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

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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.

REFERENCES

1. Hofstede-Buitenhuis SM, Malessy MJA, Pondaag W, Wijlen-Hempel vMS, Boer dK, Nelissen RGHH, et al. `Het Steindler-effect bij het obstetrisch plexus-brachialisletsel. Tijdschrift voor kindergeneeskunde. 2011;79(4):106-10.
2. Malessy MJ, Pondaag W, Yang LJ, Hofstede-Buitenhuis SM, le Cessie S, van Dijk JG. Severe obstetric brachial plexus palsies can be identified at one month of age. PLoS One. 2011;6(10):e26193.
3. Brown SH, Wernimont CW, Phillips L, Kern KL, Nelson VS, Yang LJ. Hand Sensorimotor Function in Older Children With Neonatal Brachial Plexus Palsy. Pediatr Neurol. 2016;56:42-7.
4. Krumlinde-Sundholm L, Eliasson AC, Forssberg H. Obstetric brachial plexus injuries: assessment protocol and functional outcome at age 5 years. DevMed Child Neurol. 1998;40(1):4-11.
5. Strombeck C, Krumlinde-Sundholm L, Forssberg H. Functional outcome at 5 years in children with obstetrical brachial plexus palsy with and without microsurgical reconstruction. Dev Med Child Neurol. 2000;42(3):148-57.
6. Brown SH, Noble BC, Yang LJ, Nelson VS. Deficits in elbow position sense in neonatal brachial plexus palsy. Pediatr Neurol. 2013;49(5):324-8.
7. Anguelova GV, Malessy MJ, Buitenhuis SM, van Zwet EW, van Dijk JG. Impaired Automatic Arm Movements in Obstetric Brachial Plexus Palsy Suggest a Central Disorder. J Child Neurol. 2016;31(8):1005-9.
8. Anguelova GV, Rombouts S, van Dijk JG, Buur PF, Malessy MJA. Increased brain activation during motor imagery suggests central abnormality in Neonatal Brachial Plexus Palsy. Neurosci Res. 2017;123:19-26.
9. Kahraman A, Mutlu A, Livanelioglu A, Assessment of Motor Repertoire in 3- to 5-Month-Old Infants With Obstetric Brachial Plexus Lesion. Pediatr Phys Ther, 2020 32(2):114-119
10. Lokmanoğlu BNY, Fırat T, Delioğlu K, Porsnok D, Sırtbaş G, Mutlu A. Early Spontaneous Movements and Upper Extremity Movement Score in Infants With all Narakas Types of Obstetric Brachial Plexus Palsy. Pdiatric Neurology. 2022;134.11-17.
11. Çelik G, Delioğlu K, Fırat T. The Relationship between Trunk Control and Upper Extremity Function in Children with Obstetric Brachial Plexus Palsy. Developmental Neurorehabilitation. 2021;24(3):150-158.
12. Chang, KW, Yang, LJ, Driver, L,Nelson, VS. High prevalence of early language delay exists among toddlers with neonatal brachial plexus palsy. Pediatr Neurol. 2014;51(3):384-9.
13. Alyanak B, Kilincaslan A, Kutlu L, Bozkurt H, Aydin A. Psychological adjustment, maternal distress, and family functioning in children with obstetrical brachial plexus palsy. J Hand Surg Am. 2013;38(1):137-142.
14. Buitenhuis S, van Wijlen-Hempel RS, Pondaag W, Malessy MJ. Obstetric brachial plexus lesions and central developmental disability. Early Hum Dev. 2012;88(9):731-4.
15. Capute AJ, Shapiro BK,Palmer B, Ross A, Wachtel RC. Normal gross motor development: the influences of race, sex and socio-economic status. Dev Med Child Neurol 1985 Oct;27(5):635-43.
16. Kelly Y, Sacker A, Schoon I, Nazroo J. Ethnic differences in achievement of developmental milestones by 9 months of age: The Millennium Cohort Study. Dev Med Child Neurol. 2006 Oct;48(10):825-30.

