Unravelling cossed wires : dysfunction in obstetric brachial plexus lesions in the light of intertwined effects of the peripheral and central nervous system

Anguelova, G.V.

Chapter 1

Introduction

Obstetric brachial plexus lesion (OBPL)

An obstetric brachial plexus lesion (OBPL) is a closed traction injury of the brachial plexus acquired during labour, with an incidence of 0.5 to 2.6 per 1000 live births.[1] In increasing order of severity the lesions concern neurapraxia, axonotmesis, neurotmesis and root avulsion.[2,7]While mild nerve damage does not exclude a full recovery, severe damage can cause permanent loss of arm function in OBPL.[11-15] Additionally, severe OBPL can cause secondary skeletal malformations, cosmetic deformities, behavioural problems,[16] and socioeconomic limitations.[13,17]

Typically shoulder abduction and elbow flexion are impaired caused by damage to the C5 and C6 spinal nerves. In more severe cases involving spinal nerves C7, C8 and Th1, extension and hand function are impaired as well.[2] Due to the nerve traction, axons are disrupted, and the distal end undergoes Wallerian degeneration.[3,4] In the majority of OBPL cases, there is no large gap between the proximal and distal nerve ends, in contrast to the situation in adults, in which the nerve ends retract, resulting in an appreciable gap.[5] The lack of a gap leads to the formation of a neuroma in continuity. This contains axons, some of which cross the lesion site and may find the empty distal basal laminal tubes.[6] The number of axons that successfully cross the lesion site is lower than the original number, and the number of available axons depend on lesion severity.

In addition to the abnormally low number of axons, the essentially random outgrowth of axons across the lesion may cause 'misrouting': axons may connect with an end organ differing from the original one. The result is that both sensory and motor nerve function can be impaired. Proprioceptive feedback may be disturbed as well as motor firing patterns.[2] Absent or inappropriate afferent input may in turn inhibit the development of central motor programs.[2,8-10] All of these aspects may contribute to sensory and motor arm dysfunction to various degrees. In turn, this can limit the ability of patients with OBPL to perform nor only straightforward daily tasks such as eating or writing, but also more specific tasks complex tasks restricting personal and professional choices.

Beyond the recognition of sensory, motor and central program dysfunction lie potential applications to influence or circumvent these limitations, with effects on the affected arm use, participation in society and quality of life.

Currently, intervening with the natural course of OBPL is done either before reinnervation is fully completed with various surgical techniques or, insufficient or erroneous reinnervation is treated symptomatically with muscle transpositions or botulinum toxin,[2] all aided by rehabilitation therapy. Although there is reasonable consensus on when to apply a specific technique, randomized controlled trials are lacking. This is partially due to an unclear effect of conservative treatment on sensory and motor function, lack of a reliable measure for misrouting extent, and what role the central nervous system plays in recovery.

The aim of this thesis was to gain a better understanding of sensory and motor function, misrouting and central motor program development in OBPL, with a focus on conservatively treated adults with OBPL.

Sensory function

Most studies in OBPL focused on motor functions, providing few details of sensory function.[18-22] This lack of attention may have been due to the prevailing perception that sensory function recovers almost completely in OBPL[18-25] in contrast to motor function. By itself, this motor-sensory discrepancy is surprising, as there are no reasons to assume that sensory and motor axons respond fundamentally different to injury in infants than in adults. As a result, widespread sensory dysfunction, such as occurs in adults after nerve injury, would be expected. To explore whether sensory function is indeed nearly normal in OBPL we assessed sensory function in a group of conservatively treated adults with OBPL, results are described in *Chapter 2*. In *Chapter 3* we compare our findings from *Chapter 2* with findings of Brown et al. in a comparable study [26] performed in conservatively treated older children with OBPL.

