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

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*Chapter*

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*Discussion and Summary*

The aim of this thesis was to gain a better understanding of sensory and motor function, misrouting and central motor programme development in patients with obstetric brachial plexus lesion (OBPL), focusing mostly on conservatively treated adults. In this Chapter we discuss our findings on these topics and some venues for future research.

### **Sensory function**

In *Chapter 2* we found that sensory hand function was abnormal in adults with conservatively treated OBPL, based on two tests, the Semmes-Weinstein monofilament test and the two-point discrimination test, and on a comparison with healthy control subjects. Scores for object recognition and locognosia did not differ between patients and controls.

We reviewed earlier studies on sensory function in OBPL. Sensory function in OBPL had been reported to be excellent, but only five of eight sources presented original data. Results might depend on whether surgery had been undertaken, but in four papers the operated cases represented only a small fraction of the total number of cases and in the fifth paper cases without surgery could be identified. The study populations were largely comparable to ours, though the conclusion generally differed from ours: most authors reported that sensory function had recovered excellently; only one author expressed caution about this interpretation. We suggested that the apparent discrepancy between ours and earlier conclusions originated in a difference in interpretation: most studies stressed the existence of normal sensory functions, whereas we stressed that abnormal functions were in the majority. There is an obvious difference with plexus lesions acquired later in life: in adults sensory dysfunction follows well-established areas of innervation, with profound differences between normal and abnormal areas. In OBPL, in contrast, there is a degree of sensation in all innervation areas, but that does not mean that sensory function is normal in those areas. We suggested that the absence of major 'gaps' in sensation in OBPL may be explained by the neuroma in continuity in infants, that allows reinnervation to take place, much more readily than happens in a true nerve rupture in adults. As such, the sensory and motor findings show an interesting parallel in OBPL: there is a degree of function in all myotomes and dermatomes, but there also is a functional abnormality with a unique pattern not occurring in this way in adults.

In *Chapter 3* we responded to a recent study on sensory function in conservatively treated OBPL patients, one that largely confirmed our results.

### **Motor function and misrouting**

#### ***Motor function and misrouting extent***

The main findings of the studies in *Chapter 4* revealed a pattern that does not simply fit a peripheral nerve lesion: participants with conservatively treated OBPL displayed considerable functional impairment and impaired ranges of joint movement. The expected pattern for nerve lesions would be that these impairments are the result of profound muscle weakness, and yet this was absent.

Concerning ranges of motion, shoulder abduction followed by elbow extension were most often impaired, while that of elbow flexion was normal. Muscle strength was only slightly impaired for the biceps muscle, and deltoid and triceps muscle strength was normal, while the Mallet scores, assessing function, showed a profound impairment.

The abnormal range of motion could therefore not be explained through muscle weakness, as weakness was mostly absent. Another mechanism must therefore have interfered with motor function, most probably cocontraction. This is where our misrouting studies came in.

Motor misrouting was most often found after stimulation of the biceps, deltoid, and brachioradialis muscles, innervated through the C5 and C6 roots. The high rate of misrouting in patients was not due to measurement error, because apparent misrouted responses were encountered in only four out of 1440 possible instances in controls. We attribute the abundance of misrouting in OBPL to the neuroma in continuity, allowing axons, split or not, to grow into any possible pathway, including an incorrect one, causing unintentional muscle cocontraction.

Unfortunately we could not establish an association between the degrees of functional impairment and of misrouting. We suggested several explanations for this: first, statistical significance was not obtained, perhaps because of limited variable variability, the Bonferroni correction and limited group size.

More importantly, any functional impairment due to misrouting is likely to depend on the quantitative rather than the qualitative degree of misrouting, but we could only assess the latter aspect in this chapter.

### ***Misrouting quantified***

We attempted to quantify the degree of misrouting with electromyography (EMG) in *Chapter 5* using novel approaches to overcome two problems: the first is costimulation in which electrical stimulation aimed to activate one muscle unintentionally also activates its antagonist; the second is coregistration, in which surface electrodes not only record the activity of an intended muscle, but also that of unintended muscles, such as an antagonist. We designed novel techniques to disentangle these problems.

We found no differences in the degree of cocontraction between OBPL patients and healthy subjects for either the triceps or deltoid muscles. This is odd, as we reported in *Chapter 4* that misrouting was qualitatively present in the triceps in nine out of 17 patients and in the deltoid in seven out of 17 patients. The apparent discrepancy with the findings in *Chapter 5* can be explained in several ways. The number of misrouted axons may in fact have been low; a central contribution cannot be excluded. We may also have failed to suppress the effects of costimulation and coregistration sufficiently despite of our best efforts.

In *Chapter 6* we aimed to quantify cocontraction with short range stiffness (SRS) at the elbow joint. We found that elbow stiffness was significantly higher in OBPL patients (median 250Nm/rad) than in control subjects (150Nm/rad) during voluntary levels of contraction.

