Secondly, the investigators were not formally blinded to the severity of the nerve lesion. Although the affected arm was not taken into account during the evaluation of the fidgety GMs, both investigators have substantial clinical experience in patients with an NBPP to recognise a severe or mild nerve lesion. This might have influenced the scoring of GMs one way or another.

CONCLUSION

Children with NBPP have a higher incidence of central neurological or development problems. In a cohort of 38 patients with NBPP we found a diminished quality of fidgety GMs at the age of three months. However, this could not be matched to developmental disorders at a later age. There was no relationship between the severity of the NBPP and later

developmental problems. Because the incidence of developmental disorders was quite high, the results of this study support a long-term follow-up of infants with an NBPP, with special attention to developmental disorders. A validated development test for children with a NBPP should be developed and applied in this age group.

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Chapter 8

The Milestone of Independent Walking is delayed in Infants with a Neonatal Brachial Plexus Palsy

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Submitted

Abstract

Objective

A Neonatal Brachial Plexus Palsy (NBPP) results from traction to the nerves of the arm. Developmental apraxia may occur as the nerve lesion takes place in a critical time window of brain development. The gross motor development has, so far, received little attention. One of the milestones of gross motor skill development is the age at which children can walk independently (AWI). AWI has not been systematically assessed in children with NBPP.

Patients and methods

The parents of 135 children with unilateral NBPP were questioned for the AWI during regular outpatient clinic visit. The results were compared with an international normative WHO study for a normal population (n = 794) in which the mean AWI was 12.1 months (SD 1.8). We analyzed the effects of nerve lesion severity, Apgar-score, and ethnicity.

Results

The mean AWI in NBPP was 14.49 (SD 2.99). This was significantly later than in the normal population ($p < 0.0001$). The mean delay was 2.4 months. Only two-thirds of children with NBPP walked independently, when 95% of the normal population already did. Lesion severity or Apgar did not affect AWI.

Conclusion

AWI is delayed in children with NBPP. The etiology is unclear and may be related to central developmental disability, incomplete function of the affected arm, asphyxia or immobilization during NBPP treatment. Systematic determination of AWI is important and if delayed then it is relevant to look for the cause. Additionally, it can be used to guide physical and occupational therapy.

INTRODUCTION

Neonatal brachial plexus palsy (NBPP) is a nerve traction injury that occurs during birth. The brachial plexus is formed by the spinal nerves C5 through T1; the most common NBPP lesion type involves the two upper spinal nerves (C5 and C6) affecting shoulder function and elbow flexion. The extensor function of elbow, wrist and fingers is diminished when the C7 nerve is also damaged. In more severe lesions, C8 and T1 are involved as well, resulting in partial or total loss of hand function.[1]

A NBPP does not only affect the peripheral nerves, but the development of cortical programs of the affected arm as well. This is likely due to the lack of afferent input during a critical time window resulting in what was coined 'developmental apraxia' or 'dyspraxia'.[2, 3] Central reorganization during movements of the affected arm occurs as shown in functional MRI studies.[4] Other examples of developmental apraxia are, for instance, the absence of an automatic swing of the affected arm during running and walking, the absence of unvoluntary compensatory movements of the arm to keep balance,[5] and a different gait pattern.[6]

The gross motor development of children with a NBPP has, so far, received little attention although there are some indications that it may be disturbed. For instance, increased compensatory movements on the unaffected side were seen in 3- to 5-month-old children with a NBPP, whereas the quality of fidgety movements was not found diminished.[7] In contrast, in an earlier study we found that the quality of fidgety movements was diminished and that a correlation with the severity of the NBPP lesion existed.[8]

Normally, infants begin to move their hands and use visual control to reach for an object at about 4 months of age.[9] The development of eye-hand coordination is hampered if, at that time, the positioning of the hand is impaired by muscle weakness of the shoulder and arm as is the case in NBPP. Additionally, the ability to bring both hands to the mouth may be reduced further affecting the possibility to explore objects. Moreover, leaning on both elbows to obtain a prone position might prove difficult due to disbalance, which affects the ability to explore the surroundings. When babies with a NBPP start sitting, their sitting position is often asymmetric, with their bodyweight towards the healthy side. Sometimes, children even use their knee to support the affected arm.[3] The lack of positioning of the hand in space is often compensated by rotation of the trunk and spine[10], which may be especially caused by a lack of glenohumeral external rotation.[11] Additionally, disturbance of

keeping balance was observed in NBPP.[3] The limitations change the possibilities and way the children with NBPP play which, thereby, affect the normal development of central motor programs.

In patients with a NBPP, it might be helpful to have a simple proxy which can be used to detect the presence of gross motor program disturbances. The age at which children were walking independently (AWI) is one of the gross motor milestones used to assess the overall development in child health. Other milestones are sitting, crawling and standing. The age of achieving the milestones is a signal for screening the overall development of an individual child.[12] Additionally, delay in achieving the milestones is relevant for planning rehabilitation treatment. AWI has not been systematically assessed in NBPP.

In the present paper, we studied whether AWI in children with a NBPP may be delayed.

PATIENT AND METHODS

The parents of 139 consecutive children with a unilateral NBPP who visited the outpatient clinic in the year 2003, were recruited for the study. The mean age of the children was 3.8 year (range 1-11) at that time. The parents were asked what the AWI of their child was, as most parents can remember this milestone.[13] The age was noted in months. The severity of the NBPP lesion, nerve surgical treatment, the Apgar scores were extracted from the patient files and ethnic background was asked at the parents. The Apgar score at 5 minutes[14] was analyzed (n = 86) as dichotomous variable. We employed a cut-off value of 7 as infants with an Apgar score lower than 7 have greater risk for developmental delay.[15] Four children were diagnosed with cerebral palsy at a later age and were excluded, which left 135 parents for analysis, see Table 1 for patient characteristics.

We compared AWI with an international normative WHO study, which prospectively assessed 794 healthy children in six countries worldwide.[12, 16]

Table 1 Patient characteristics

Number of patients		135
Gender	Male / Female	71 / 64
Age (years)	Mean	3.8
	Range	1 – 11
Nerve surgery	yes / no	115 / 20
Level of lesion	C5-C6	77
	C5-C7	36
	C5-T1	8
	C5-C8	14
Apgar score 5 min (n = 88)	Apgar < 7	n = 24
	Apgar 7 - 10	n = 64
	Mean (SD)	7.35 (2.23)
Ethnicity	Caucasian / non-Caucasian	89 / 46

Legend Table 1
SD: Standard Deviation.

Statistical analysis

Data were analyzed with SPSS Statistics for Windows, version 28 (IBM Corp. Armonk, NY). The error level was set at $p < 0.05$. For continuous outcome variables, t-test were used for comparison of means; linear regression was employed for multivariate analysis, under the assumption of the central limit theorem for the current large sample size.

RESULTS

The mean AWI was 14.5 months (median 14, range 9-24, SD 3.0). For the normal population, the mean AWI was 12.1 months (SD 1.8; n = 794).[16] The difference between the AWI of the NBPP group and normal population was significant ($P< 0.0001$). We analyzed the effect of gender, nerve surgery, Apgar score and ethnicity on AWI using t-tests. The only statistically significant factor was ethnicity ($p = 0.001$, Table 2). We performed linear regression, which showed that ethnicity remained a factor in the multivariate analysis.

Table 2 Univariate analysis of the age (month) of independent walking

Factor		AWI (SD)	p (t-test)
Gender	Male	14.31 (2.98)	0.174
	Female	14.91 (3.07)	
Nerve surgery	Yes	14.59 (3.02)	0.327
	No	13.9 (2.82)	
Ethnicity	Caucasian	15.09 (0.318)	0.001*
	Non-Caucasian	13.33 (0.255)	
Apgar-score	< 7 (n = 24)	15.04 (3.043)	0.722
	7-10 (n = 64)	14.78 (3.026)	
Lesion severity	C5-C6	14.44 (2.53)	#
	C5-C7	14.05 (3.25)	#
	C5-C8	14.83 (3.71)	#
	C5-T1	15.79 (4.15)	#

Legend Table 2

Four different factors were analyzed to assess its effect on the age of walking independently.

AWI: mean age in months; SD: standard deviation;

* statistically significant; # all combinations were tested, p > 0.05 for all.

We additionally analyzed whether lesion severity (number of affected roots) had a relationship with AWI. There were no statistically significant differences when comparing all combinations of severity groups (p > 0.05, Table 2).

We performed linear regression in two ways, a) including all 135 children b) including 88 children for whom the Apgar score was available (Table 3). In both analyses ethnicity was a significant factor, in the second analysis nerve surgery was a significant factor.

The distribution across percentiles and the cumulative percentage of NBPP for age comparing the study group and the normative WHO group is presented in Table 4 and Figure 1. Only 31.1% of children in the NBPP group was walking independently (4th column), when 50% of the normal population already did (1st column). When 95% of the normal population had started walking independently, only two-thirds of children with NBPP had reached this developmental milestone.

Table 3a Linear regression analysis for n = 135, all children

Parameter		B	SE	t	Significance	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept		14.650	1.128	12.989	0.000*	12.418	16.882
Severity	C5-C6	-1.143	0.847	-1.351	0.179	-2.818	0.531
	C5-C7	-1.396	0.914	-1.528	0.129	-3.205	0.412
	C 5-C8	-1.306	1.427	-0.915	0.362	-4.129	1.517
	C5-T1	0[a]	-	-	-	-	-
Ethn	Caucasian	1.604	0.539	2.976	0.003*	0.538	2.670
	Non-Caucasian	0[a]	-	-	-	-	-
Nerve Surgery	Yes	0.259	0.720	0.360	0.720	-1.165	1.684
	No	0[a]	-	-	-	-	-
Gender	male	-0.639	0.508	-1.257	0.211	-1.644	0.366
	female	0[a]	-	-	-	-	-

Table 3b Linear regression analysis for n = 88, for children of whom the 5 minute Apgar score was available.

Parameter		B	SE	t	Significance	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept		17.018	1.433	11.875	0.000*	14.166	19.870
Severity	C5-C6	-1.764	0.970	-1.818	0.073	-3.695	0.167
	C5-C7	-2.531	1.052	-2.406	0.018	-4.624	-0.438
	C 5-C8	-2.420	1.656	-1.462	0.148	-5.716	0.875
	C5-T1	0[a]	-	-	-	-	-
Ethn	Caucasian	2.437	0.676	3.606	0.001*	1.092	3.782
	Non-Caucasian	0[a]	-	-	-	-	-
Nerve Surgery	Yes	-2.163	1.021	-2.118	0.037*	-4.196	-0.130
	No	0[a]	-	-	-	-	-
Gender	male	-0.299	0.611	-0.490	0.626	-1.516	0.917
	female	0[a]	-	-	-	-	-
Apgar 5 min	7 - 10	0.249	0.665	0.375	0.709	-1.074	1.572
	< 7	0[a]	-	-	-	-	-

Legend Table 3

Parameter estimates from multiple linear regression; dependent variable: Age (months) of independent walking.

B: regression coefficient; SE: standard error of B; t: coefficient divided by its standard error; [a]: set to zero because it is redundant, * statistically significant

Table 4 Overview of percentiles of walking independently of NBPP and controls

Percentile	Normal (n = 794) Age (months)	NBPP (n = 135) Age (months)	NBPP (n = 135) Cum%
1	8.2	9.4	0
3	9	10	0.7
5	9,4	10	0.7
10	10	11	5.2
25	11	12	14.8
50	12	14	31.1
75	13.1	17	44.4
90	14.4	18	57.0
95	15.3	20	64.4
97	16	21	74.1
99	17.6	23.6	79.3

Legend Table 4

Cum%: Cumulative percentage in NBPP for age of normal children.
Only 31.1% of children in the NBPP group was walking independently (4th column), when 50% of the normal population already did (1st column). When 95% of the normal population (1st column) started walking independently, only 64.4% of children with NBPP (4th column) had reached this developmental milestone.

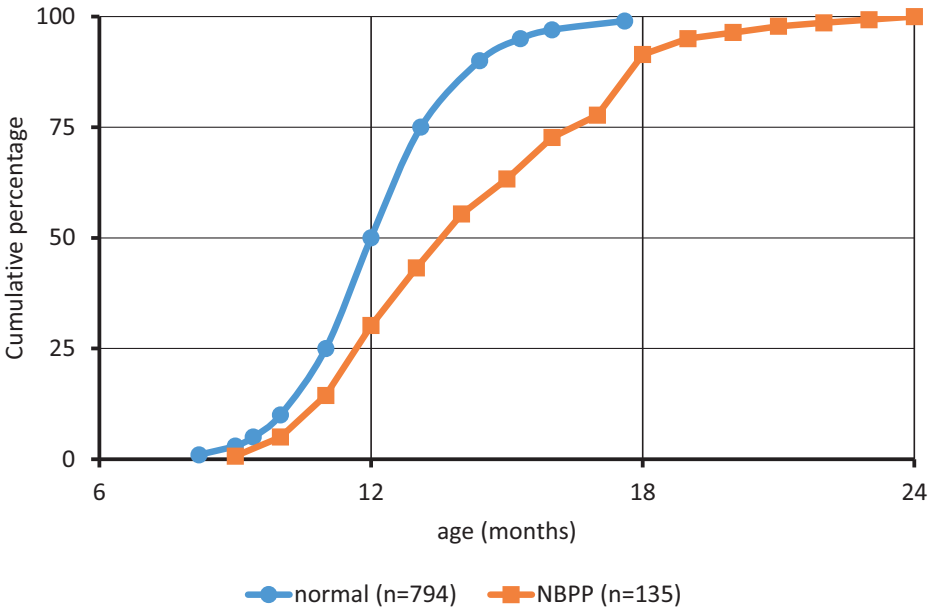

Figure 1 *Cumulative percentage of children (Y-axis) that attained walking independently per age (in months) on the X-axis*

DISCUSSION

In the present study, we found that AWI in children with a NBPP was significantly later than in a normative WHO group.[16] The mean AWI was 14.5 and 12.1 months, respectively. Although this 2.4-month delay may not be relevant for the individual child, this finding is relevant as it may signal delayed gross motor development in patients with NBPP, a possibly underestimated feature in this patient group. It is an important aspect for therapists to include in their evaluation and therapy, and it is important for parents also to know that independent walking may be delayed.

More than half of the children with a NBPP were later than the 75th percentile of the normative group. In our multivariate analysis, ethnicity and nerve surgery were predictive factors. As ethnicity was also a factor in the normative control group, this finding was expected. Nerve surgery was a significant factor in one of the linear regression models, while it was not in the univariate analysis. Children with a more severe NBPP (as they were indicated for nerve surgery) had a 2 months shorter AWI in the regression analysis. This

seemingly contradictory finding may be due to the small number of conservatively treated children (n = 9) in the second linear regression model. Nerve lesion severity as expressed as the number of roots affected, did not correlate with AWI. No significant difference was found in AWI between four levels of neurological lesion severity. Therefore, motor performance of the arm may not be the sole or most important determining factor. Central nervous system development may be of key influence on AWI. The exact mechanism why AWI is delayed in children with a NBPP remains unclear.

The delay of AWI in children with a NBPP can be explained in four ways. Firstly, gross motor development is delayed and the milestone AWI is a representative feature of this delay. The risk of having central developmental disability in children with a NBPP is increased. In as much as 13% of 35 children with a NBPP had a central developmental disability at the age of 5.[8] In addition, functional MRI analysis of patients with a NBPP suggested that brain functional disturbances are present and extend beyond the sensorimotor network, and cascades serial remodeling in the brain.[17] NBPP occurs at a critical period of development of the sensorimotor cortex and premotor cortical areas. As both proprioceptive and sensory afferent nerves and efferent nerves are damaged in this timeframe, this may have a profound effect on cortical development of motor programming. If gross motor development is indeed delayed, other milestones such as sitting, crawling and standing, should than also be delayed, which should be the subject of further study.