Motor function and misrouting

Functional recovery following OBPL depends not only on the number of outgrowing motor axons that reinnervate muscle fibres, but also on the extent of misrouting[27-29] As said, misrouting occurs when a regenerating axonal sprout grows into a distal basal lamina tube other than the original one.[2] There are indications that misrouting occurs more often in children than in adults.[27] In misrouting, an outgrowing axon may reinnervate muscle fibres in another than

the intended muscle. These fibres may lie in an agonist (e.g. an axon meant for the biceps ends up in the brachialis muscle), an antagonist (e.g. triceps instead of biceps), or a muscle with another function (e.g. deltoid instead of biceps). As regenerating axons tend to branch at the site of injury, the various branches of one axon may even end up in different muscles, thereby forming a motor unit with muscle fibres in more than one muscle.[30-33] If a sizable number of axons are misrouted, two muscles may tend to contract together, a phenomenon known as cocontraction. Misrouting in OBPL was studied exhaustively by Roth, who reported that abnormal motor connections were present in 38% of 618 investigated muscle pairs.[30] The assessment was based on the principle that stimulating any part of a neuron will excite all its branches, so stimulating nerve endings in one muscle and recording a response in another muscle suggested a motor unit with branches in separate muscles. Not all possible connections were systematically assessed by Roth, however. In *Chapter 4* we used the same principle to assess how often motor misrouting occurred in conservatively treated adults with OBPL, to link its occurrence to the site of the lesion, and to compare its presence with the degree of clinical motor dysfunction.

Cocontraction due to misrouting causes serious problems in OBPL, possibly more so than primary muscle weakness.[28,34,35] However, previous studies mainly rested on qualitative assessments; triceps and deltoid muscle cocontraction during biceps activation has not been quantified yet. One possible way to assess the quantity of misrouted axons is with electromyography (EMG). In *Chapter 5* we quantified triceps and deltoid muscle cocontraction during biceps activation in conservatively treated adults with OBPL and compared it with healthy subjects.

As EMG has some disadvantages, such as costimulation and coregistration, we explored an alternative measure possibly quantifying cocontraction at different functional force levels: this was joint stiffness originating from muscle short-range stiffness (SRS). SRS represents the resistance of a muscle against lengthening and is observed during the first 40 milliseconds or so of a rapidly stretched muscle[36], after which stretch reflexes become active, complicating stiffness and its assessment. The stiffness is proportional to the active force exerted by the muscle.[37,37] SRS is thought to be due to the elastic properties of the cross-bridges in the muscle fibres.[38] A large stiffness means much force is

needed to rotate the joint one degree. Both the agonist and antagonist muscles exhibit stiffness, so the total joint SRS is the sum of their stiffness, while the actual torque is the difference between agonist and antagonist torque.[39] Therefore cocontraction in OBPL patients is expected to increase the total joint stiffness through adding antagonist activation at a given torque compared to healthy individuals. In *Chapter 6* we quantified elbow SRS for varying flexion and extension torques and compared the results between OBPL patients and healthy subjects.

Central motor programming

As explained in the previous sections, functional recovery depends on the number of outgrowing axons and the correct routing of outgrowing axons.[40,41] Apart from the direct consequences of a peripheral nerve injury, the brain has to learn to cope with new and possibly erroneous input and output signals. Functional recovery of OBPL may therefore be additionally impaired because these central motor programs may not develop normally in young children.[40] A number of clinical observations suggested that motor programming is indeed impaired in OBPL, such as the observation that children 'forget' to flex their arm when they do not focus on using it, while they can actually flex the arm when the task at hand requires focused attention.[40,42] Some past studies collected neurophysiological evidence for such defective motor programming in OBPL.[43,44]

In *Chapter 7* we studied central motor programming in children with OBPL by systematically observing arm movements during balancing tasks and volitional movement. If the observed functional deficit in the affected arm would be wholly due to peripheral nerve, muscle or joint damage, then the deficit would not depend on whether a movement is made in a voluntary or an automatic context. Any discrepancy would suggest a central component. We reasoned that movements of the unaffected arm would serve as a control to indicate volitional or automatic action. Accordingly, we reasoned that arm movements in OBPL that can be performed volitionally by both arms, but that do not occur in the context of automatic movements of the affected arm, suggest the presence of a central deficit.