17. Bellows D, Bucevska M, Verchere C. Coordination and balance in children with birth-related brachial plexus injury: a preliminary study. Physiother Can. 2015;67(2):105-12.
18. Pin, TW, Butler, PB., Cheung, HM, Shum, SL, Relationship between segmental trunk control and gross motor development in typically developing infants aged from 4 to 12 months: a pilot study. BMC Pediatr. 2019;19(1):425.
19. Gülay Ç, Tüzün F, How brachial plexus birth palsy affects motor development and upper extremity skill quality. Childs Nerv Syst. 2021;37(2):2865-2871
20. Hadders-Algra M. Early human motor development: From variation to the ability to vary and adapt. Neurosci Biobehav Rev. 2018;90:411-27.
21. Hadders-Algra M, Heineman KR. The Infant Motor Profile [eBook]. London: Taylor & Francis Group; 2021.
22. Corkum JP, Kuta V, Tang DT, Bezuhly M. Sensory outcomes following brachial plexus birth palsy: A systematic review. Journal of plastic, reconstructive & aesthetic surgery : JPRAS. 2017;70(8):987-95.
23. Sundholm LK, Eliasson AC, Forssberg H. Obstetric brachial plexus injuries: assessment protocol and functional outcome at age 5 years. DevMed Child Neurol. 1998;40(1):4-11.
24. Strombeck C, Remahl S, Krumlinde-Sundholm L, Sejersen T. Long-term follow-up of children with obstetric brachial plexus palsy II: neurophysiological aspects. DevMed Child Neurol. 2007;49(3):204-9.
25. Palmgren T, Peltonen J, Linder T, Rautakorpi S, Nietosvaara Y. Sensory evaluation of the hands in children with brachial plexus birth injury. DevMed Child Neurol. 2007;49(8):582-6.
26. Kirjavainen M, Remes V, Peltonen J, Rautakorpi S, Helenius I, Nietosvaara Y. The function of the hand after operations for obstetric injuries to the brachial plexus. J Bone Joint Surg Br. 2008;90(3):349-55.
27. Ho ES, Davidge K, Curtis CG, Clarke HM. Sensory Outcome in Children Following Microsurgery for Brachial Plexus Birth Injury. J Hand Surg Am. 2019;44(2):159 e1- e8.
28. van Vliet AC, Tannemaat MR, van Duinen SG, Verhaagen J, Malessy MJ, De Winter F. Human Neuroma-in-Continuity Contains Focal Deficits in Myelination. J Neuropathol Exp Neurol. 2015;74(9):901-11.
29. Chen L, Gao SC, Gu YD, Hu SN, Xu L, Huang YG. Histopathologic study of the neuroma-in-continuity in obstetric brachial plexus palsy. Plast Reconstr Surg. 2008;121(6):2046-54.
30. Pondaag W, van der Veken LP, van Someren PJ, van Dijk JG, Malessy MJ. Intraoperative nerve action and compound motor action potential recordings in patients with obstetric brachial plexus lesions. J Neurosurg. 2008;109(5):946-54.
31. van Dijk JG, Malessy MJ, Stegeman DF. Why is the electromyogram in obstetric brachial plexus lesions overly optimistic? Muscle Nerve. 1998;21(2):260-1.
32. Anguelova GV, Malessy MJ, van Zwet EW, van Dijk JG. Extensive motor axonal misrouting after conservative treatment of obstetric brachial plexus lesions. Dev Med Child Neurol. 2014;56(10):984-9.
33. Kislay K, Devi BI, Bhat DI, Shukla DP, Gupta AK, Panda R. Novel Findings in Obstetric Brachial Plexus Palsy: A Study of Corpus Callosum Volumetry and Resting-State Functional Magnetic Resonance Imaging of Sensorimotor Network. Neurosurgery. 2018;83(5):905-14.
34. Hadders-Algra M. The neuronal group selection theory: a framework to explain variation in normal motor development. Dev Med Child Neurol. 2000;42(8):566-72.