Secondly, the delay in AWI might be explained by the incomplete function of the affected arm. After all, movements that precede walking or aid in walking, are hampered. The children can't pull themselves up properly which is necessary to stand and later walk, or they missed the crawling stage which is preliminary to walking. Parents frequently mention that their child shoves on the buttocks to move around for a prolonged period of time, instead of crawling or walking. A previous study showed significant difficulties with keeping balance at the age of 5-15 years.[3] Children with a NBPP may, therefore, be hampered to walk in the absence of balance control. In the current study, the severity of the nerve lesion, either expressed as the necessity of nerve surgery, or expressed as the number of roots involved in the lesion, did not correlate with AWI. This finding makes it less likely that the nerve lesion itself is the main limiting factor for independent walking.

Thirdly, most children with a NBPP have suffered a traumatic birth which may in itself lead to developmental delay as a result of asphyxia. As such, this factor would probably be reflected

in a relationship with the Apgar score. The risk of developmental vulnerability at 5 years of age was found to be inversely associated with the 5 min Apgar score across its entire range.[14] In the present study, however, the Apgar score at 5 minutes was not independently related to AWI, so it seems unlikely that this factor is explanatory in this patient cohort. Fourthly, in children who have undergone nerve surgery at an early age, the surgery itself and the postoperative immobilization may play a role. We believe that this factor is of minor importance.

The mean weakness of our study was that the age of AWI was retrieved from the memory of the parents. They were questioned retrospectively after about four years. Correct parental recall of developmental milestones like AWI has been shown to be accurate frequently, although there was a greater discrepancy associated with an increased lapse of time from the event.[13] In our cohort, the distribution of walking independently showed two peaks, at 12 and 18 months. This is most likely caused by the way parents answered AWI as 'one year' or 'one-and-a-half year', as they could not exactly remember the age in months. Additionally, the definition of AWI was broadly defined in the present study. Parents may have remembered when their child made their first few wobbly steps, or when they could make several steps in a row. We feel, however, that these uncertainties do not disregard the findings of our paper due to the large cohort we studied and the big difference we found compared with the normative group. A second weakness was that the NBPP study population was from a tertiary referral center for nerve lesions, which most likely is skewed towards the more severely affected children. This is reflected in the high percentage of children who were treated with nerve surgery at a young age. An additional weakness, is that the AWI in our cohort was compared with a cohort from the literature instead of a control group from our own region, which may have reduced straight statistical comparison. A recent meta-analysis showed that most physical therapy interventions focus only on the affected arm.[18] The main significance of our paper is to draw attention to the relevance of monitoring the general development of children with an NBPP. Physical and occupational therapy should not only focus on the affected arm, but a broader view is necessary. Therapy needs to start as early as possible to signal any delay of the general senso-motor development, and to attempt supportive therapy. Special attention is needed for the development of proper balance.

CONCLUSION

Children with a NBPP have a delay of 2 months in AWI. More than half of the children with an NBPP are later than the 75th percentile of a WHO normative group. The underlying cause for the delay in AWI is unclear, but could be related to a delay in gross general motor development. Other factors, such as a diminished balance, may play an additional role. Since AWI is delayed, physical and occupational therapy should not only focus on the affected arm, but on general motor development as well.

Acknowledgements: we thank Ron Wolterbeek, Department of Medical Statistics, for his advice and aiding in the analysis.

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Chapter 9

Summary and General Discussion

The main findings of this thesis

1. The sensibility of the thumb and index finger in healthy children is superior to that of the third, fourth and fifth fingers.
2. Children with an upper NBPP have a diminished sensibility of the thumb and index finger.
3. A diminished sensibility of the thumb and index finger in upper NBPP correlates with diminished dexterity.
4. The ability to localize stimuli to the thumb, index, third and fourth fingers is disturbed in children with an upper NBPP.
5. Most children with an upper NBPP are not aware of the diminished sensibility in their affected hand.
6. NBPP is a peripheral nervous lesion, which affects the developing central nervous system as well.
7. Grip force of the hand is reduced in children with an upper NBPP lesion.
8. Despite paralysis of the biceps, most children with an upper NBPP lesion can flex their elbow by using their wrist extensors, the so-called Steindler effect.
9. The age at which children with NBPP can walk independently is delayed, which does not depend on the severity of the lesion.

SUMMARY

The aim of the research underlying this thesis was to gain a better understanding of the deleterious effects of NBPP on central development by analyzing sensory and motor function. Recommendations for further research and physiotherapy treatment are provided, based on the research presented in this thesis and my own 40 years of experience with NBPP treatment. All children with NBPP who participated in the studies were treated at the LUMC, where I got the opportunity to join the Nerve Center more than twenty years ago.

At the start of my research in this field, the focus was on improving the early identification of severe NBPP lesions which require nerve surgical reconstruction. In the first months after birth, mild NBPP lesions are difficult to distinguish from severe lesions, because they feature the same type of paralysis. In the course of several months, mild lesions recover spontaneously, whereas severe lesions do not. Early identification of severe lesions is essential because the interval between the onset of the lesion and surgery is inversely related to the outcome of reconstruction. The earlier it is established that spontaneous recovery will not be sufficient, the sooner the nerve lesion should be operated on.

At that time, the function of the biceps muscle was used as the indicator for surgery: if the biceps was paralytic at three months of age, nerve surgery was performed. The biceps muscle is the main driver of elbow flexion, but biceps function and elbow flexion are not interchangeable. We found that a substantial number of infants could flex their elbow even though the biceps muscle was paralytic, by using a trick movement. This elbow flexion movement was based on activity of the wrist extensors, which originate just above the elbow joint. Contraction of the wrist extensors effectuates not only wrist extension, but elbow flexion as well, the so-called Steindler effect.[1] A typical feature of this trick movement is that the forearm is in pronation, whereas when the biceps is functional, some level of supination is seen during flexion. The explanation of the Steindler effect in upper NBPP lesions involving the C5, C6 (C7) spinal nerves is that in this lesion type, the innervation of the wrist extensors remains intact, and thereby their function, whereas the biceps is paralytic because of a lesion to the innervating axons. Proper differentiation between elbow flexion based on biceps muscle activity and that based on a Steindler effect in the process of selecting infants for surgery is crucial in order not to miss severe lesions requiring reconstruction. This differentiation has proved to be very difficult in the clinical situation.

Therefore, there was a need to optimize the selection for surgery by developing an objective approach. With this purpose in mind, we performed a prospective study including serial neurological examinations and EMG analyses of several muscles. We found that the severity of NBPP can be reliably predicted at one month of age when needle EMG of the biceps muscle is included in the assessment.[2]

In general, the focus of research in the field of NBPP in past decades was on whether and how muscle paresis or paralysis influenced motor function, and how this could be improved. The analysis of the quality and level of sensory function received little attention. It was generally assumed and accepted that sensibility was not affected in children with an upper NBPP, or at least not to such an extent that it diminished arm and/or hand function. By observing children with NBPP at the Leiden Nerve Center and hearing their parents speak about the functionality of the arm, it became clear that this assumption was probably not correct. Whereas the explanation for problems with hand function was clear in children with a NBPP lesion involving the spinal nerves C7, C8 and T1, it was less so for children who had an upper NBPP. After all, in the latter, only the C5 and C6 spinal nerves are affected, which predominantly innervate the shoulder and elbow flexion. However, it appeared that the children with an upper NBPP also experienced problems with their hand and awkward hand function. Our observations and the input of the parents motivated us to analyze the hand function in upper NBPP.

We therefore started a study of the sensibility of the hand and fingers in children with a NBPP with a lesion of the upper trunk. To assemble baseline data, we first studied the hand and fingers in a healthy group of children using four different sensibility tests. All developed test forms can be found in Annex B. **Chapter 2** presents the outcome of this study. **Chapters 3, 4** and **5** present the results of our sensibility studies in patients with an upper NBPP lesion. To further analyze the awkward hand functioning in children with an upper NBPP, we measured whether the grip force of the affected hand was reduced; the results are presented in **Chapter 6**.

The reduced arm function caused by NBPP can be further compromised by a concurrent mental and/or central neurological impairment. It is important to know whether additional factors compromising function are present, as it might mean that therapy has to be adapted. Therefore, we studied the incidence of cerebral palsy or other motor or mental issues in children with a NBPP and looked at correlations with the severity of the NBPP lesion. The

results of this study are presented in **Chapter 7.** Furthermore, not much is known about gross motor development in children with NBPP. Should this development be delayed, this might also have consequences for therapy. In order to gain insight into the gross motor development, we studied the age at which children with NBPP were able to walk independently; the results are reported in **Chapter 8**.

GENERAL DISCUSSION

Chapter 1 of this thesis provides an extensive introduction to the NBPP lesion, its management and consequences. The underlying mechanism of the injury is described, as is the way different types of injuries are classified. Neurotmetic lesions and root avulsions do not recover spontaneously, and nerve surgery is then indicated. Severe and mild NBPP lesions initially present with the same neurological features. The Leiden three-item test can be used to correctly predict lesions requiring exploration in 94% of cases. The different treatment modalities for children with NBPP are presented. These consist of nerve grafting, nerve transfers, tendon transfers, osteotomies, botulinum toxin, splinting, occupational therapy and physiotherapy. The outcomes of surgical therapies are briefly described. Furthermore, the problem of reduced passive joint mobility in the shoulder and elbow is outlined and the specific therapeutic options are described. Additionally, previous studies at the Leiden Nerve Center regarding the sequelae of NBPP which patients encounter during their lifetime are discussed, based on the International Classification of Functioning, Disability and Health model. Ongoing studies to develop standardized outcome assessments which enable comparison of the treatment and results attained at different centers are briefly mentioned.

Chapter 2 describes how sensibility of the hand can be evaluated in healthy children. Baseline measurements have become relevant in view of developments in peripheral nerve reconstructive surgery, especially for severe NBPP, other peripheral nerve lesions and cerebral palsy. The implementation of a proper sensory function assessment of the hand of children was so far hampered by the absence of a set of instruments for objective evaluation. Twenty-five healthy children aged 7-12 years (mean 9.5 years) participated in this study. The sensibility of both hands was assessed using four different methods: (1) Semmes-Weinstein monofilament test (SW); (2) two-point discrimination (2-PD); (3)

localization test (LT) and (4) stereognosis object recognition (SOR). Modifications were made to suit the smaller size of the children's hands and their ability to understand the assigned task while remaining concentrated. We found that light pressure with an SW filament (D: 2.83 mm) was sufficient to detect the stimulus at 94% of the examined points on the fingertips. The best ability to distinguish two adjacent points was found for the index finger, closely followed by the thumb. A 2-PD distance of 2 mm on the index finger was present in the majority of the children. The 2-PD distance was significantly less on the little finger. These findings most likely reflect a higher density of sensibility receptors in the tip of the index finger than in the other fingertips. The LT required a lot of concentration from the children. They often asked whether they were allowed to move their fingers because thereby they could feel better. Localization scores were close to the maximum in both the dominant and non-dominant hands. Scores for SOR were 100% for both the dominant and non-dominant hands. Overall, we observed no significant difference between the dominant and non-dominant hands in any of the four tests. This study enabled us to establish baseline values for healthy children, with which we could compare the sensibility of the hand in children with an upper NBPP.

The study reported on in **Chapter 3** examined a cohort of 50 children with an upper NBPP. We found that the results of sensibility testing with SW Monofilament and 2-PD of the thumb and the index finger were reduced. Normal sensory input to the somatosensory cortex in early life is essential for the development of motor skills. Good sensory feedback of these two fingers is essential, for instance, to perform a tweezer grip. The reduction of sensory feedback likely hampers activities that need to be carried out two-handed, and likely requires additional visual control. Studies performed by other groups used a Nine-Hole Peg Test[3] or pick-up test.[4] Properly performing these tests, however, requires normal active external rotation. Since this function is usually limited in children with an upper NBPP, we found these tests unsuitable to evaluate hand function. To assess hand function in children with NBPP, we evaluated dexterity and used a single item of the Movement Assessment Battery for Children-2 (MABC-2). This test concerns a specific age-related bimanual activity: for 7-10 years of age, this involves threading a wire through holes in a board, and for 11-12 years of age this involves constructing a triangle with bolts and nuts. As these specific tasks are bimanual, both the dominant and the assisting hand were simultaneously tested.

Children were not allowed to put either the wire or the triangle down on the table, but were required to hold them with both hands. Children with an upper NBPP not only have impaired shoulder and elbow function, but their hand function is also impaired. In this study, not all factors that cause impaired hand function were identified. Finger sensation also includes the ability to localize a stimulus, in addition to 2-PD and pressure. Therefore, we also performed an in-depth analysis of the tactile hand sensibility, especially the ability to correctly localize a sensory stimulus on the fingers.

Chapter 4 presents a study of children with an upper NBPP in which we analyzed the ability to localize a sensory stimulus on the fingertips The thickest SW monofilament was pressed on the radial or ulnar part of each fingertip (10 regions in total), while a screen was placed in front of the child so that they could not see their hand. The results were compared with those of the non-dominant hand of a control group of comparable age. We found that the ability to localize stimuli on the tips of the fingers of children with an upper NBPP was significantly diminished for all fingers, except for the little finger. Localization was diminished in regions belonging to dermatomes C6 and C7, but not to C8. This finding shows that children with an upper NBPP are not only affected by an impaired motor function of the shoulder and elbow, but also by a diminished and incorrect ability to localize sensory stimuli to their fingers. This finding is probably one of the factors underlying hand function impairment and should be addressed with therapy focusing on the improvement of sensibility. Interestingly, during regular follow-up at the outpatient clinic of the Leiden Nerve Center, neither the children nor their parents spontaneously mentioned the presence of sensibility disturbances in the hand.

In **Chapter 5,** we describe a study in which we used a simple questionnaire to systematically assess subjective sensory disturbances and pain in children with a C5, C6 NBPP lesion. Additionally, we assessed whether parents were aware of diminished sensation or pain in their child's affected hand. The questionnaire was delivered to the children and their parents just prior to the sensibility assessment with 2PD and SW filaments (Chapter 3). The objective testing that we performed showed that sensibility in the affected hand was actually reduced as compared to the non-affected hand. However, less than one third of the children actually perceived reduced sensibility as such. We concluded that in this series, the majority of the

children with an upper NBPP had a diminished sensibility of their affected hand, but that not all of them were aware of this. We hypothesized that this lack of awareness resulted from the early lack of sensibility input to the brain, resulting in habituation: the affected children simply do not know otherwise.