SRS was significantly higher in OBPL patients than in control subjects but not for torque level zero, suggesting more cocontraction in patients but not due to joint deformities. The SRS measurement method is not hampered by the entangled factors that played a role in *Chapters 4* and *5*. SRS takes all muscles contributing to flexion and extension into account. Additional advantages of SRS compared to EMG to measure cocontraction in OBPL are that surface EMG preferentially samples superficial layers of a muscle and EMG requires a good signal-to-noise ratio which makes it less accurate for low muscle force levels.

## **Central motor programming**

### ***Children with OBPL***

In *Chapter 7* we found that children with OBPL abducted the affected arm over 90 degrees less often than the unaffected arm in automated balance tasks even though they were able to abduct the affected arm over 90 degrees on request. The discrepancy can therefore not be explained by incomplete peripheral nerve regeneration or joint problems, suggesting a central deficit.

We discussed four explanations why automatic movements are impaired in OBPL. The first concerned sensory deprivation during a critical period for the formation of automatic motor control. The second was that automatic movement programmes are formed later than normal in OBPL because the affected arm is not used often or well enough for movement automation to occur. The third held that the decreased use of the affected arm represented compensation to counter disruptive effects of abnormal arm movements, but this seemed unlikely. Finally, the lower mass of the affected arm might play a role, but adding mass to one arm decreases movement of that arm, so a lowered mass should do the opposite.

### ***Adults with OBPL***

In *Chapter 8* we found that OBPL patients showed more cortical activity than healthy individuals during motor imagery flexion of the affected arm. The increase was found in cortical premotor areas of both hemispheres, as well as in contralateral motor areas in right-handed OBPL patients. Cortical premotor areas were also more activated in right-handed OBPL patients than in controls during motor imagery flexion of the unaffected arm. Additionally, higher cortical activation was associated with an increasing lesion extent and a decreasing biceps muscle force. In contrast, the actual flexion task showed no increase of cortical activation in OBPL patients.

Our findings suggest that OBPL patients require an increased central effort to plan actions. Motor imagery in OBPL appears to be carried out as a newly learned task requiring much attention. We discussed several explanations for the increased ipsilateral cortical activation in OBPL patients during imagery flexion of the affected arm, of which the most intriguing one may be that this represents pre-existing cortical connections with the ipsilateral hemisphere. Central pathways involved in actual elbow flexion apparently evolved enough to result in a normal degree of activation.



## Future research

### Sensory function

One possible future research topic in OBPL may concern its pathophysiology, for instance, in which dermatomes will sensory axons passing the neuroma end up? Through which nerves and roots do the regenerated fibres run? This may be possible to visualize in the future using viral vectors and MRI-tracking.<sup>5,6</sup>

Having established in *Chapter 2* that sensory function is abnormal in OBPL, sensory function rehabilitation should be explored in the future. There is some evidence for a positive effect on sensory function in adult peripheral nerve injuries using sensory re-education before and after evident reinnervation.<sup>7,8</sup> Protocols based on observation of touch, mirror visual feedback, audio-tactile substitution or temporary anaesthesia of parts of the ipsi- or contralateral arm may prove useful after adjustment for children. The rationale for such interventions is that they prevent the shrinkage of the original sensory cortical areas in the time frame prior to reinnervation. In this light, the use of brain-machine interfaces<sup>9</sup> may be useful as well. In order to accomplish better sensory reinnervation, operative techniques favouring sensory function<sup>10</sup> and possibly using viral vectors in the future<sup>5</sup>, deserve further study.

Is there also sensory misrouting, and can this be demonstrated and quantified? We performed an unpublished pilot study attempting to capture this phenomenon, but the attempt failed as measuring sensory misrouting was too challenging using surface EMG methods. Sensory nerves commonly overlie muscles in which motor misrouting may be present: after sensory nerve stimulation it was unclear whether any resulting potentials originated from the sensory nerve, as intended, or from the muscle, unintended, or both. However, it may be possible to quantify afferent misrouting as we have done for motor misrouting in *Chapter 6* with the SRS method by choosing a different response time frame which coincides with the latency of the afferent signal.

Another avenue for future research concerns the consequences of sensory dysfunction for the quality of life in patients with OBPL.

### Motor function and misrouting

The current treatment of cocontraction with the injection of botulinum toxin

in antagonist muscles is of necessity based on fairly subjective parameters. Besides, there is a necessity for a multicentre randomized controlled trial with botulinum toxin. A method to measure cocontraction such as SRS may guide treatment efforts and may be useful in such a trial. Future research should elucidate the applicability of the SRS method in children with OBPL. The computer interface used in *Chapter 6* with adjustments to resemble a video game may be particularly useful to raise motivation in children.

### Central motor programming

To investigate how central motor programmes evolve over time in OBPL, a study can be performed with the balancing tasks used in *Chapter 7* in the group of conservatively treated adults with OBPL or the same children but at an older age. Another venue to study this would be to perform an fMRI study with the same tasks as in *Chapter 8* in children with OBPL. It would be of interest as well to study whether sensory cortical processing is complicated in OBPL in a manner similar to the one we found for motor tasks in *Chapter 8*.