35. Hadders-Algra M. Variation and variability: key words in human motor development. Phys Ther. 2010;90(12):1823-37.
36. Chen A, Yao J, Kuiken T, Dewald JP. Cortical motor activity and reorganization following upper-limb amputation and subsequent targeted reinnervation. Neuroimage Clin. 2013;3:498-506.
37. Longo E, Nishiyori R, Cruz T, Alter K, Damiano DL. Obstetric Brachial Plexus Palsy: Can a Unilateral Birth Onset Peripheral Injury Significantly Affect Brain Development? Dev Neurorehabil. 2020;23(6):375-82.
38. Lundborg G. Richard P. Bunge memorial lecture. Nerve injury and repair--a challenge to the plastic brain. J Peripher Nerv Syst. 2003;8(4):209-26.
39. Edwards LL, King EM, Buetefisch CM, Borich MR. Putting the "Sensory" Into Sensorimotor Control: The Role of Sensorimotor Integration in Goal-Directed Hand Movements After Stroke. Front Integr Neurosci. 2019;13:16.
40. Pondaag W, Malessy MJA. Outcome assessment for Brachial Plexus birth injury. Results from the iPluto world-wide consensus survey. J Orthop Res. 2018;36(9):2533-41.
41 Brown, H, van der Looven, R, , Ho, ES, Pondaag, W, Patient reported outcomes in brachial plexus birth injury: results from the iPLUTO world-wide consensus survey. Disabil Rehabil. 2024 Jan 4:1-7
42. Duff SV, DeMatteo C. Clinical assessment of the infant and child following perinatal brachial plexus injury. J Hand Ther. 2015;28(2):126-33; quiz 34.
43. Sarac C, Nelissen R, van der Holst M, Malessy MJA, Pondaag W. Differences in the perspectives of functioning and health in the ICF model between patients with brachial plexus birth injury and their parents versus healthcare professionals. Disability and rehabilitation. 2022:1-6.
44 Van der Holst M, Groot J, Steenbeek D, Pondaag W, Nelissen RG, Vliet Vlieland TP. Participation restrictions among adolescents and adults with neonatal brachial plexus palsy: the patient perspective. Disability and rehabilitation. 2018;40(26):3147-3155.
45. Lundborg G, Rosen B. Hand function after nerve repair. Acta Physiol (Oxf). 2007;189(2):207-17.
46. Zink PJ, Philip BA. Cortical Plasticity in Rehabilitation for Upper Extremity Peripheral Nerve Injury: A Scoping Review. Am J Occup Ther. 2020;74(1):7401205030p1-p15.
47. Werner JM, Berggren J, Loiselle J, Lee GK. Constraint-induced movement therapy for children with neonatal brachial plexus palsy: a randomized crossover trial. Dev Med Child Neurol. 2021;63(5):545-51.
48. Yang LJ, Anand P, Birch R. Limb preference in children with obstetric brachial plexus palsy. PediatrNeurol. 2005;33(1):46-9.
49. Ho ES, Kim D, Klar K, Anthony A, Davidge K, Borschel GH, et al. Prevalence and etiology of elbow flexion contractures in brachial plexus birth injury: A scoping review. Journal of pediatric rehabilitation medicine. 2019;12(1):75-86.
50. Nikolaou S, Garcia MC, Long JT, Allgier AJ, Goh Q, Cornwall R. Brachial plexus birth injury and cerebral palsy lead to a common contracture phenotype characterized by reduced functional muscle length and strength. Front Rehabil Sci. 2022;3:983159.
51. Op de Coul LS, Bleeker S, de Groot JH, Nelissen R, Steenbeek D. Elbow flexion contractures in neonatal brachial plexus palsy: A one-year comparison of dynamic orthosis and serial casting. Clin Rehabil. 2022:2692155221121011.
52. Duijnisveld BJ, van Wijlen-Hempel MS, Hogendoorn S, de Boer KS, Malessy MJ, Keurentjes JC, et al. Botulinum Toxin Injection for Internal Rotation Contractures in

Brachial Plexus Birth Palsy. A Minimum 5-Year Prospective Observational Study. J Pediatr Orthop. 2017;37(3):e209-e15.
53. Arad E, Stephens D, Curtis CG, Clarke HM. Botulinum toxin for the treatment of motor imbalance in obstetrical brachial plexus palsy. Plast Reconstr Surg. 2013;131(6):1307-15.