The study reported on in **Chapter 6** investigated the grip force of both hands of children with an upper NBPP. We compared the grip force with that of a healthy control group and assessed correlations with hand sensibility, bimanual use and external rotation. The grip force was assessed with a Jamar dynamometer while external rotation was assessed using the Mallet score. Bimanual use was measured using one of the three dexterity items of the MABC-2. For children aged 7, 8, 9 or 10, the specific bimanual task consisted of threading a wire through holes in a board. Children aged 11 or 12 were instructed to construct a triangle with nuts and bolts, as described in MABC-2. We selected this bimanual task because it requires using the affected hand. Children were not allowed to put either the wire or the triangle down on the table, but were instructed to hold them with both hands. The mean grip force of the non-dominant hand in the control group was 92% of that of the dominant hand, while it was only 76% in the NBPP group ($p = 0.04$). Our findings clearly show that grip force is reduced in children with an upper NBPP lesion. Previously, it had been stated that 50% of children with C5–C6 lesions have reduced grip force.[4, 5] The discrepancy with the higher percentage that we found in our study might be explained by the different outcome criteria used in the different studies. In any case, the proportion of patients with a diminished grip force is substantial. We looked at the factors which may cause this reduced grip force, for instance limited shoulder function. We found no statistically significant correlation between grip force and external rotation. Nor did we find a statistically significant correlation between grip force and skin sensibility. In a future study, it might be of interest to correlate grip force with proprioception, rather than with the tactile sensibility we tested.[6] We did not find a statistically significant correlation between grip force and bimanual use either. Theoretically, a shift of hand dominance affects the dominant-unaffected side at a central level of movement control. This might cause an additional disadvantage when learning bimanual activities. More research is required to assess the function of the dominant non-injured hand and its role in dexterity and bimanual activities.

Additionally, there are several factors which have so far not been defined or measured and which may play a causative role in the reduction of grip force. One of these might be cerebral control, which is potentially disturbed in the development of central motor programs. We did find some evidence of changes in central control in clinical observations and fMRI data. [7, 8]

In the study presented in **Chapter 7**, we analyzed 38 children from our prospective cohort study, focusing specifically on general movements (GMs) and central neurological developmental disability (CDD). These 38 children had severe (n = 14) or mild (n = 24) NBPP. A severe nerve lesion was defined as neurotmesis or avulsion of the C5 and C6 roots (irrespective of the function of the C7-C8-T1 roots). A mild lesion was defined as an axonotmesis lesion of C5 and C6 showing spontaneous recovery, after two years of follow-up, of a full range of active elbow flexion, a normal or subnormal range of supination and a normal or nearly normal shoulder function without prominent secondary abnormalities. CDD was defined as any mental and/or neurological impairment diagnosed by an independent specialist. Children with NBPP usually have a history of difficult delivery. An additional potential consequence of a traumatic delivery is damage to the central nervous system, which in turn might lead to CDD. The presence of central neurological disabilities in three-months-old children can be predicted by scoring GMs. The last screening for the presence of CDD took place at a mean age of 4.8 years. We found that 5 out of 38 children (13 %) had CDD, which is higher than the incidence reported for the general population. The conclusion was that children with NBPP have a higher incidence of central neurological problems. There was no relationship between the severity of the NBPP and later developmental problems. We also found that 6 out of 38 children (5 with a severe and 1 with a mild brachial plexus lesion) had a diminished quality of fidgety GMs at the age of three months. However, this finding could not be correlated to developmental disorders at a later age. Only 1 out of 5 children with CDD had abnormal GMs
Since our study, three other papers investigating GMs for children with NBPP have been published. In 2020 a group of 20 infants with NBPP were compared to a healthy control group ranging in age from 9 to 17 weeks. The conclusion was that the NBPP did not affect the quality of the GMs of the infants, but lead to compensatory movements on the unaffected site [9]. Another study about GMs was published in 2022 in which 54 infants with

NBPP were compared to 50 healthy infants. In the NBPP group, 78% of the infants had normal fidgety movements, 4% had abnormal fidgety movements and 19 % displayed no fidgety movements. The median of the optimal score was significantly lower in children with NBPP compared to the control group. There was no difference in optimal scores in relation to the Narakas classification. The authors recommended to assess GMs in infants with NBPP to determine the risk of developmental problems at later age.[10]
In our series, 5 out of 38 children (13 %) eventually had CDD. This finding is consistent with a recently reported study in which 19 of 148 NBPP children (13 %) had CDD. Of the 19 patients, 15 were diagnosed with a neuromuscular disorder and 4 children had an upper motor neuron disease or a cognitive disorder. [11]
Other groups have investigated various cognitive functions. A language impairment was found in 30% of toddlers with a NBPP and the overall risk of psychiatric disorder and ADHD was greater in children with NBPP. [12,13]
Due to the significant incidence of developmental disorders, both our study and more recent investigations emphasize the importance of long-term follow-up for infants with NBPP, with a particular focus on monitoring developmental issues.

It was evident that parents visiting our clinic consistently expressed concerns about their child's motor development. Building on the findings from Chapter 7, **Chapter 8** presents an exploration of the age of independent walking in children with NBPP. The objective was to investigate whether there was a delay in achieving this milestone of gross motor development. We had previously noticed that as much as 13% of children with NBPP had a central developmental disability at the age of 5 years.[14] The parents of 135 children with unilateral NBPP were asked at what age their child was able to walk independently. The results were compared with those of an international normative WHO study for the normal population. Children with NBPP had a mean delay of 2.4 months relative to the normal population, a difference which was statistically significant. We analyzed the effects of nerve lesion severity, Apgar-score, and ethnicity on the age of independent walking. The only statistically significant factor was ethnicity. In earlier research, ethnic background was highlighted as a significant factor, indicating that children from one ethnic group achieved developmental milestones sooner than those from another ethnic group.[15, 16] It is uncertain

whether ethnicity is the sole factor or whether socio-economic influences are a confounder.[16]

One of the weaknesses of our study was that the recollection of just one developmental milestone by parents may not be precise to evaluate motor development, and that the data for normal controls was based on the literature.

The delay in walking independently of children with a NBPP may be explained by a delay in the use of postural muscles. A previous study showed significant difficulties of maintaining balance at the age of 5-15 years.[17] Trunk control may be considered an essential part of gross motor development.[18] One study examined trunk control in children with NBPP aged 10-18 months and discovered that there was impairment in trunk control. This impairment correlated with the severity of the brachial plexus injury.[11] In the same cohort, additional gross motor functions were assessed and related to developmental skills of the upper arm for different grades of NBPP severity. These were: head control, midline crossing and rolling. The results show that the developmental skill capacity decreased and the upper extremity skill quality deteriorated with increasing severity of the brachial plexus injury.[19]

In a previous study from our center, it was found that children with NBPP abducted their affected arm less often in automated balance, even though they were able to do so on request.[7] Children may experience difficulty in learning to walk if they cannot control their balance properly. The ability to walk independently strongly depends on postural control, which develops from a varied use of postural muscles.[20, 21] An alternative explanation is that, due to the brachial plexus injury, the child is unable to pull itself up properly, which is necessary for standing and walking, or they may have missed the crawling phase that precedes walking.

Our study and those of others support the view that physicians and therapists who treat children with NBPP should not only focus on the affected arm, but on the total motor development of the child as well. Future studies should increase insights so that better emphasis can be placed on specific pediatric physiotherapeutic treatment to minimize these adverse effects as much as possible.

HAND SENSIBILITY IN CHILDREN WITH NBPP

Sensibility input from the fingers is important for proper cerebral control of hand function. Finger sensibility involves different qualities, such as pressure threshold, two-point

discrimination and localization. All sensibility qualities together are processed centrally to enable delicate finger movements. A systematic review concluded that sensibility outcomes following NBPP are underreported.[22] Significant deficits were commonly found and these problems are likely underappreciated in this patient population. There are substantial discrepancies between published studies regarding the outcome of sensibility in NBPP. (See Annex A) These discrepancies were likely caused by the many different assessment methods used to test sensibility, the low numbers of patients included and the different types of nerve surgical interventions and conservative treatment modalities used. This also made comparisons difficult.

The strength of our sensibility studies as reported in this thesis is that we compared our NBPP cohort with a control group consisting of healthy age-matched children, whereas most other studies that focused on sensibility did not include a healthy control group. Furthermore, to exclude confounding, we only analyzed children whose dominant hand was the unaffected side. We defined the dominant hand as the hand in which a child holds a pencil to write. Additionally, we compared the affected hand in children with NBPP with the non-dominant hand of the healthy children, whereas studies by others used the unaffected side for comparison.[3, 23-27] In the study in which we analyzed grip force in NBPP (Chapter 6), the grip force of the unaffected dominant hand appeared to be 10-15% lower than that of the dominant hand of the controls. These findings concern children who had undergone nerve repair as well as children who had a presumed dominance shift. The reduction of the grip force of the unaffected dominant hand was statistically non-significant, which may be due to the relatively small number of patients we studied. We therefore feel that more research should be done to further explore this issue. The use of the unaffected side for comparison, if indeed reduced, will skew results and is then methodologically inappropriate.

IMPLICATIONS OF NBPP WITH A NEUROMA-IN-CONTINUITY FOR CENTRAL PROGRAMMING

In contrast to traumatic brachial plexus lesions in adults, it is very rare to find completely ruptured spinal nerves in NBPP. Even in severe cases, a neuroma-in-continuity in the supraclavicular region of the brachial plexus is most commonly found.[28] The consequence of a tissue bridge spanning the proximal and distal undamaged parts of the nerves is that in the majority of cases at least some axons successfully cross the neuroma-in-continuity.[29] We

found electrical continuity in a study of per operative neurophysiology.[30] This successful crossing of axons, however, does not always lead to adequate functional recovery. In severe NBPP, not only is the number of axons that successfully cross a neuroma-in-continuity reduced, but the number of axons that connect to their original targets is also reduced, due to misrouting.[31] The regenerative response that follows the traction NBPP lesion takes place during a critical period of sensorimotor development. The consequence of the reduced number of functional axons and their misrouting is that a disorganized peripheral axonal network is formed. This abnormal wiring results in the central nervous system receiving inappropriate feedback information, which affects the development of central motor programs. The subsequent alteration of programs in the central nervous system has been used as an argument to explain the decrease in hand sensorimotor function in children with NBPP following conservative treatment.[3] Our group found that adults with conservatively treated NBPP had significantly more motor misrouting than healthy controls. In addition, we showed that these patients had motor function impairments not explained by pronounced muscle weakness.[7, 32] In another study, MRI analysis of the corpus callosum volume revealed significant differences between a cohort of patients with NBPP and healthy controls, especially in the motor association areas.[33] All these findings together reflect the deleterious implications of NBPP on central program development. This knowledge should be integrated in adapting the traditional approach to children with NBPP.

CENTRAL NERVOUS SYSTEM CHANGES DUE TO NBPP

An Explanation Based on the Principles of the Neuronal Group Selection Theory[21]

Neurobiologist Gerald Edelman developed the Neuronal Group Selection Theory. This theory divides motor development into two phases: primary and secondary variability. In the primary variability phase, locomotion is highly varied. The infant tries out motor outputs independently of environmental factors during movements, and processes the afferent information. The secondary phase of variability starts around the age of three months. In this phase, the child chooses the best option from a repertoire of varied motor skills, based on its own experiences.

Spontaneous motor behavior is based on sensory information in which proprioceptive sensibility and the cutaneous, visual and auditory systems play a crucial role.[20, 34, 35] The age at which the infant adapts the movement repertoire is function-specific. For instance,

reaching with the arm develops between five and thirteen months, while fine manipulation develops at eight months. The development of the adaptability is marked by individual variations, but infants generally have reached the phases of secondary adaptability of all basic motor functions (reaching, grasping, postural control and locomotion) in the second half of the second postnatal year.

Applying this theory to the sensorimotor development of a child born with NBPP has the following implications. Children with NBPP present with limited variation, due to the paralysis of the shoulder, elbow, and hand muscles. Their brain will support the best option out of a limited repertoire and store it as the most appropriate strategy. The absent, limited, or erroneous sensory feedback hampers normal development.

The hypothesis is that when brachial plexus elements are recovering, incompletely restored motor and sensory functions may cause deficient ways of executing tasks. Examples of this reduced adaptability include the absence of swinging the affected arm while walking, even after the muscle strength of the arm has recovered sufficiently. Another example is the impaired automatic arm abduction during balancing.[7] Early intensive sensorimotor therapy is considered very important to minimize the maladaptive changes in the brain.[36-39]

Awareness of this theory is important for all those who are involved in the treatment of children with NBPP. On the one hand, this helps surgeons who treat these children with nerve surgery or secondary surgery in estimating the expectations regarding surgical outcomes. On the other hand, it is also very important for occupational therapists and physiotherapists who have to design therapeutic programs.

CRITICAL NOTES ON FUTURE RESEARCH TOPICS

Future research should focus on different aspects of improving functional recovery in children with NBPP. The following topics are of importance.

Early intervention

Children with NBPP have a birth injury affecting a critical period of sensorimotor development, which affects not only the sensory and motor function of the arm, but the whole central nervous system. Early treatment with physical and occupational therapy is indicated to stimulate the sensorimotor development.[36-39] Sensorimotor therapy may promote cortical changes and improve function.

International Plexus oUtcome sTudy grOup (iPluto)

Currently, there is no worldwide consensus on how to evaluate the outcome in children with NBPP. In an effort to reach consensus, an international survey was performed, called iPluto.[40] The first iPluto paper, however, did not include the evaluation of sensory function. The current test protocol at the Leiden Nerve Center may serve as a step towards a validated, universally accepted test protocol for sensibility in infants with NBPP. The most recent iPluto study discusses the use of patient reported outcome measures.[41]

International Classification of Functioning Disability and Health (ICF) model

Each domain of the ICF model is relevant for all ages, but it is important to realize that treatment priority may shift from 'Body structures and functions' in the early ages (from birth to toddler) to increasing emphasis on 'Activity and Participation' as the child gets older.[42] Perspectives on functioning and health in the ICF model may differ between patients and their parents versus healthcare professionals.[43] Regarding the environmental and personal factors, it is important to create awareness of the diminished sensibility and the possible consequences for the child and the parents.[42] A cross-sectional study of adolescents (> 16 years) with a NBPP showed that overall HRQoL was not impaired.[44] However, a substantial proportion of the patients reported that NBPP had an impact on choices regarding education and profession, as well as on work-performance. There was no association between participation restrictions and severity of the lesion, nerve surgery or affected site. These findings indicate that all patients with NBPP, regardless of the initial severity of the lesion, may experience limitations in their participation later in life.[44] Apart from focusing on 'Activity and Participation' it would be valuable to conduct a prospective study with a focus on gross motor development in children with a NBPP, with special attention to developmental milestones.

Dedicated therapy to stimulate sensibility

Our study has yielded data regarding diminished and inappropriate sensibility localization feedback.[45] To minimize the maladaptive changes that will take place in the brain during development, early intensive sensorimotor therapy is important. Although it is difficult to assess the beneficial effects of most interventions, it is necessary to include therapy to

improve sensation.[46] Sensory re-education therapy is usually not provided in the Netherlands. Specific brain areas require interaction of simultaneous inputs from several senses like visual, tactile and acoustic. Simultaneous stimulation of hand sensibility with visual and acoustic inputs may optimize the perception in the affected hand.[37, 38] In a pilot study in Sweden, a sensor glove was used to improve sensory relearning after median nerve repair. The goal was to stimulate beneficial reorganization of the cortical hand representation, for instance 'feeling' by listening to the friction sound. This type of therapy was found to improve sensibility compared to control cases.[38]

At the Maartenskliniek center in Nijmegen, the Netherlands, therapists offer MuSSAP treatment (Multi-Sensory Stimulation and Priming) to infants with a unilateral brain lesion. The child wears a special wristband around the affected arm for 30 minutes a day, which can generate light, vibration and sound in order to stimulate the use of the arm and hand. The underlying mechanism of frequent application of different types of sensory stimuli to the fingers may stimulate synaptogenesis and dendritic sprouting. This should ultimately lead to improvement of the interpretation of sensory input and, thereby, hand function.[38, 46] Care providers should explain to both children with NBPP and their parents the need for additional visual control to properly perform a task. This should also be incorporated in physiotherapy.