The effects of rehabilitation on the central component of the functional motor deficit in OBPL should be studied. To elucidate the role of the healthy arm in movements of the affected arm a functional MRI study may be useful with EMG recordings during scanning of both arms with similar tasks as we used in *Chapter 8*. The role of the healthy arm in rehabilitation deserves further study as well. Motor function improvement of an agonist muscle persistent after botulinum toxin injection in the antagonist has been proposed to facilitate central motor learning<sup>11</sup> and a future functional MRI study may elucidate this.

### Issues regarding nerve surgical intervention

There are various surgical techniques for OBPL, depending on the lesion.<sup>12</sup> The selection criteria for surgery and the optimal time of surgery are debated.<sup>2,12</sup> There is consensus that severe cases, including neurotmesis and root avulsions, should be operated. Establishing the severity of OBPL can be difficult for various reasons, including limitations of the neurological examination in infants and apparent discrepancies between electromyographic and clinical findings.<sup>2,13</sup> OBPL patients are usually operated between 3 and 9 months of age.<sup>2,12</sup> This time represents a compromise between waiting long enough to allow spontaneous recovery to occur on the one hand and, on the other hand,

the wish to perform surgery early after the injury.<sup>2</sup> Unfortunately, no thorough randomized controlled trial has been performed comparing surgery with conservative treatment in OBPL. Performing such a trial may be complicated by existing beliefs about the benefits of surgery; Strombeck and colleagues found that parents interfered with the randomization process.<sup>14</sup>

A major issue in comparing surgical and conservative treatment is selection bias: cases selected for surgery may be more severely afflicted than those who are not operated. A systematic literature search by Pondaag and colleagues regarding the natural history of OBPL showed that seven studies met a maximum of two of the predefined four evaluation criteria: study design, population, duration of follow-up, and end-stage assessment.<sup>15</sup> The two prospective studies, closest to what was defined as the 'ideal study', showed that functional deficits in the cases without brachial plexus reconstruction occurred at a rate of 20-30%, much higher than the previously assumed 10%.<sup>15</sup>

In summary, no randomized controlled trial comparing surgery and conservative treatment is available and one may not be feasible. However, this thesis may aid in a future systematic comparison with surgery despite the small sample size and heterogeneity of the group. We studied mainly conservatively treated adults with OBPL: cases from the time when brachial plexus surgery was either not possible or not widely used. These patients were recruited from records of the Rehabilitation department of Leiden University Medical Centre and the Dutch Erb's Palsy Association. This introduces a certain selection bias: the patients with residual deficit were more likely to participate in our studies. However, this selected group may be more comparable with patients that would be operated nowadays.

Despite the identification of risk factors for OBPL such as shoulder dystocia, operative vaginal delivery, macrosomia, gestational diabetes, and breech presentation,<sup>16,17</sup> OBPL still occurs, and there still is a group with residual deficit despite treatment options including surgery. Therefore, future research may also be focused on prevention and a new paradigm may be necessary. In shoulder dystocia the child's shoulder is impacted behind the mother's symphysis.<sup>18</sup> In other words, the shoulders are the broadest part of the child relative to the mother's pelvis. We performed electrical stimulation of the accessory nerve

in one healthy adult and measured a 20% reduction of the distance between the shoulders. Theoretically accessory nerve stimulation might therefore also reduce shoulder diameter in infants, which might conceivably be of value during birth, to prevent OBPL. Whether or not this is feasible will require various preliminary steps.

## **Summary and clinical importance**

### **Summary**

Sensory function is impaired in adults with conservatively treated OBPL. There is widespread motor misrouting together with motor functional impairment in conservatively treated OBPL, not explained by muscle weakness. There were no differences in the degree of cocontraction between OBPL patients and healthy subjects for either the triceps or deltoid muscles during supramaximal biceps stimulation. However, elbow stiffness was approximately 1.7 times higher in OBPL patients than in control subjects during voluntary levels of contraction, suggesting a significant effect of misrouting in the patients. In children with OBPL the deficit during automatic arm abduction was not observed during voluntary movements and therefore cannot be explained by a peripheral deficit, suggesting a central component. In adults OBPL affected imagined but not actual elbow flexion suggested an impairment of motor planning.

### **Clinical importance**

The existence of sensory impairment in OBPL and its contribution to functional impairment need to be acknowledged, as sensation is of paramount importance in daily tasks. Our findings support the view that treatment may also have to be focused on sensation improvement, with the caveats that we did not study this directly and that sensory function can in fact be improved.

The current treatment of cocontraction, injection of botulinum toxin in antagonist muscles, is of necessity based on fairly subjective parameters.<sup>19</sup> Clinical assessment methods such as measuring the range of motion of a joint or measuring muscle strength cannot distinguish between weakness of one muscle and cocontraction of its antagonist.<sup>19</sup> A method to measure cocontraction such as SRS may guide treatment efforts.

If there is a delay rather than an irreversible nonconsolidation of central motor programmes in OBPL, the component of functional deficit due to central impairment might improve with rehabilitation.

A better understanding and future improvement of both peripheral and central factors in OBPL will hopefully lead to an improvement of the affected arm use in daily tasks, and in turn remove some of the obstructions patients with OBPL face in participation in society.

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