In *Chapter 8* we studied central motor programming in adult OBPL patients who were conservatively treated by measuring cortical activity during motor execution and imagery tasks with functional MRI. An expansion of motor cortical representation occurs not only at the onset of learning a new motor skill in healthy subjects, but also in patients following upper extremity injury and reconstruction.[45] While a skill is being mastered, the degree of cortical representation and excitability decrease again.[45] We used motor execution tasks to assess whether a central motor impairment in OBPL can be linked to a different motor cortical representation compared to controls. With increasing practice motor tasks become automatic and require less planning effort.[46] A decreased cortical activation has been found in the primary motor cortex contralateral to the attempted limb movement in paraplegics compared to healthy controls studied with motor imagery functional MRI, which was attributed to an increased need for attention allocation.[47] Therefore, we used imagery tasks to assess whether an increased planning effort contributes to the central motor impairment.

References

1 Walle T, Hartikainen-Sorri AL. Obstetric shoulder injury. Associated risk factors, prediction and prognosis. Acta Obstet Gynecol Scand 1993; 72: 450-4.

2 van Dijk JG, Pondaag W, Malessy MJ. Obstetric lesions of the brachial plexus. Muscle Nerve 2001; 24: 1451-61.

3 Waller A. Experiments on the Section of the Glossopharyngeal and Hypoglossal Nerves of the Frog, and Observations of the Alterations Produced Thereby in the Structure of Their Primitive Fibres. Philosophical Transactions of the Royal Society of London 1850; 140: 423-9.

4 Ransom BR. Organization of the Nervous System. In: Boron FB, Boulpaep EL, eds. *Medical Physiology*. Philadelphia: Elsevier Inc. 2005:272.

5 Malessy MJ, Pondaag W, van Dijk JG. Electromyography, nerve action potential, and compound motor action potentials in obstetric brachial plexus lesions: validation in the absence of a "gold standard". Neurosurgery 2009; 65: A153-A159.

6 Malessy MJ, Pondaag W, van Dijk JG. Electromyography, nerve action potential, and compound motor action potentials in obstetric brachial plexus lesions: validation in the absence of a "gold standard". Neurosurgery 2009; 65: A153-A159.

7 Sunderland, S. Nerve injuries and their repair: a critical appraisal. 1991. Edinburgh, Churchill Livingstone.

8 van Dijk JG, Malessy MJ, Stegeman DF. Why is the electromyogram in obstetric brachial plexus lesions overly optimistic? Muscle Nerve 1998; 21: 260-1.

9 Zalis OS, Zalis AW, Barron KD, Oester YT. Motor patterning following transitory sensory-motor deprivations. Arch Neurol 1965; 13: 487-94.

10 Brown T, Cupido C, Scarfone H, Pape K, Galea V, McComas A. Developmental apraxia arising from neonatal brachial plexus palsy. Neurology 2000; 55: 24-30.

11 Bellew M, Kay SP, Webb F, Ward A. Developmental and behavioural outcome in obstetric brachial plexus palsy. J Hand Surg Br 2000; 25: 49-51.

12 Adler JB, Patterson RL, Jr. Erb's palsy. Long-term results of treatment in eighty-eight cases. J Bone Joint Surg Am 1967; 49: 1052-64.

13 Pearl ML, Edgerton BW. Glenoid deformity secondary to brachial plexus birth palsy. J Bone Joint Surg Am 1998; 80: 659-67.

14 Gjorup L. Obstetrical lesion of the brachial plexus. Acta Neurol Scand 1966; 42: Suppl-80.

15 Pollock AN, Reed MH. Shoulder deformities from obstetrical brachial plexus paralysis. Skeletal Radiol 1989; 18: 295-7.

16 McGuire J, Richman N. Screening for behaviour problems in nurseries: the reliability and validity of the Preschool Behaviour Checklist. J Child Psychol Psychiatry 1986; 27: 7-32.

17 Bellew M, Kay SP, Webb F, Ward A. Developmental and behavioural outcome in obstetric brachial plexus palsy. J Hand Surg Br 2000; 25: 49-51.