Recommendations for constraint-induced-movement therapy for children with NBPP

Some centers perform constraint-induced-movement therapy (CIMT), which implies three weeks of immobilization of the unaffected arm followed by five weeks of bi-manual activities. The outcome of the CIMT therapy has been shown to be encouraging for both children with NBPP and those with unilateral cerebral palsy.[47] In CIMT, the child is forced to use the most affected side, thereby triggering the central nervous system to adapt to the situation. There are, however, several important issues to take into account when considering CIMT.

Muscle strength can only be improved to a certain extent, depending on the quality of the innervation. Children with NBPP have a diminished function of the peripheral axonal network, caused by the brachial plexus lesion, either after nerve surgery or non-surgical treatment. It is therefore not possible to achieve normal muscle strength or to reduce muscle fatigue by exercising. The limitation of the functional recovery is in the degree of

nerve recovery, either spontaneously or after nerve repair. Stimulating partially paralyzed muscles can induce the child to introduce compensation mechanisms, which may involve overuse of normally functioning muscles, for example the trapezius muscle. Such overactivity of the affected arm may induce pain.

Research has shown that simultaneous bilateral tactile stimulation of the affected and the non-affected hand may help influence the central substrate for sensory relearning.[38] The introduction of bilateral activation in therapy sessions in therapy may therefore be beneficial. Currently, CIMT is very popular amongst parents, because they assume that it replaces the elaborative stretching exercises applied to reduce contractures. This is, however, not the case and explaining to parents the priorities of therapy remains important. Therapists and parents should be aware and accept that children will use their affected arm less, and that a shift of hand dominance may occur. In our series, a shift of hand preference was found in 87% of operated children with NBPP, compared to 33% in conservatively treated children. These data are in line with those of other studies which also showed a shift of hand preference in children with an NBPP lesion.[48] In children with a right-handed plexus lesion, it may be advantageous to develop preferred left-handedness. In most children, the process of writing, eating and cutting with the left hand develops by itself. The affected arm rarely fully recovers either after conservative treatment or following surgery, and muscle fatigue further reduces the arm function. It is therefore advisable to try and spread the total activity load over the day: writing with the unaffected hand at school and performing activities with both hands, for example sports, music, or other hobbies, after school.

Prevention of contractures.

The joints of children with NBPP that are specifically at risk of becoming stiff are the elbow (flexion contracture) and the shoulder (internal rotation contracture). The prevalence of the formation of an elbow contracture with a magnitude ranging from 5 to 90 degrees is nearly 50%.[49] In this study an elbow flexion contracture of more than 30 degrees was found in 21% to 36% of the children. The etiology is not yet clearly understood, and there are various explanations involving a combination of passive restriction of the joint, muscle facia, subcutis, and skin as well as active resistance by contraction of the biceps muscle, and coordination. There is evidence that elbow contractures are largely caused by denervation, which causes growth failure of the affected flexor muscles.[49] Other studies compared the

muscle phenotypes of the elbow contracture in children with NBPP and cerebral palsy. Both contractures were caused by a lack of muscle length rather than excess muscle strength.[50] These findings support contracture treatments that lengthen rather than weaken the affected muscles, for instance by botulinum toxin. Children with an elbow flexion contracture of 30 degrees or more need active therapy to treat the contracture. Serial casting or the use of a dynamic orthosis is the treatment of choice to reduce elbow contractures.[51]

As regards the shoulder internal contracture, favorable results have been obtained with botulinum toxin.[52] (See Chapter 1) BTX-A injection into the subscapular muscle can reduce internal rotation contractures and hence the need for tendon transfer surgery. In many children, however, botulinum toxin injection proved to be only temporarily beneficial: at 5 years of follow-up, relapse was seen in 67% of the patients from our center treated with BTX-A.[52] Other authors have confirmed that the effect of botulinum toxin is not long-lasting.[53]

FUTURE RESEARCH, FINAL THOUGHTS

The key question is how sensory recovery can be improved. The first aspect that needs to be studied is whether the deleterious effects of denervation on the central nervous system which occur after the lesion can be reduced. This requires a fundamental understanding of the effects of motor and sensory denervation on central programming. It might even be necessary to select children for surgery at an earlier age than is currently the standard, in order to overcome these effects. The second aspect that needs attention is how axonal regeneration can be improved. This may include optimization of surgical techniques and may also include electrical stimulation or gene therapy. It is recommended to initiate a qualitative research project on the experience of parents with children diagnosed with NBPP. This project should explore how parents handle the information provided, implement it at home, and cope with an infant having a plexus lesion in terms of caregiving and concerns for the future. Additionally, conducting a literature review to assess interventions worldwide and their effectiveness would be beneficial. Finally, further efforts should be made to improve paediatric physiotherapy / occupational therapy. Such improvements will only be feasible by paying dedicated attention to the role of sensation in future studies. The treatment protocols in future studies should be organized for each specific age category according to the ICF model. Training of specialized therapists may be needed, leading to more attention being directed towards the evaluation of sensibility in daily clinical practice and to therapeutic intervention options. All of these may lead to improvement of functional outcomes in children with NBPP, resulting in better limb control and improved quality of life.

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Chapter 10

Samenvatting en Algemene Discussie

(Summary in Dutch)

De belangrijkste bevindingen van dit proefschrift

1. De sensibiliteit van de duim en wijsvinger is bij gezonde kinderen nauwkeuriger dan de sensibiliteit van de derde, vierde en vijfde vinger.
2. Kinderen met een C5-C6 NBPP hebben een verminderde sensibiliteit van de duim en wijsvinger.
3. Een verminderde sensibiliteit van de duim en wijsvinger bij een C5-C6 NBPP correleert met een verminderde handfunctie.
4. Het vermogen om prikkels te lokaliseren naar de duim, wijsvinger, derde en vierde vinger is verstoord bij kinderen met een C5-C6 (C7) NBPP.
5. De meeste kinderen (en hun ouders) met een C5-C6 NBPP zijn zich niet bewust van de verminderde sensibiliteit in hun aangedane hand.
6. Het NBPP is een perifere zenuwlaesie die ook het centrale zenuwstelsel beïnvloedt.
7. De knijpkracht van de hand is verminderd bij kinderen met een C5-C6 NBPP-laesie.
8. Ondanks een verlamde m. biceps kunnen de meeste kinderen met een C5-C6 NBPP-laesie hun elleboog buigen door hun polsextensoren te gebruiken, het zogenaamde Steindler-effect.
9. De leeftijd om zelfstandig te lopen bij kinderen met een NBPP is vertraagd, wat niet verklaard kan worden door de ernst van de plexuslaesie.

SAMENVATTING

Het doel van dit proefschrift was om meer inzicht te krijgen in de blijvende gevolgen van een obstetrisch plexus brachialis letsel (OPBL) / Neonatal Brachial Plexus Palsy (NBPP) met betrekking tot sensibel herstel en de senso-motorische ontwikkeling, met als uiteindelijk doel de behandeling van NBPP te optimaliseren. Op basis van het onderzoek in dit proefschrift en mijn 40 jaar ervaring met NBPP-behandeling, worden aanbevelingen gedaan voor verder onderzoek en therapeutische behandelingen. Alle kinderen met een NBPP die deelnamen aan de onderzoeken werden behandeld in het LUMC.

Aan het begin van mijn onderzoek op het gebied van NBPP lag de focus op het verbeteren van de vroege identificatie van ernstige NBPP-laesies waarvoor een zenuwchirurgische behandeling geïndiceerd is. In de eerste maanden na de geboorte zijn milde NBPP-laesies moeilijk te onderscheiden van ernstige laesies, omdat ze dezelfde klinische presentatie hebben, namelijk verlamming van de spieren die geïnnerveerd worden door de aangedane zenuwen. In de loop van enkele maanden herstellen milde zenuwletsels spontaan, terwijl ernstige letsels dat niet doen. Vroege identificatie van een ernstig zenuwletsel is essentieel. Hoe eerder wordt vastgesteld dat spontaan herstel onvoldoende zal zijn om een goede arm functie te bereiken, hoe eerder het zenuwletsel kan worden geopereerd en hoe beter de resultaten van operatieve zenuwreconstructie zullen zijn. De functie van de m. biceps werd in die periode gebruikt als belangrijkste indicator : bij een paralytische biceps is een zenuw-operatie nodig. De m. biceps is de belangrijkste spier voor elleboogflexie, maar bicepsfunctie en elleboogflexie zijn niet hetzelfde. We ontdekten dat bij sommige baby's de elleboog werd gebogen zonder dat daarbij de m.biceps actief werd aangespannen, maar met een truc-beweging waarbij de polsextensoren worden aangespannen, het zogenaamde Steindler-effect. We spreken van een 'bovenste' plexusletsel als met name de spinale zenuwen C5 en C6 zijn aangedaan. Bij een dergelijk C5-C6 letsel functioneren de polsextensoren goed, terwijl de biceps verlamd is. Als de origo van de polsextensoren net proximaal van het ellebooggewricht ligt, dan zal bij aanspannen niet alleen de pols extenderen, maar ook de elleboog buigen. Bij een bovenste plexusletsel is het cruciaal om een goed onderscheid te maken tussen elleboogflexie op basis van spieractiviteit van de biceps of door middel van het Steindler-effect, omdat anders een ernstig zenuwletsel gemist kan worden dat een operatie zou vereisen. Dit onderscheid bleek in de klinische situatie vaak moeilijk vast te stellen.

Daarom was er behoefte om de selectie voor zenuwchirurgie te optimaliseren door een objectieve manier te ontwikkelen. Met dit doel voor ogen hebben we een prospectieve studie uitgevoerd (2002-2004) met een cohort van 48 kinderen met NBPP. We concludeerden dat de ernst van NBPP betrouwbaar kan worden voorspeld op de leeftijd van één maand wanneer naald-EMG van de m. biceps wordt opgenomen in het algoritme.
In het algemeen lag de focus van onderzoek op het gebied van NBPP de afgelopen decennia op de evaluatie van uitkomsten van interventies die als doel hadden de motoriek en motorische functie te verbeteren. Er was weinig aandacht en kennis over sensibiliteit, zowel kwalitatief als kwantitatief. Het was algemeen aanvaard dat de sensibiliteit bij kinderen met een bovenste NBPP niet was verminderd, of in ieder geval niet in die mate dat het de arm- en/of handfunctie beïnvloedde. Tijdens observatie van veel kinderen met NBPP in het Leids Zenuwcentrum en na van hun ouders te horen over verminderde functie en inzet van de hand kwam naar voren dat deze veronderstelling misschien niet klopt. Bij kinderen met een NBPP-letsel waarbij de spinale zenuwen C7, C8 en T1 betrokken zijn, is het duidelijk dat de handfunctie verminderd zal zijn. Bij kinderen met een bovenste NBPP is dit minder vanzelfsprekend. Bij deze groep zijn immers alleen de spinale zenuwen C5 en C6 aangetast die de schouderbewegingen en elleboogflexie innerveren. Het bleek echter dat kinderen met een bovenste NBPP ook problemen met de handfunctie ondervonden en 'onhandigheid' lieten zien. Onze eigen klinische observaties en verhalen van ouders motiveerden ons om te onderzoeken of handfunctie aangedaan was bij een bovenste plexusletsel, en zo ja, hoe dit verklaard kan worden.
We hebben een studie opgezet om te onderzoeken of de sensibiliteit van de hand bij kinderen met een bovenste plexusletsel een rol kon spelen bij deze waargenomen 'onhandigheid'.
Als uitgangspunt hebben we eerst de sensibiliteit van de hand en vingers onderzocht bij een groep gezonde kinderen. We gebruikten vier verschillende sensibiliteitstesten; in Bijlage B zijn de gebruikte testformulieren bijgevoegd. In **Hoofdstuk 2** worden de resultaten van het onderzoek bij gezonde kinderen gepresenteerd. In **Hoofdstukken 3, 4** en **5** worden de resultaten gepresenteerd van onze sensibiliteitsstudies bij kinderen met een bovenste plexus letsel. Om de gebruiksstoornis van de hand bij kinderen met een NBPP aanvullend te analyseren, hebben we onderzocht of de knijpkracht van de hand een rol zou kunnen spelen bij de verminderde hand inzet door kinderen met een bovenste plexus letsel. We

presenteren de resultaten van de knijpkracht meting in **Hoofdstuk 6**. De door NBPP verminderde armfunctie kan nog meer worden beperkt als er gelijktijdig een mentale en/of centrale neurologische stoornis aanwezig is. Het is belangrijk om te weten of dergelijke bijkomende factoren aanwezig zijn, omdat de consequentie kan zijn dat de therapie moet worden aangepast. Daarom hebben we de incidentie van cerebrale parese of andere motorische of mentale problematiek bij kinderen met een NBPP bestudeerd en gekeken naar potentieel gerelateerde factoren zoals bv. zogenaamde fidgety movements. De resultaten van dit onderzoek worden gepresenteerd in **Hoofdstuk 7**. Er is niet veel onderzoek gedaan naar de ontwikkeling van grove motoriek bij kinderen met een NBPP. Als deze ontwikkeling vertraagd is, dan kan dit de ontwikkeling van de armfunctie belemmeren en kan dit ook gevolgen hebben voor therapie. Om inzicht te krijgen in de grove motorische ontwikkeling hebben we gekeken naar de leeftijd waarop kinderen met een NBPP zelfstandig konden lopen, waarvan de resultaten worden gerapporteerd in **Hoofdstuk 8**.

ALGEMENE DISCUSSIE

Hoofdstuk 1 van dit proefschrift geeft een uitgebreide inleiding over NBPP. De oorzaak van het letsel wordt beschreven en de manier waarop verschillende gradaties van zenuwletsels worden uitgelegd. Een letsel met voornamelijk axonotmesis (Sunderland graad 2 letsel) zal spontaan herstellen. Wanneer er een neurotmesis (Sunderland graad 4 of 5 letsel) of wortelavulsies bestaan, zal spontaan herstel niet optreden en is een operatieve zenuwreconstructie nodig. De moeilijkheid is dat minder ernstige en ernstige NBPP-letsels aanvankelijk dezelfde klinische presentatie hebben. De in Leiden ontwikkelde drie-item-test voorspelt in 94% van de gevallen correct welke laesies ernstig zijn en moeten worden doorverwezen naar een gespecialiseerd centrum. De verschillende behandelingsopties voor kinderen met een NBPP worden besproken: zenuwtransplantatie, zenuwtransfer, peestransfer, osteotomie, botulinetoxine injectie, spalken en fysiotherapie. Het resultaat van chirurgische behandelingen wordt kort beschreven. Verder wordt de problematiek van contractuurvorming in schouder en elleboog besproken en de behandelmogelijkheden.

In **Hoofdstuk 2** wordt beschreven hoe de sensibiliteit van de hand bij gezonde kinderen kan worden geëvalueerd. Normaalwaarden zijn relevant geworden met het oog op ontwikkelingen in reconstructieve chirurgie van perifere zenuwen, met name van ernstige

NBPP letsels, andere perifere zenuwlaesies en cerebrale parese. Het vaststellen van de sensibiliteit van de hand bij kinderen werd tot nu toe belemmerd door het ontbreken van meetmethoden om de sensibiliteit objectief te beoordelen. Aan dit onderzoek namen 25 gezonde kinderen in de leeftijd van 7-12 jaar (gemiddeld 9,5 jaar) deel. De sensibiliteit van beide handen werd geanalyseerd met behulp van vier verschillende methoden: (1) Semmes-Weinstein Monofilament-test (SW); (2) twee-punts discriminatie (2-PD); (3) lokalisatietest (LT) en (4) stereognostische objectherkenning (SOH). Er werden aanpassingen gedaan aan de daarvoor bij volwassenen gebruikte instrumenten vanwege de kleinere omvang van de handen van de kinderen en hun vermogen om de toegewezen taak te begrijpen en geconcentreerd te blijven. We vonden dat lichte druk met een SW-filament (D; 2,83 mm) voldoende was om als stimulus te detecteren in 94% van de onderzochte punten op de vingertoppen. Twee aangrenzende punten werden het best onderscheiden in de wijsvinger, gevolgd door de duim. De meeste kinderen hadden een 2-PD afstand van 2 mm van de wijsvinger. De 2-PD was aanmerkelijk minder in de pink. Deze bevindingen weerspiegelen waarschijnlijk een hogere dichtheid van sensorische receptoren in de top van de wijsvinger in vergelijking met de andere vingertoppen. De lokalisatie-test vergde veel concentratie van de kinderen. Ze vroegen vaak of ze hun vingers mochten bewegen, omdat ze daardoor beter konden voelen. Zowel in de dominante als in de niet-dominante handen lagen de lokalisatiescores dicht bij het maximum. Scores voor SOH waren 100% voor zowel de dominante als niet-dominante handen. Over het algemeen zagen we in geen van de vier tests een significant verschil tussen de dominante en niet-dominante handen. Dankzij de in deze studie verzamelde basiswaarden konden we de sensibiliteit van de hand bij kinderen met een bovenste NBPP vergelijken met gezonde controles.

In **Hoofdstuk 3** bestudeerden we een cohort van 50 kinderen met een bovenste NBPP. We ontdekten dat ze een verminderde sensibiliteit van de duim en van de wijsvinger hadden, getest met SW Monofilament en 2-PD. Normale sensorische input naar de somatosensorische cortex vroeg in het leven is essentieel voor de ontwikkeling van motorische vaardigheden. Een goede sensibele feedback van deze twee vingers is bijvoorbeeld belangrijk bij het maken van een pincetgreep. De verminderde sensibele feedback kan het voor de kinderen met NBPP noodzakelijk maken om activiteiten die met twee handen moeten worden uitgevoerd onder visuele controle te verrichten. Om de

handfunctie bij kinderen met NBPP te beoordelen, evalueerden we de behendigheid en gebruikten we één enkel item van de Movement Assessment Battery for Children-2 (MABC-2). De testen hadden betrekking op een specifieke leeftijd gerelateerde bimanuele activiteit. De kinderen van 7-10 jaar haalden een draad door gaten in een plankje en de kinderen van 11-12 jaar maakten een driehoek met bouten en moeren. Aangezien deze specifieke taken bimanueel zijn, werden zowel de dominante als de assisterende hand gelijktijdig getest. Kinderen mochten de draad en de driehoek niet op tafel leggen, maar moesten ze met beide handen vasthouden. Eerdere studies uitgevoerd door andere onderzoeksgroepen maakten gebruik van de Nine-Hole Peg Test, of pick-up test. Voor het uitvoeren van deze testen is een goede actieve exorotatie van de schouder nodig om de hand zijwaarts in de ruimte te positioneren. Omdat deze functie meestal beperkt is in een bovenste NBPP, vonden we deze testen niet geschikt om de handfunctie te evalueren.
Uit de studie beschreven in Hoofdstuk 3 is gebleken dat kinderen met een bovenste NBPP niet alleen een verminderde schouder- en elleboogfunctie hebben, maar ook een verminderde handfunctie. Verschillende kwaliteiten dragen bij aan het normaal functioneren van de hand. Vingersensibiliteit omvat naast 2-PD en druk ook het vermogen om een prikkel te lokaliseren. Daarom hebben we in een vervolgstudie een gedetailleerde analyse van de tactiele handsensibiliteit uitgevoerd, met name gericht op het vermogen om een sensibele stimulus op de vingers correct te lokaliseren.

Hoofdstuk 4 bevat een studie van kinderen met een bovenste NBPP waarin we analyseerden in welke mate een prikkel op de vingertoppen correct gelokaliseerd kan worden. Het dikste SW-Monofilament werd op het radiale of ulnaire deel van elke vingertop gedrukt (in totaal vijf vingers 10 gebieden), waarbij door middel van een verticaal scherm het kind zijn of haar hand niet kon zien. De resultaten werden vergeleken met de niet-dominante hand van een controlegroep van vergelijkbare leeftijd. We ontdekten dat het vermogen om een prikkel op de vingertoppen te lokaliseren bij kinderen met een bovenste NBPP significant was verminderd in alle vingers, behalve in de pink. De lokalisatie was verminderd in regio's die passen bij de dermatomen C6 en C7, maar niet in C8. Deze bevinding is waarschijnlijk een van de factoren die ten grondslag ligt aan de verminderde handfunctie bij kinderen met een bovenste NBPP.

Kinderen met een bovenste NBPP worden niet alleen beperkt door een verminderde motorische functie van de schouder en elleboog, maar ook door een verminderd en onjuist vermogen om sensibele prikkels op hun vingers te lokaliseren. Aan het feit dat lokalisatie verminderd is moet aandacht worden besteed met sensorisch gerichte therapie. Interessant is dat tijdens de reguliere controle op de polikliniek van het Leids Zenuwcentrum noch de kinderen, noch hun ouders spontaan melding maakten van de aanwezigheid van sensibele stoornissen in de hand.

In **Hoofdstuk 5** beschrijven we een studie waarin we een eenvoudige vragenlijst gebruikten om systematisch subjectieve sensibele stoornissen en pijn te beoordelen bij kinderen met een bovenste NBPP-laesie. Daarnaast beoordeelden we of ouders zich bewust waren van een mogelijk aanwezig verminderd gevoel of pijn in de hand van hun kind. De vragenlijst werd aan de kinderen en hun ouders voorgelegd, vlak voor het testen van de sensibiliteit met 2-PD en SW-filamenten. De objectieve tests die we verrichtten lieten zien dat de kinderen een verminderd gevoel hadden in de aangedane hand in vergelijking met de niet-aangedane hand. Minder dan één-derde van de kinderen ervoer het verminderde gevoel echter ook als zodanig. We concluderen uit dit onderzoek dat de meerderheid van de kinderen met een bovenste NBPP een verminderde sensibiliteit van hun aangedane hand hadden, maar dat sommigen zich daarvan niet bewust waren. Dat deze kinderen zich niet bewust zijn van de verminderde sensibiliteit is het gevolg van het vroege gemis aan sensibele input naar de hersenen, resulterend in gewenning: de betreffende kinderen weten gewoon niet anders.

In **Hoofdstuk 6** onderzochten we de knijpkracht van beide handen van kinderen met een bovenste NBPP. We vergeleken de knijpkracht met een gezonde controlegroep en beoordeelden correlaties met handsensibiliteit, bimanueel gebruik en exorotatie. De knijpkracht werd beoordeeld met een Jamar-dynamometer. Exorotatie werd beoordeeld met behulp van de Mallet-score. Bimanuele vaardigheid werd gemeten door één van de drie behendigheidsitems van de MABC-2 te gebruiken. Voor kinderen van 7, 8, 9 of 10 jaar bestond de specifieke bimanuele taak uit het rijgen van een draad door gaten in een plankje. Kinderen van 11 of 12 jaar kregen de opdracht om een driehoek te construeren met moeren en bouten in overeenstemming met MABC-2. We hebben voor deze bimanuele taak gekozen

zodat de aangedane hand altijd moest worden ingezet om de taak te volbrengen. Kinderen mochten zowel het draad als de driehoek niet op tafel leggen, maar kregen de instructie om ze met beide handen vast te houden.
De gemiddelde knijpkracht van de niet-dominante hand in de controlegroep was 92% van die van de dominante hand, terwijl dit slechts 76% was in de NBPP-groep (p = 0,04). Onze bevindingen laten duidelijk zien dat de knijpkracht verminderd is bij kinderen met een bovenste NBPP-laesie. Eerder werd door anderen vastgesteld dat 50% van de kinderen met C5-C6 laesies een verminderde knijpkracht heeft. De discrepantie met betrekking tot het hogere percentage dat wij vonden, kan worden verklaard door de verschillende uitkomstcriteria die in elk onderzoek werden gebruikt. Het aantal patiënten met een verminderde knijpkracht is aanzienlijk.
We hebben factoren onderzocht die mogelijk ten grondslag kunnen liggen aan de verminderde knijpkracht, bijvoorbeeld een beperkte schouderfunctie. We vonden geen statistische correlatie tussen knijpkracht en exorotatie van de schouder. We vonden ook geen statistische correlatie tussen knijpkracht en sensibiliteit. De correlatie tussen knijpkracht en proprioceptie zou een interessant nieuw onderzoek kunnen zijn om beter te begrijpen hoe de vermindering in knijpkracht te verklaren is. We hebben geen statistische correlatie gevonden tussen knijpkracht en bimanueel gebruik. Een verschuiving van handdominantie (zoals vaak voorkomt bij NBPP) zal waarschijnlijk invloed hebben op het leren van bimanuele activiteiten op centraal zenuwstelselniveau. Meer onderzoek is nodig om de dominante niet-aangedane handfunctie en de rol daarvan in behendigheid en bimanuele activiteiten te beoordelen.
Bovendien kunnen andere factoren die tot nu toe niet gedefinieerd of gemeten zijn, een oorzakelijke rol spelen bij de vermindering van de knijpkracht. Een daarvan kan de cerebrale controle zijn die mogelijk verstoord is bij de ontwikkeling van centrale motorische programma's. In eerdere studies van onze groep beschreven we klinische observaties en functionele MRI gegevens, waarbij we deze veranderingen in de centrale controle inderdaad hadden gevonden.

Hoofdstuk 7 beschrijft een prospectieve cohortstudie om te onderzoeken of kinderen met een NBPP een hogere incidentie van centrale neurologische ontwikkelingsstoornissen (Central Developmental Disability - CDD) hebben in vergelijking met de algemene bevolking.

CDD werd in deze analyse gedefinieerd als elke mentale en/of neurologische stoornis die werd gediagnosticeerd door een onafhankelijke specialist. Kinderen met NBPP hebben meestal een voorgeschiedenis van een moeilijke bevalling. Een bijkomend gevolg van een traumatische bevalling kan schade aan het centrale zenuwstelsel zijn, wat kan leiden tot CDD. Deze centrale neurologische ontwikkelingsstoornissen kunnen bij kinderen van drie maanden oud worden voorspeld door General Movements (GMs) te beoordelen. De laatste beoordeling voor CDD vond plaats toen de kinderen een gemiddelde leeftijd van 4,8 jaar hadden. We ontdekten dat 5 van de 38 kinderen (13%) een CDD hadden, wat hoger is dan in de algemene bevolking. De conclusie is dat kinderen met een NBPP vaker centrale neurologische problemen hebben. Er was geen relatie tussen de ernst van de NBPP en latere ontwikkelingsproblemen. We vonden ook een verminderde kwaliteit van de GMs op de leeftijd van drie maanden, maar dit bleek niet voorspellend voor ontwikkelingsstoornissen op latere leeftijd. Nadat onze studie is verschenen zijn er nog drie andere artikelen over GMs bij kinderen met een NBPP gepubliceerd. In 2020 werd een groep van 20 kinderen met een NBPP (leeftijd van 9-17 weken) vergeleken met een controlegroep. Deze studie liet zien dat het plexus brachialis letsel geen effect had op de kwaliteit van de GMs, maar dat de kinderen meer compensatie bewegingen maakten aan de niet-aangedane zijde. In een andere studie (uit 2022) werden eveneens de GMs van 54 kinderen met een NBPP vergeleken met een controlegroep. Uit deze studie kwam dat 78% van de kinderen normale GMs had, 4% had abnormale GMs en 19% liet geen GMs zien. De mediaan van de optimale GMs waren significant lager dan die van de controlegroep. Er werd geen relatie tussen de optimal GMs score en de ernst van het plexus brachialis letsel gevonden. De auteurs adviseerden om GMs te scoren bij kinderen met een NBPP, om een verhoogd risico op ontwikkelingsproblemen tijdig te signaleren. In ons onderzoek bleek dat 5 van de 38 kinderen (13%) een CDD hadden. Een gelijke proportie werd ook gevonden bij een recent onderzoek (in 2021) waarbij 19 van 148 (13%) kinderen met een NBPP (13%) een CDD hadden. Andere studies vonden problemen in andere cognitieve domeinen , zoals taalstoornissen en psychiatrische stoornissen. De aanzienlijke incidentie van ontwikkelingsstoornissen uit onze en recente studies, GMs ondersteunt de noodzaak om in de toekomst een langdurige follow-up studie te verrichten van kinderen met een NBPP, met specifieke aandacht voor ontwikkelingsstoornissen.

Ouders die onze poli zenuwcentrum bezochten, gaven regelmatig aan dat ze ongerust waren over de algemene motorisch ontwikkelingen van hun kinderen. Voortvloeiend uit de bevindingen in hoofdstuk 7 hebben we in **Hoofdstuk 8** bestudeerd op welke leeftijd kinderen met een NBPP zelfstandig konden lopen. Het doel was om te onderzoeken of er een vertraging was bij het bereiken van deze mijlpaal van de grove motorische ontwikkeling. In een eerdere studie hadden we vastgesteld dat maar liefst 13% van de kinderen met een NBPP een centrale ontwikkelingsstoornis had op de leeftijd van bijna vijf jaar. Een andere en eerder door ons verrichte studie toonde significante problemen aan met het balanceren van het evenwicht tijdens het lopen over een lijn op de leeftijd van 5-15 jaar. Het vermogen om zelfstandig te lopen is sterk afhankelijk van houdingsregulatie die ontstaat uit een gevarieerd gebruik van houdingsspieren. Eerder onderzoek verricht door anderen evalueerde rompcontrole bij kinderen met een NBPP in de leeftijd van 10 tot 18 maanden. Deze bleek verminderd hetgeen correleerde met de ernst van het plexus brachialis letsel.
Aan de ouders van 135 kinderen met unilaterale NBPP werd tijdens het reguliere polikliniekbezoek gevraagd op welke leeftijd hun kind zelfstandig kon lopen. De resultaten werden vergeleken met een internationale normatieve WHO-studie voor een normale populatie. Kinderen met een NBPP bleken gemiddelde 2,4 maanden later los te lopen in vergelijking met de normale populatie, hetgeen significant was. We analyseerden de effecten van de ernst van het plexus letsel en de Apgarscore op de leeftijd van zelfstandig lopen; hierbij werden geen significante correlaties gevonden. Etniciteit bleek de enige significante factor te zijn. In eerder onderzoeken werd etnische afkomst al geïdentificeerd als belangrijke factor bij het behalen van motorische mijlpalen. Het is onduidelijk of etniciteit per se de enige factor is of dat concomitante sociaaleconomische invloeden de verschillen konden verklaren. Een van de zwakke punten van ons onderzoek was, dat de leeftijd van slechts één ontwikkelingsmijlpaal zoals deze werd aangegeven door de ouders niet nauwkeurig genoeg is om de algemene motorische ontwikkeling voldoende te bepalen. Een andere beperking was dat de uitkomst vergeleken werd met normaalwaardes uit de literatuur in plaats van een adequate controlegroep. Hoe de vertraging in het zelfstandig lopen van kinderen met een NBPP te verklaren is, zal verder moeten worden onderzocht. Ons onderzoek en dat van anderen ondersteunen de opvatting dat artsen en therapeuten die kinderen met een NBPP behandelen zich niet alleen op de aangedane arm moeten richten, maar ook op de algemene motorische ontwikkeling van het kind. Toekomstig

onderzoek zou meer inzicht moeten geven of en hoe specifieke kinderfysiotherapeutische behandelingen deze factoren kunnen adresseren.