18 Strombeck C, Remahl S, Krumlinde-Sundholm L, Sejersen T. Long-term follow-up of children with obstetric brachial plexus palsy II: neurophysiological aspects. Dev Med Child Neurol 2007; 49: 204-9.
19 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: 148-57.
20 Sundholm LK, Eliasson AC, Forssberg H. Obstetric brachial plexus injuries: assessment protocol and functional outcome at age 5 years. Dev Med Child Neurol 1998; 40: 4-11.
21 Palmgren T, Peltonen J, Linder T, Rautakorpi S, Nietosvaara Y. Sensory evaluation of the hands in children with brachial plexus birth injury. Dev Med Child Neurol 2007; 49: 582-6.
22 Anand P, Birch R. Restoration of sensory function and lack of long-term chronic pain syndromes after brachial plexus injury in human neonates. Brain 2002; 125: 113-22.
23 Lundborg G, Rosen B. Sensory relearning after nerve repair. Lancet 2001; 358: 809-10.
24 Lundborg G, Rosen B. Hand function after nerve repair. Acta Physiol (Oxf) 2007; 189: 207-17.
25 Brown KL. Review of obstetrical palsies. Nonoperative treatment. Clin Plast Surg 1984; 11: 181-7.
26 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.
27 van Dijk JG, Pondaag W, Malessy MJ. Obstetric lesions of the brachial plexus. Muscle Nerve 2001; 24: 1451-61.
28 van Dijk JG, Pondaag W, Malessy MJ. Botulinum toxin and the pathophysiology of obstetric brachial plexus lesions. Dev Med Child Neurol 2007; 49: 318-9.
29 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: 946-54.
30 Roth G. [Reinnervation in obstetrical brachial plexus paralysis]. J Neurol Sci 1983; 58: 103-15.
31 Roth G. Intranervous regeneration. The study of motor axon reflexes. J Neurol Sci 1979; 41: 139-48.
32 Roth G. Intranervous regeneration of lower motor neuron.--1. Study of 1153 motor axon reflexes. Electromyogr Clin Neurophysiol 1978; 18: 225-88.
33 Esslen E. Electromyographic findings on two types of misdirection of regenerating axons. Electroencephalogr Clin Neurophysiol 1960; 12: 738-41.
34 de Ruiter GC, Malessy MJ, Alaid AO et al. Misdirection of regenerating motor axons after nerve injury and repair in the rat sciatic nerve model. Exp Neurol 2008; 211: 339-50.

35 Tannemaat MR, Boer GJ, Eggers R, Malessy MJ, Verhaagen J. From microsurgery to nanosurgery: how viral vectors may help repair the peripheral nerve. Prog Brain Res 2009; 175: 173-86.
36 de Vlugt E., van Eesbeek S., Baines P, Hilte J, Meskers CG, de Groot JH. Short range stiffness elastic limit depends on joint velocity. J Biomech 2011; 44: 2106-12.
37 Cui L, Perreault EJ, Maas H, Sandercock TG. Modeling short-range stiffness of feline lower hindlimb muscles. J Biomech 2008; 41: 1945-52.
38 Campbell KS, Lakie M. A cross-bridge mechanism can explain the thixotropic short-range elastic component of relaxed frog skeletal muscle. J Physiol 1998; 510 (Pt 3): 941-62.
39 van Eesbeek S, de Groot JH, van der Helm FC, de VE. In vivo estimation of the short-range stiffness of cross-bridges from joint rotation. J Biomech 2010; 43: 2539-47.
40 van Dijk JG, Pondaag W, Malessy MJ. Obstetric lesions of the brachial plexus. Muscle Nerve 2001; 24: 1451-61.
41 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.
42 Nelson VS. Discrepancy between strength and function in adults with obstetric brachial plexus lesions. Dev Med Child Neurol 2014; 56: 919.
43 Brown T, Cupido C, Scarfone H, Pape K, Galea V, McComas A. Developmental apraxia arising from neonatal brachial plexus palsy. Neurology 2000; 55: 24-30.
44 Colon AJ, Vredeveld JW, Blaauw G. Motor evoked potentials after transcranial magnetic stimulation support hypothesis of coexisting central mechanism in obstetric brachial palsy. J Clin Neurophysiol 2007; 24: 48-51.
45 Anastakis DJ, Chen R, Davis KD, Mikulis D. Cortical plasticity following upper extremity injury and reconstruction. Clin Plast Surg 2005; 32: 617-34, viii.
46 Willingham DB. A neuropsychological theory of motor skill learning. Psychol Rev 1998; 105: 558-84.
47 Hotz-Boendermaker S, Funk M, Summers P et al. Preservation of motor programs in paraplegics as demonstrated by attempted and imagined foot movements. Neuroimage 2008; 39: 383-94.