HANDSENSIBILITEIT BIJ KINDEREN MET EEN NBPP

Sensibele input van de vingers is belangrijk voor een goede cerebrale controle van de handfunctie. Vingersensibiliteit bevat verschillende kwaliteiten, zoals druk, twee-punts discriminatie en lokalisatie. Alle zintuiglijke kwaliteiten samen worden in het centraal zenuwstelsel verwerkt om vingerbewegingen mogelijk te maken. In een systematische review werd geconcludeerd dat te weinig over sensibiliteit na een NBPP wordt gerapporteerd. Significante beperkingen werden gevonden en deze uitkomsten worden waarschijnlijk ondergewaardeerd in deze patiëntenpopulatie. We vonden in eerder gepubliceerde onderzoeken behoorlijk grote discrepanties met betrekking tot de uitkomst van de sensibiliteit bij patiënten met een NBPP. Deze discrepanties werden mogelijk veroorzaakt door de vele verschillende beoordelingsmethoden die werden toegepast, het lage aantal geïncludeerde patiënten en de verschillende soorten zenuwchirurgische ingrepen en conservatieve behandelingsmodaliteiten die werden toegepast. Vergelijken was daarom ook moeilijk. (Zie bijlage A)

De kracht van onze sensibiliteitstudies zoals in dit proefschrift beschreven bestaat er uit dat we ons NBPP-cohort vergeleken met een controlegroep van gezonde kinderen van dezelfde leeftijd. Bovendien hebben we alleen kinderen geanalyseerd van wie de dominante hand de niet-aangedane kant was. We hebben de aangedane hand bij NBPP-kinderen vergeleken met de niet-dominante hand van gezonde kinderen. Veel onderzoeken die door anderen zijn uitgevoerd, hadden de aangedane met de niet-aangedane zijde vergeleken. Bij de meeste kinderen met een NBPP is echter de niet-aangedane hand de dominante hand geworden. Uit ons onderzoek naar de knijpkracht bij NBPP (Hoofdstuk 6) bleek dat de knijpkracht van de niet-aangedane dominante hand 10-15% minder was in vergelijking met de knijpkracht in de dominante hand van controles. We vonden dit bij kinderen die een plexus reconstructie hadden ondergaan en een (veronderstelde) dominantieverschuiving hadden. Hoewel dit verschil in ons cohort niet statistisch significant was, vinden we dat er verder onderzoek moet worden gedaan naar de gevolgen van NBPP op de niet-aangedane hand. Het valt nu

niet uit te sluiten dat statistische significantie niet werd bereikt vanwege het relatief kleine aantal patiënten dat werd bestudeerd.

IMPLICATIES VAN EEN NBPP MET EEN NEUROMA-IN-CONTINUÏTEIT VOOR CENTRALE PROGRAMMERING

Bij kinderen met een NBPP wordt peroperatief zelden een complete verscheuring (onderbreking) van spinale zenuwen gevonden, dit in tegenstelling tot traumatische laesies van de plexus brachialis bij volwassenen. Zelfs in ernstige NBPP letsels wordt meestal een neuroma-in-continuïteit van de betrokken plexus brachialis elementen gevonden. Het gevolg van de aanwezigheid van zo'n weefselbrug tussen de proximale en distale onbeschadigde delen van de zenuwen, is dat een klein aantal regenererende axonen het neuroom-in-continuïteit kunnen passeren. Deze succesvolle uitgroei van een beperkt aantal axonen leidt lang niet altijd tot volledig functioneel herstel. Bij ernstige NBPP is het aantal axonen dat met succes een neuroma-in-continuïteit passeert laag. Ook het aantal axonen dat verbinding maakt met hun oorspronkelijke eindorgaan is laag ten gevolge van misrouting.
De regeneratieve respons die volgt na het plexus brachialis tractie letsel vindt plaats in een kritieke periode van sensomotorische ontwikkeling. Het gevolg van het lage aantal axonen dat contact maakt met een eindorgaan en hun verkeerde route is dat er een onvolledig en foutief perifeer axonaal netwerk wordt gevormd Door de abnormale perifere connecties ontvangt het centrale zenuwstelsel verkeerde feedbackinformatie die de ontwikkeling van stuurprogramma's in het centraal zenuwstelsel verstoort. Deze foutieve opbouw van motorprogramma's in het centrale zenuwstelsel is een verklaring voor de afname van de sensomotorische functie van de hand bij kinderen met NBPP na conservatieve behandeling. Onze groep stelde eerder vast bij volwassenen met een NBPP dat conservatief werd behandeld, dat significant meer motorische misroutering had plaatsgevonden dan bij gezonde controles. Bovendien toonden we aan dat deze patiënten een functionele beperking van de motorische functie hadden die niet kon worden verklaard door uitgesproken spierzwakte. In een ander onderzoek toonde MRI-analyse significante verschillen aan in het volume van het corpus callosum volume bij een cohort van patiënten met een NBPP en dat bij gezonde controles, vooral bij de motorische associatiegebieden. Al deze bevindingen samen onderschrijven de schadelijke gevolgen van een NBPP op de

ontwikkeling van centrale programma's. Deze kennis dient te worden gebruikt bij de behandeling van kinderen met een NBPP.

VERANDERINGEN VAN HET CENTRALE ZENUWSTELSEL ALS GEVOLG VAN NBPP,

Een uitleg gebaseerd op de Principes van de Neuronal Group Selection Theory

De neurobioloog Gerald Edelman ontwikkelde de Neuronal Group Selection Theory. Deze theorie verdeelt de motorische ontwikkeling in twee fasen: de primaire en de secundaire variabiliteit. In de fase van primaire variabiliteit zijn bewegingen zeer gevarieerd: het kind beweegt de ledematen onafhankelijk van omgevingsfactoren en verwerkt de afferente informatie. Rond de leeftijd van drie maanden begint de secundaire fase van variabiliteit. In deze fase wordt op basis van eigen ervaringen uit een repertoire van gevarieerde motorische vaardigheden de beste optie gekozen.
Spontaan motorisch gedrag is gebaseerd op zintuiglijke informatie waarbij de proprioceptie, sensibiliteit, de huid, en het visuele en auditieve systeem een cruciale rol spelen. De leeftijd waarop het kind het bewegingsrepertoire aanpast hangt af van het soort beweging. Reiken met de arm ontwikkelt zich bijvoorbeeld tussen 5 en 13 maanden en fijne manipulatie met de vingers pas na acht maanden. De ontwikkeling van het aanpassingsvermogen kent een individuele variatie, maar kinderen hebben over het algemeen in de tweede helft van hun tweede jaar de fase bereikt van secundair aanpassingsvermogen van alle basis motorische functies (reiken, grijpen, houdingscontrole en voortbeweging).
Het toepassen van deze theorie op de sensomotorische ontwikkeling van een kind met een NBPP heeft een aantal belangrijke implicaties. Kinderen met een NBPP presenteren zich met een beperkende variatie door verlamming van de schouder-, elleboog- en handspieren. De hersenen zullen de beste optie uit een beperkt bewegingsrepertoire ondersteunen en opslaan als de meest geschikte strategie. De afwezige, beperkte of verkeerde feedback belemmert de normale ontwikkeling van motorische controle.
De hypothese is dat wanneer in de loop van de tijd het plexus brachialisletsel (perifere zenuwstelsel) gaat herstellen - hetzij spontaan, hetzij na een zenuw-operatie-, de onvolledig of foutieve ontwikkelde motorische en sensorische functies van het centraal zenuwstelsel veroorzaken dat taken worden uitgevoerd op een gebrekkige manier. Een voorbeeld hiervan is het uitblijven van onwillekeurig meebewegen van de aangedane arm tijdens hardlopen

terwijl de spierkracht van de arm voldoende is hersteld om deze beweging willekeurig uit te voeren. Een ander voorbeeld is de verstoorde onwillekeurige abductie van de arm tijdens balanceren over een dunne lijn. Vroegtijdige intensieve sensomotorische therapie is waarschijnlijk zeer belangrijk om de verkeerde of onvolledige aanleg van hersen programma's te verbeteren.

KRITISCHE OPMERKINGEN OVER TOEKOMSTIGE BEHANDELINGEN

Toekomstig onderzoek bij kinderen met NBPP moet zich richten op verschillende aspecten van het verbeteren van functioneel herstel. De volgende onderwerpen zijn van belang.

Vroege interventie

Kinderen met een NBPP hebben een geboorteletsel in een kritieke periode van ontwikkeling hetgeen niet alleen de sensorische en motorische functie van de arm aantast, maar de ontwikkeling van het hele centrale zenuwstelsel. Vroege behandeling is geïndiceerd om de sensomotorische ontwikkeling te stimuleren. Sensomotorische therapie kan corticale veranderingen bevorderen en de functie verbeteren.

internationale Plexus uitkomst studiegroep (iPluto)

Er is momenteel geen consensus over hoe de sensibiliteit van kinderen met een NBPP moet worden getest. Om tot consensus te komen is internationale afstemming nodig. Het iPluto testprotocol van het Leids Zenuwcentrum kan een opstap zijn naar een gevalideerd, universeel geaccepteerd testprotocol voor sensibiliteit bij kinderen met NBPP. De meest recente iPluto studie beschrijft het gebruik van PROm (Patient Reported Outcome measures) als uitkomstmaat.

De internationale classificatie van functionele beperkingen en gezondheid (ICF-model)

Elk domein van het ICF-model (International Classification of Functioning, Disability and Health) is relevant voor alle leeftijden, maar het is belangrijk om te beseffen dat de prioriteiten van de behandeling kunnen verschuiven met de leeftijd. In het begin (van geboorte tot peuter) zal de nadruk liggen op lichaamsstructuur en functie en naarmate het kind ouder wordt, komt de nadruk meer op activiteit en participatie. Perspectieven van functioneren en gezondheid in het ICF-model kunnen verschillen tussen patiënten en hun

ouders versus zorgverleners. Voor persoonlijke en omgevingsfactoren is het belangrijk om bewustheid te creëren van de verminderde sensibiliteit en de mogelijke gevolgen voor het kind en de ouders. Een cross-sectioneel onderzoek uit ons centrum onder adolescenten (> 16 jaar) met een NBPP toonde aan dat de algemene kwaliteit van leven niet was verminderd. Een aanzienlijk deel van de patiënten gaf echter aan dat hun NBPP invloed had op keuzes met betrekking tot opleiding en beroep, evenals op werk en prestatie. Er was geen verband tussen beperkingen in participatie en de ernst van het letsel of noodzaak van een zenuwoperatie. Deze bevindingen geven aan dat alle patiënten met NBPP, ongeacht de aanvankelijke ernst van het letsel, op latere leeftijd beperkingen kunnen ervaren. Naast de focus op 'Activiteit en Participatie' zou het waardevol zijn om een prospectief onderzoek uit te voeren met een focus op de grove motorische ontwikkeling bij kinderen met een NBPP, met speciale aandacht voor ontwikkelingsmijlpalen.

Specifieke therapie om de sensibiliteit te stimuleren

Onze studie levert nieuwe inzichten op over de verminderde en foutieve sensorische lokalisatiefeedback. Om foutieve patronen die tijdens de ontwikkeling in de hersenen zullen plaatsvinden te verminderen, is vroege intensieve sensomotorische therapie belangrijk. Hoewel de gunstige effecten van zulke interventies moeilijk te beoordelen zijn, is het noodzakelijk om therapie toe te passen om de sensibiliteit te verbeteren. Speciale sensorische integratie voor de sensibiliteit wordt in Nederland meestal niet aangeboden. Specifieke hersengebieden vereisen gelijktijdige interactie van verschillende zintuigen, zoals visuele, tactiele en akoestische input. De gelijktijdige stimulatie van handsensibiliteit met visuele en akoestische input kan een verbeterde waarneming van de aangedane hand bereiken. In een pilotstudie in Zweden werd een Sensor-handschoen gebruikt om de sensibiliteit te verbeteren na zenuwchirurgisch herstel van de n. medianus. Het doel was om de reorganisatie van de corticale handrepresentatie te stimuleren, bijvoorbeeld door te luisteren naar het wrijvingsgeluid. Met deze therapie verbeterde de sensibiliteit in vergelijking met een controlegroep.

In de Maartenskliniek in Nijmegen bieden therapeuten MuSSAP-behandeling (Multi-Sensory Stimulation and Priming) aan bij zuigelingen met een unilateraal hersenletsel. Hierbij draagt het kind 30 minuten per dag een speciaal polsbandje om de aangedane arm. Dit polsbandje kan licht, trillingen en geluid genereren om het gebruik van arm en hand te stimuleren. Het

onderliggende mechanisme van frequente toepassing van verschillende soorten sensorische prikkels op de vingers kan synaptogenese en dendritische uitgroei stimuleren. Dit moet uiteindelijk leiden tot een verbetering van de interpretatie van sensorische input en daarmee van de handfunctie. Behandelaars moeten aan het kind en hun verzorgers uitleggen dat er extra visuele controle nodig is om een taak goed uit te voeren. Dit moet ook worden opgenomen in de fysiotherapeutische behandeling.

Aanbevelingen van de bestaande Constraint-Induced Movement Therapie (CIMT) bij kinderen met een NBPP

Bij de CIMT wordt de niet-aangedane arm voor 3 weken geïmmobiliseerd, gevolgd door 5 weken bimanuele activiteiten. Het resultaat van de CIMT-therapie was bemoedigend voor zowel kinderen met NBPP als kinderen met unilaterale cerebrale parese. Bij het toepassen van de CIMT wordt het kind gedwongen om de aangedane zijde te gebruiken en wordt het centrale zenuwstelsel daardoor uitgedaagd om een oplossing te ontwikkelen. Er is echter een aantal belangrijke punten waarmee rekening gehouden moet worden.

De spierkracht kan slechts tot op zekere hoogte worden verbeterd, ten gevolge van de verminderde kwaliteit van de innervatie. Kinderen met een NBPP hebben ook na een zenuwoperatie een verminderd functioneren van het perifere axonale netwerk. Het is daarom niet mogelijk om door sporten of trainen een normale spierkracht te bereiken of spiervermoeidheid te verminderen. De beperking van het functieherstel ligt in de mate van zenuwherstel, hetzij spontaan of na een zenuwoperatie. Het stimuleren van gedeeltelijk verlamde spieren kan het kind stimuleren om compensatiemechanismen te ontwikkelen. Hierbij kunnen normaal functionerende spieren overbelast raken, bijvoorbeeld de m.trapezius. Tevens kunnen pijnklachten ontstaan door overactiviteit van de aangedane arm. Onderzoek heeft aangetoond dat gelijktijdige bilaterale tactiele stimulatie van de aangedane en de niet-aangedane hand kan helpen het centrale substraat voor sensorisch her-leren te beïnvloeden. De introductie van bilaterale activiteiten in therapiesessies kan daarom nuttig zijn. Momenteel is CIMT erg populair onder ouders, omdat ze ervan uitgaan dat CIMT een vervanging is voor de uitgebreide rekoefeningen die moeten worden gedaan om contracturen te verminderen. Dit is echter niet het geval en het blijft belangrijk om de ouders uit te leggen wat de prioriteiten van de therapie zijn.

Therapeut en ouders dienen zich bewust te zijn en te accepteren dat het kind de aangedane arm minder zal gebruiken en dat er een verschuiving van handdominantie kan optreden. In onze serie werd een verschuiving van handvoorkeur gevonden bij 87% van de geopereerde kinderen met NBPP. Bij de conservatief behandelde kinderen was dit 33%. Deze gegevens komen overeen met die van anderen die ook een verschuiving lieten zien in de handvoorkeur van kinderen met een NBPP. Bij kinderen met een rechtshandige plexuslaesie kan het een voordeel zijn om een voorkeur voor linkshandigheid te ontwikkelen. Bij de meeste kinderen ontwikkelen schrijven, eten en knippen met de linkerhand vanzelf. De aangedane arm herstelt zelden volledig, noch na conservatieve behandeling noch na een zenuwoperatie. De functie van de arm is ook verminderd door de sneller optredende spiervermoeidheid. Het is daarom aan te raden om te proberen de totale belasting van activiteiten over de dag te verdelen: op school schrijven met de niet-aangedane hand, en na school activiteiten met beide handen doen tijdens sport, muziek of andere hobby's.

Preventie van contracturen

De gewrichten bij kinderen met NBPP die specifiek risico lopen om stijf te worden, zijn de elleboog (flexiecontractuur) en de schouder (endorotatiecontractuur). De prevalentie van elleboogcontracturen met een range tussen 5 tot 90 graden is bijna 50%. Bij 21% tot 36% van de kinderen werd een elleboogflexie contractuur gevonden van meer dan 30 graden. De etiologie is multifactorieel. In de literatuur worden verschillende verklaringen genoemd, zoals de passieve beperking van het gewricht door de spierfascie, de huid en onderhuids weefsel, maar ook door actieve spiercontractie van de biceps. Ook een slechte coördinatie tussen m. biceps en m. triceps kan een rol spelen. Er zijn sterke aanwijzingen dat elleboogflexie contracturen grotendeels te wijten zijn aan de denervatie van de elleboogflexoren hetgeen een groeiachterstand van de spier veroorzaakt. De spierfenotypes van de elleboogcontractuur werden onderzocht bij kinderen met NBPP en cerebrale parese. In beide gevallen werd de contractuur veroorzaakt door een spierverkorting en niet door overmatige spierkracht. Deze bevindingen ondersteunen contractuurbehandelingen die de aangedane spieren verlengen in plaats van verzwakken, zoals wordt gedaan door botulinetoxine (BTX) behandeling. De voorkeursbehandeling voor het verminderen van de elleboogflexiecontractuur is een gipsspalk of een dynamische orthese voor de nacht.

Voor de endorotatiecontractuur van de schouder werden positieve resultaten verkregen met botulinetoxine om de endorotatie tijdelijk te verzwakken. BTX-A-injectie in de m. subscapularis kan een endorotatie contractuur verminderen en daarmee vervalt soms de noodzaak om een peestransferoperatie uit te voeren. Na 5 jaar follow-up werd echter bij 67% van de met BTX-A behandelde patiënten een recidief van de endorotatiecontractuur gevonden.

TOEKOMSTIG ONDERZOEK, SLOTGEDACHTEN

Een belangrijke vraag is hoe het sensibel herstel kan worden verbeterd. Het eerste wat moet worden onderzocht is of de schadelijke effecten van denervatie op het niveau van het centrale zenuwstelsel kunnen worden verminderd. Dit vereist een fundamenteel begrip van de gevolgen van motorische en sensorische denervatie op de centrale programmering. Een zenuw-operatie op jongere leeftijd dan momenteel standaard is, vormt misschien een mogelijkheid om deze gevolgen voor ontwikkeling van het centraal zenuwstelsel te verminderen. Het tweede probleem dat aandacht behoeft, is de wijze waarop axonale regeneratie kan worden verbeterd. Hierbij kan worden gedacht aan optimalisatie van chirurgische technieken, maar ook aan elektrische stimulatie of gentherapie om zenuwuitgroei te stimuleren.
Het wordt aanbevolen om een kwalitatief onderzoek te starten naar de ervaringen van ouders met kinderen met een NBPP. Zo'n project zou moeten onderzoeken hoe ouders omgaan met verstrekte informatie, hoe ze deze informatie thuis toepassen en hoe ouders omgaan met een kind met een plexusletsel vanuit het oogpunt van zorgverlening en ongerustheid over de toekomst. Bovendien zou het nuttig zijn om een literatuuronderzoek uit te voeren dat interventies wereldwijd kritisch op hun effectiviteit beoordeelt.

Ten slotte moeten verdere inspanningen worden geleverd om de kinderfysiotherapie en ergotherapie te verbeteren. Dergelijke verbeteringen zullen alleen haalbaar zijn door in toekomstige studies speciale aandacht te besteden aan de rol van de sensibiliteit. De behandelprotocollen in toekomstige onderzoeken zouden voor elke specifieke leeftijdscategorie moeten worden georganiseerd volgens het ICF-model. Het kan nodig zijn om gespecialiseerde therapeuten op te leiden, waardoor er meer aandacht komt voor de

evaluatie van de sensibiliteit in de dagelijkse klinische praktijk en voor therapeutische interventiemogelijkheden. Dit alles kan leiden tot verbetering van de functionele uitkomsten bij kinderen met NBPP, wat resulteert in een betere controle van de arm en een betere kwaliteit van leven.

LIST OF PUBLICATIONS

This thesis

- Obstetric Brachial Plexus Lesions and Central Developmental Disability; -Sonja M. Buitenhuis, Rietje S. van Wijlen-Hempel, Willem Pondaag, Martijn J.A. Malessy; Early Hum Dev. 2012 Sep;88(9):731-4. doi: 10.1016/j.earlhumdev.2012.03.004. Epub 2012 Jun 30
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- Tactile Perception of the Hand in Children with an upper Neonatal Brachial Plexus Palsy; Buitenhuis SM, Pondaag W, Wolterbeek R, Malessy MJA; Arch Phys Med Rehabil. 2022.
- The Milestone of Independent Walking is delayed in Infants with a Neonatal Brachial Plexus Palsy Sonja M. Buitenhuis, Willem Pondaag, Rietje M. van Hempel -Wijlen, Martijn J.A. Malessy; Submitted
- Children with an upper Neonatal Brachial Plexus Palsy: Awareness of Diminished Sensibility and Pain in the Hand Sonja M. Buitenhuis, Willem Pondaag, Ron Wolterbeek, Martijn J.A. Malessy; Submitted

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- External rotation as a result of suprascapular nerve neurotization in obstetric brachial plexus lesions; Pondaag W, de Boer R, van Wijlen-Hempel MS, Hofstede-Buitenhuis SM, Malessy MJ; Neurosurgery. 2005;57(3):530-7.
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CURRICULUM VITAE

Sonja Buitenhuis werd op 19 november 1957 geboren te ’s-Gravenhage. Zij deed in 1976 eindexamen Atheneum aan het Huygens Lyceum te Voorburg. In 1980 studeerde zij af als fysiotherapeut. De Master kinderfysiotherapie bestond toentertijd uit verschillende Post HBO modules en een aanvullingscursus Kindergeneeskunde. In 1995 werd ze als kinderfysiotherapeut geregistreerd.
Van juli 1980 tot oktober 1983 werkte ze in het Juliana kinderziekenhuis en in een particuliere praktijk, waarna ze ruim 18 jaar werkte in het Rijnlands Revalidatie Centrum. Vanaf 1995 startte ze haar eigen praktijk voor kinderfysiotherapie, wat samen met nog vijf collega’s, kinderpsychiater, logopediste en ergotherapeut uitgroeide tot een multidisciplinaire praktijk. Vanaf januari 2000 tot nu is ze naast haar werkzaamheden in haar praktijk, verbonden aan het zenuwcentrum van het LUMC.
Vanaf 2008 tot heden is ze docent op de Master kinderfysiotherapie opleiding te Rotterdam. In 2015 en 2016 is ze 3x op missie gegaan voor Artsen zonder Grenzen, waar ze training gaf over de Bayley Scales of Infant Development III aan kinderartsen in Haïti. Naar aanleiding van deze ervaringen heeft ze een verdiepingscursus op de motoriekschaal van de Bayley-III-NL ontwikkelt en geeft ze hier cursus over.
In 2015 werd haar onderzoek naar sensibiliteit bij kinderen met een obstetrisch plexus brachialis letsel door de medisch ethische toetsingscommissie van de Leids Universitair Medisch Centrum goedgekeurd. Dit vormde feitelijk de start van haar promotieonderzoek.

DANKWOORD

Mijn proefschrift was niet tot stand gekomen zonder de medewerking van de ouders en kinderen die het zenuwcentrum van het LUMC bezochten en bereid waren om mee te doen aan de onderzoeken. Mijn dank ervoor! Ook dank aan alle kinderen met een obstetrisch plexus brachialis letsel, zowel in het LUMC als in de kinderfysiotherapie praktijk Voorburg die mij zoveel geleerd hebben over hun klachten en ervaringen. Het vertrouwen dat zij mij gaven, door aan mij duidelijk te maken waar ze tegenaan liepen. Zij hebben mij met hun verhalen geleerd dat we zo veel kunnen leren van hun kijk op hun letsel. Zij hebben mij gestimuleerd om al die ervaringen op te schrijven en tot dit proefschrift te komen.

Prof.dr. M.A. Malessy, geachte promotor, beste Martijn veel dank voor je overdracht van jouw kennis, je geduld, je stimulans voor de publicaties en voor de vele keren dat je de teksten kon vinden die niet goed liepen en zo pakkend hebt aangepast. Dank Martijn, voor je vertrouwen dat je in mij heb gesteld.
Dr.W.Pondaag, geachte copromotor, beste Willem, jouw eindeloze hoeveelheid energie maakte dat je ondanks jouw drukke programma altijd wel een gaatje voor overleg wist te vinden. Dank voor je humor, je enorme hoeveelheid geduld en je vermogen om mijn verwarde geest weer te ontrafelen tot wat ik nu precies bedoelde.

Dr R. Woltersbeek, beste Ron, dank voor al je hulp bij de statistieke berekeningen. Vele middagen en avonden hielp je mij om op een rustige manier samen te kijken hoe we de beste syntax konden maken en mooie resultaten konden zien. In een pauze even nasi eten in het restaurant van het LUMC en dan weer met koffie terug naar de tafel voor de berekeningen. Zelfs na je pensionering bleef je mij statistisch ondersteunen en zo nodig controleren.

Dank aan de leden van het zenuwcentrum, Rob Nelissen en Jochem Nagels orthopedische chirurgen, wat heb ik veel geleerd van jullie kennis van gewrichten en spieren en hoe je deze kennis het beste kunt onderzoeken en interpreteren. Justus neurochirurg, dank voor jouw stimulerende- en ondersteunende woorden. Rietje, jij overtuigde mij dat ik dit proefschrift moest gaan doen. We hebben samen cursussen en symposia gevolgd, maar ook levenswijsheden uitgewisseld. We hebben twee artikelen samen gemaakt. Jouw

optimistische kijk, wijsheden en meedenken met ingewikkelde materie bracht mij telkens weer een stap verder. Ook dank aan de mensen van het zenuwcentrum secretariaat, Wilma en Melanie voor jullie ondersteuning. Roxanne, physician assistant van de neurochirurgie, dank dat je ons bent komen versterken.

Eric Vermeulen, hoofd fysiotherapie, dank voor je betrokkenheid. Ines dank voor je hulp als ik het HIX systeem niet meer kon volgen.

Veel dank aan mijn familie Berry, Ruud, Nanda, Marijn en Maaike voor het meeleven, het geduld en jullie acceptatie dat ik weinig tijd voor jullie had.

Dank aan Floor, mijn buurvrouw. Wat hebben we veel avondjes “gezellig“ aan de statistiek gezeten. Jouw nuchtere kijk op resultaten bracht mijn denken weer op een ander spoor.

Paranimf Vida, wij hebben samen zoveel meegemaakt in onze privé en professioneel dat het voor mij een heel logische keuze was om jou als paranimf te kiezen. Dank voor je altijd meeleven en belangstelling. Jij was altijd één van de eersten die mijn artikelen wilde lezen.

Mijn meeste dank gaat uit naar mijn partner Rob. Lieve Rob, wat heb ik veel aan jou te danken. Veel meer dan ik hier kort kan weergeven. Natuurlijk moet jij mijn paranimf zijn.

Annex A

Overview of the Most Cited Articles on Sensibility

Literature search was done from 2013 until 2020.

A total of 175 references taken from:

PubMed, Embase, Web of Science, Cochrane and CINAHL

The search criteria for inclusion were:

Children, NBPP, Sensibility, Sensibility test, Hand sensation and Sensory outcome.

Reference	Methods	Sample size	Results	Characteristics Evaluation of results
Sundholm 1998[1]	2PD with a paper clip with a prong spacing of 3 mm. Comparison with the unaffected hand	N = 55 out of 105 children, age 5 years with lesion of C5 C6	69/105 managed to discriminate two points spaced 3 mm, 16 out of 55 with C5 C6 lesion had impaired 2PD 17 didn't finish the test, not enough concentrated	paperclip 3mm is normal sensation.
Arnand 2002[2]	six sensory modalities: SW monofilaments, cotton wool, pinprick, warm/cool sensation, joint position sense and vibration	N = 24, aged 3-23 years 16 out of 20 operated cases.	6 out of 20 operated patients recovered to normal SW testing results,	Their definition of 'excellent restoration' of sensory function was recovery to normal limits in all dermatomes 'for at least one modality'
Strombeck 2007[3]	2PD with paperclip with a prong spacing of 3 mm, or 7 mm. Comparison with the unaffected hand	N = 41 aged 3-23 years with C5-C6 lesion	4/41 decreased sensibility	2PD with paperclip with a prong spacing of 3 mm is normal, 7 mm is abnormal
Palmgren 2007[4]	SW monofilament on 32 palmar areas was tested. Abnormal SW 4.31-4.56 Comparison with the unaffected hand	N = 64 aged two groups: 6- 8 years and 12-14 years with C5 C6 lesions 1 nerve surgery	7/64 abnormal findings one child, nerve surgery: most abnormal SW	All (minus one)[5] conservative treatment Abnormal: SW 4.31
Kirjavainen 2008[6]	SW monofilamenten on 32 different palmar areas. Abnormal SW 4.31-to 6.65 Comparison with the unaffected hand	N = 49 with C5 C6 lesion, all with surgery in first year. Mean follow up for 13.4 years (5.0 to 31.5)	34 normal: 2.83 to 3.61 filament 12: abnormal: 4.31 filament 3: loss of protective:4.56 filament	Abnormal if 4.31 filament or higher, 3.61 filament borderline abnormal/ diminished light touch, normal touch 2.83 filament

Reference	Methods	Sample size	Results	Characteristics Evaluation of results
Anguelova, G.V. 2013[5]	SW, 2PD, object recognition, locognosia test. Comparison with hand of healthy people	N = 17, all conservative treated adults, 7 with C5 C6	SW and 2PD significant worse in those with NBPP but not object recognition and locognosia	Population: adults
Brown/Yang 2016[7]	SW monofilament , tactile spatial test and stereognosis test. Comparison with the unaffected hand and comparison with controls	N = 17, mean age 11,6 years 4 children with C5-C7 en 13 children with C5-T1	SW **median** (2.83)monofilament was normal in the NBPP group. SW 3.61 was seen in one patient Tactile spatial perception was impaired in the neonatal brachial plexus palsy group.	SW score 3.61 indicate of a diminished touch threshold. Tactile spatial perception was tested by measuring the ability to identify raised pin patters applied to the tip of the index finger
Ho/Clarke 2019[8]	SW monofilament and stereognosis test Comparison with the unaffected hand	N = 63 children participated (aged 10.92 +/- 3.29 years), all nerve surgery	12 / 63 children with upper plexus and 12 / 63 with total plexus injury had sensory impairment Impairment of the Stereognosis: 5 children with an upper plexus and 13 in the total group	Children with sensory impairment in the upper plexus group versus the total plexus group were not statistically different.
Buitenhuis[9-11] 2018	SW monofilamenten, 2PD, object recognition, locognosia test Comparison with controls	N = 50 children with C5 C6(20 conservative and 30 nerve surgery)	SW and 2PD: thumb and index finger (either surgically or conservatively treated) is diminished Locognosia test: incorrect ability to localize sensory stimuli to their fingers dig I- IV Stereognosis test: normal	The decreased sensibility has a negative impact on hand function

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Annex B

Test Forms

(in English and Dutch)

ENGLISH FORMS

INTAKE FORM

General data	
Date of birth	
Gender	
Dominant hand	
Affected side	
School	Grade .....
Additional Info	
Number	

OBPL-specifical history	
Nerve surgery	1. No 2. Yes, 2.a Diagnosis..... 2.b Operation date..... 2.c Which operation.....
Secondary surgery	1. No 2. Yes, 2.a Diagnosis..... 2.b Operation date..... 2.c Which operation.....

Motor skills - Movement results (taking over 'usual care')		
	Movement passive	*Movement active*
Abduction		
External rotation (in abd)		
External rotation (in add)		
Elbow flexion		
Elbow extension		
Supination		
Wrist extension		

Motor skills - Muscle strength MRC (0-5)	
Biceps	
Triceps	
Extension Pols	
gripforce	

Annex B

SW MONOFILAMENTS TEST

There are three filaments. The thinnest filament is started (D 2.83). This filament is tested twice per fingertip. If the child feels at least 1 of the 2 attempts, then the next thicker filament does not need to be applied to that finger. Indicate with **+** when the child feels the filament and with a **-** if the child does not feel it.

Number: ..... Date:.../.../...

Date of birth:.../.../... Carried out by: .....

Start time: ___:___

Right hand	Thumb	Forefinger	Middle finger	Ring finger	Little finger
D 2.83					
D 2.83					
F 3.61					
F 3.61					
J 4.31					
J 4.31					
....					

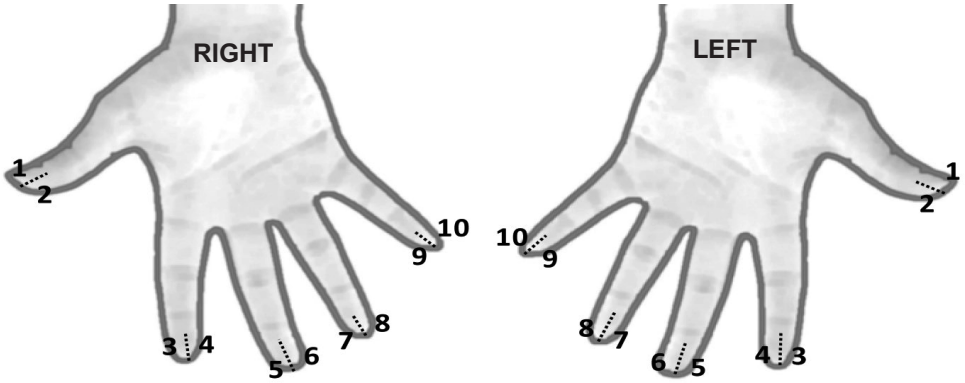
Left hand	Thumb	Forefinger	Middle finger	Ring finger	Little finger
D 2.83					
D 2.83					
F 3.61					
F 3.61					
J 4.31					
J 4.31					
....					

End time: ___:___ time of this section: ___:___

LOCALIZATION TEST

A nylon thread with thickness A6.65 of the Semmes-Weinstein Monofilament test is pressed on the fingertips.

In front of the child, a drawing is placed of the hand, in which the fingertips are divided into two halves. These half fingers are numbered ascendingly from 1 (radial side of the thumb) to 10 (ulnar side of the little finger). The thickest SW monofilament is placed on a fingertip for 2 seconds at the radial or ulnar half. The child must indicate the number where he felt the pressure. Each correctly identified localization is counted as 2 points. When the pressure is localized in the right half of the adjacent finger or in the wrong half of the right finger, 1 point is given.



Number: ..... Date:.../.../...

Date of birth:.../.../... Carried out by: .....

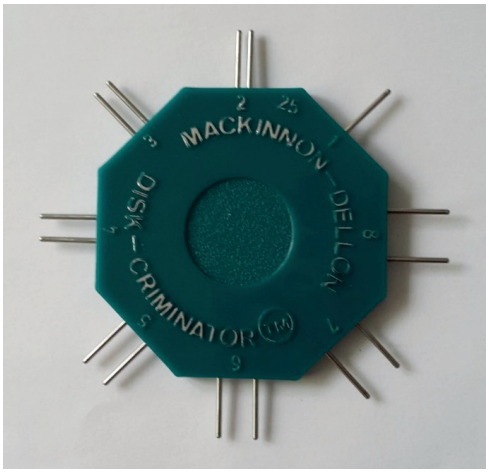
Start time: ___:____

Right	10	2	8	4	5	2	7	5	8	9	3	1	6	3	9	10	1	4	7	6	Total
Score																					
Points																					
Left	1	9	7	3	2	5	8	7	6	2	10	1	5	3	8	6	4	10	9	4	
Score																					
Points																					

End time: ___:_____ time of this part: ___:____

TWO POINTS OF DISCRIMINATION

Tested with a Disk-Criminator ™. This is a disc with 1 or 2 rounded pins. The 2 rounded pins are rising from 2 to 8 mm distance from each other.



The thumb (C6), index finger tip (C6 and C7) and the pinky tip (C8) of both hands are tested statically. In the static test, the discriminator with only the weight of the instrument is placed longitudinally on the fingertip. Varying distances between the dots of 2 to 8 mm must be indicated by the subject as 1 or 2 dots. The smallest distance observed between the dots is noted.

Start time: ___:___

Right hand

Step 1. Determine the smallest tangible distance

Test moment	Index finger (static - mm)			Pink (static – mm)			Thumb (static – mm)		
		1p	2p		1p	2p		1p	2p
1	7 mm			7 mm			6 mm		
2	6 mm			6 mm			7 mm		
3	0 mm			0 mm			0 mm		
4	4 mm			4 mm			4 mm		
5	2 mm			0 mm			2 mm		
6	0 mm			3 mm			0 mm		
7	3 mm			2 mm			3 mm		

Step 2. Validate the smallest tangible distance per fingertip

	Forefinger	Little finger	Thumb
Smallest tangible distance	..... mm	..... mm	..... mm
Validated by having felt the smallest tangible distance 5 times in a row	Yes/no	Yes/no	Yes/no

Left hand

Step 1. Determine the smallest tangible distance

Test moment	Index finger (static - mm)			Pink (static – mm)			Thumb (static – mm)		
		1p	2p		1p	2p		1p	2p
1	7 mm			7 mm			6 mm		
2	6 mm			6 mm			7 mm		
3	0 mm			0 mm			0 mm		
4	4 mm			4 mm			4 mm		
5	2 mm			0 mm			2 mm		
6	0 mm			3 mm			0 mm		
7	3 mm			2 mm			3 mm		

Step 2. Validate the smallest tangible distance per fingertip

	Forefinger	Little finger	Thumb
Smallest tangible distance	..... mm	..... mm	..... mm
Validated by having felt the smallest tangible distance 5 times in a row	Yes/no	Yes/no	Yes/no

End time: ___:_____ time of this part: ___:____

STEREOGNOSIS

Both hands are put behind a screen. Six small objects (eraser, small paper ball, Lego brick, bead, coin, button) were successively placed between the fingertips, in alternating sequence, starting with the dominant hand.

The child had to identify the object. A similar series of objects remained in sight in front of the screen to facilitate recognition.

Start time: ___:____

Right hand		
	Object	Points (1 point per item)
1	Eraser	
2	Paper wad	
3	Coin	
4	Button	
5	Bead	
6	Lego brick	
	Total points	

Left hand		
	Object	Points (1 point per item)
1	Bead	
2	Coin	
3	Lego brick	
4	Button	
5	Eraser	
6	Paper wad	
	Total points	

End time: ___:_____ time of this part: ___:____

NEDERLANDSE FORMULIEREN

INTAKE FORMULIEREN

Algemene gegevens	
Geboortedatum	
Geslacht	
Voorkeurshand	
Aangedane kant	
School	Groep…..
Rugzakje ja/nee	
Nummer	

OBPL-specifieke voorgeschiedenis	
Zenuw-operatie	1. Nee 2. Ja, 2.a Diagnose…… 2.b Operatie datum…… 2.c Welke operatie……..
Secundaire operatie	1. Nee 2. Ja, 2.a Diagnose…… 2.b Operatie datum…….. 2.c Welke operatie……..

Motoriek Bewegingsuitslagen (overnemen van 'usual care')		
	Bewegingsuitslag passief	*Bewegingsuitslag actief*
Abductie		
Exorotatie (in abd)		
Exorotatie (in add)		
Elleboog flexie		
Elleboog extensie		
Supinatie		
Pols extensie		

Motoriek - Spierkracht MRC (0-5)	
Biceps	
Triceps	
Extensie Pols	
Knijpkracht	

Annex B

SW MONOFILAMENT TEST

Er zijn drie filamenten. Er wordt begonnen met het dunste filament (D 2.83). Dit filament wordt per vingertop twee keer getoetst. Als het kind minimaal 1 van de 2 pogingen voelt, dan hoeft het volgende dikkere filament niet toegepast te worden op die vinger. Geef met + aan wanneer het kind het filament voelt en met een - als het kind het niet voelt.

Nummer: ..... Datum:.../.../...

Geboortedatum:.../.../... Afgenomen door .....

Starttijd: ___:___

Rechter hand	Duim	Wijsvinger	Middelvinger	Ringvinger	Pink
D 2.83					
D 2.83					
F 3.61					
F 3.61					
J 4.31					
J 4.31					
....					

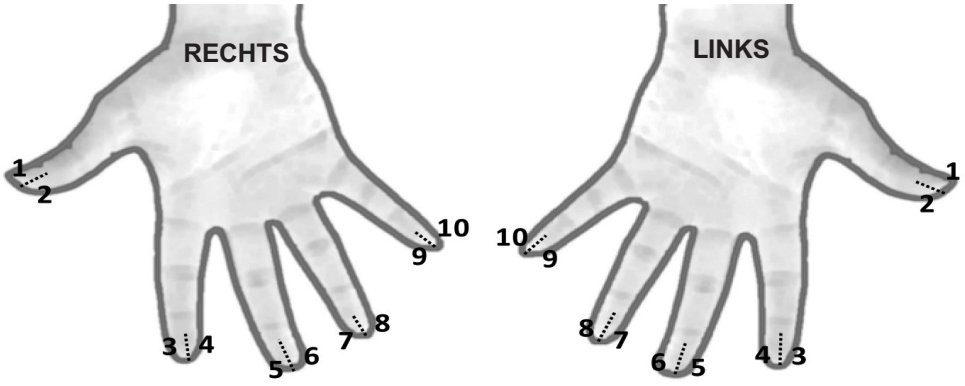
Linker hand	Duim	Wijsvinger	Middelvinger	Ringvinger	Pink
D 2.83					
D 2.83					
F 3.61					
F 3.61					
J 4.31					
J 4.31					
....					

Eindtijd: ___:___ Tijd van dit onderdeel: ___:___

LOCALISATIE TEST

Een nylondraadje met dikte A6.65 van de Semmes-Weinstein Monofilamententest wordt op de vingertoppen gedrukt.

Voor het kind wordt een tekening geplaatst van de hand, waarbij de vingertoppen verdeeld zijn in twee helften. Deze halve vingers zijn oplopend genummerd van 1 (radiaire zijde van de duim) tot 10 (ulnaire zijde van de pink). Het dikste SW monofilament wordt 2 seconden op een vingertop geplaatst aan de radiaire of ulnaire helft. Het kind moet het nummer aangeven waar hij de druk heeft gevoeld. Elke juist geïdentificeerde lokalisatie wordt geteld als 2 punten. Wanneer de druk wordt gelokaliseerd in de juiste helft van de aangrenzende vinger of in de verkeerde helft van de juiste vinger wordt er 1 punt gegeven.



Nummer: .....

Datum:.../.../...

Geboortedatum:.../.../...

Afgenomen door .....

Starttijd: ___:___

Rechts	10	2	8	4	5	2	7	5	8	9	3	1	6	3	9	10	1	4	7	6	Total
Score																					
Punten																					
Links	1	9	7	3	2	5	8	7	6	2	10	1	5	3	8	6	4	10	9	4	
Score																					
Punten																					

Eindtijd: ___:___

tijd van dit onderdeel: ___:___

TWEE PUNTS DISCRIMINATIE

Getest wordt met een Disk-Criminator ™. Dit is een schijf met 1 of 2 afgeronde pinnetjes. De 2 afgeronde pinnetjes staan oplopend van 2 tot 8 mm afstand van elkaar.
Van beide handen worden de duim (C6), wijsvingertop (C6 en C7) en de pinktop (C8) statisch getest. Bij de statische test wordt de discriminator met alleen het gewicht van het instrument longitudinaal op de vingertop gezet. Wisselende afstanden tussen de puntjes van 2 tot 8 mm moet door de proefpersoon juist worden aangegeven als 1 of 2 puntjes. De kleinste afstand die wordt waargenomen tussen de puntjes wordt genoteerd.

Starttijd: ___:___

Rechterhand

Stap 1. Bepaal de kleinst voelbare afstand

Testmoment	Wijsvinger (static – mm)			Pink (static – mm)			Duim (static – mm)		
		1p	2p		1p	2p		1p	2p
1	7 mm			7 mm			6 mm		
2	6 mm			6 mm			7 mm		
3	0 mm			0 mm			0 mm		
4	4 mm			4 mm			4 mm		
5	2 mm			0 mm			2 mm		
6	0 mm			3 mm			0 mm		
7	3 mm			2 mm			3 mm		

Stap 2. Valideer de kleinst voelbare afstand per vingertop

	Wijsvinger	Pink	Duim
Kleinst voelbare afstand	……mm	……mm	……mm
Gevalideerd door 5x achter elkaar de kleinst voelbare afstand te hebben gevoeld	Ja/nee	Ja/nee	Ja/nee

Linkerhand

Stap 1. Bepaal de kleinst voelbare afstand

Testmoment	Wijsvinger (static – mm)			Pink (static – mm)			Duim (static – mm)		
		1p	2p		1p	2p		1p	2p
1	7 mm			7 mm			6 mm		
2	6 mm			6 mm			7 mm		
3	0 mm			0 mm			0 mm		
4	4 mm			4 mm			4 mm		
5	2 mm			0 mm			2 mm		
6	0 mm			3 mm			0 mm		
7	3 mm			2 mm			3 mm		

Stap 2. Valideer de kleinst voelbare afstand per vingertop

	Wijsvinger	Pink	Duim
Kleinst voelbare afstand	……mm	……mm	……mm
Gevalideerd door 5x achter elkaar de kleinst voelbare afstand te hebben gevoeld	Ja/nee	Ja/nee	Ja/nee

Eindtijd: ___:___ tijd van dit onderdeel: ___:___

STEREOGNOSIS

Starttijd: ___:___

Rechterhand		
	Voorwerp	Punten (1 punt per object)
1	Gum	
2	Papierpropje	
3	Munt	
4	Knoop	
5	Kraal	
6	Legoblokje	
	Totaal aantal punten	

Linkerhand		
	Voorwerp	Punten (1 punt per object)
1	Kraal	
2	Munt	
3	Legoblokje	
4	Knoop	
5	Gum	
6	Papierpropje	
	Totaal aantal punten	

Eindtijd: ___:___ tijd van dit onderdeel: ___:___