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

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Extensive motor axonal misrouting after conservative treatment of obstetric brachial plexus lesions

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Abstract

Aim The aim of this cross-sectional study was to systematically assess motor function and motor misrouting in adult conservatively treated participants with obstetric brachial plexus lesion (OBPL).

Method Seventeen adults with OBPL (median age 38y; five male) and 16 comparison participants (median age 26y; eight male) were investigated. Motor function in OBPL participants was assessed through passive and active motion, muscle strength of the deltoid, biceps, and triceps muscles, and Mallet aggregate score and five subscores. Motor misrouting was quantified by electrically stimulating each of 10 arm muscles and recording activity from the other nine in response to this. Motor function and motor misrouting were statistically analysed using the Mann–Whitney U test and Spearman correlation.

Results Motor function testing showed excellent strength but poor functional Mallet scores. Participants with OBPL had significantly more motor misrouting than comparison participants (Mann–Whitney U=31.5 [df=28], p<0.001, median difference=–4.00, 95% confidence interval [CI]=–7.00 to –1.00). Most misrouting was observed when stimulating the biceps (Mann–Whitney U=38.5 [df=31], p<0.001, median difference=–3.00, 95% CI=–4.00 to –1.00), deltoid (Mann–Whitney U=68.5 [df=31], p=0.003, median difference=–1.0, 95% CI=–4.00 to 0.00) and brachioradialis muscles (Mann–Whitney U=72.0 [df=31], p=0.002, median difference=0.00, 95% CI=–3.00 to 0.00). There were no significant correlations between the presence of motor misrouting and impairment of motor function.

Interpretation There is extensive motor misrouting in conservatively treated OBPL patients. The presence of this, in addition to motor functional impairment, suggests that motor misrouting should be further studied in OBPL.

Introduction

Obstetric brachial plexus lesion (OBPL) is a closed traction injury of the brachial plexus incurred during birth, with an incidence of 0.5 to 2.6 per 1000 live births.1 Although the prognosis is generally considered to be good, a systematic literature search has shown that there is a residual deficit in 20% to 30% of cases.2 Severe OBPL can result in the permanent impairment of arm function, skeletal malformation, cosmetic deformity, behavioural problems, and socio-economic limitations.3,4 Functional recovery following OBPL is dependent not only on the number of outgrowing motor axons that reinnervate muscle fibres but also on the extent of misrouting.5–7 There are indications that misrouting occurs more often in children than in adults.5 Misrouting occurs when a regenerating axonal sprout grows into a distal basal lamina tube that is not the original one.8 In misrouting, an outgrowing axon reinnervates muscle fibres in areas other than where they are intended. These fibres may lie in an agonist (e.g. an axon meant for the biceps reinnervates in the brachialis muscle), an antagonist (e.g. triceps instead of biceps), or a muscle with another function (e.g. deltoid instead of biceps; see Fig. 1). As regenerating axons tend to branch at the site of injury, the branches may even end up in different muscle groups and form a motor unit in more than one muscle.9–12 If a sizable number of axons are misrouted, two muscles may tend to contract together, a phenomenon known as co-contraction. Misrouting in OBPL was studied by Roth,9 who reported that abnormal motor connections were present in 38% of 618 investigated muscle pairs. 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 would suggest that there was a motor unit with branches in separate muscles. However, not all possible connections were systematically assessed by Roth.

Co-contraction causes serious problems in OBPL, possibly to a greater extent than primary muscle weakness.6,13,14 Co-contraction in OBPL might also be due to disturbed central motor programming, owing to factors such as deafferentation,15 misrouting, and the fact that the lesion occurs before motor programmes have been developed fully.5,6,16 Peripheral factors may, therefore, be involved in co-contraction in addition to central factors.5
The aim of this study was to assess how often motor misrouting occurred in patients with conservatively treated OBPL, to link its occurrence to the site of the lesion, and to probe its clinical significance by comparing it with clinical motor function.

**Method**

**Participants**
Seventeen adults with OBPL and 16 comparison participants, all over 18 years of age, participated. Adults were investigated to reduce cooperation problems and ethical considerations in this study regarding children. It is unlikely that misrouting would disappear after childhood, and adult participants would, therefore, equally demonstrate misrouting. Some participants with OBPL had participated in previous research and others were contacted through the Erbs Palsy Association in the Netherlands. Exclusion criteria for all participants consisted of any surgery undertaken for plexus injury and presence of any other disease affecting arm function. A flow chart indicating the numbers of potentially eligible participants, those examined for eligibility, confirmed eligible, and those included in the study, was published in a previous paper. The protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center. All participants provided informed consent.

**Motor function assessment**
Motor function in the OBPL group was assessed by a neurosurgeon with extensive experience in nerve lesions. Comparison participants were not investigated clinically, as reliable normal values were available. The assessment concerned three aspects: muscle strength, joint range of motion (ROM), and the Mallet classification. The method used to determine lesion level was described in a previous paper. The patient’s hand dominance was based on patient’s opinion and corroborated by observing which hand they wrote with.

The muscle strength of various shoulder, elbow, wrist, and finger movements was noted using the Medical Research Council (MRC) scale, with a range per muscle of zero (complete paralysis) to five points (normal strength). The ROM of the shoulder down to the finger joints of the arm was measured during passive and active motion and noted in degrees. Glenohumeral motion was assessed and used for further analysis. The scores for active and passive movement were reported as the median with 10th and 90th centile values for three muscles representative of the upper brachial plexus: the deltoid (mostly C5), biceps (mostly C6), and triceps muscles (mostly C7). Normal values for ROM were taken from reference works.

The five items of the modified Mallet classification were scored: global abduction, global external rotation, hand to neck range, hand on spine range, and hand to mouth range. For each item grade I denotes no active motion and grade V denotes normal function. Aggregate Mallet scores were calculated by summing the grades for these five items, so the minimal score was five points and the maximal score 25 points, reported as the median (10th and 90th centiles).

To compare the degree of impairment between the three functional assessments, we expressed the median value of parameters in the OBPL group as a percentage of the corresponding normal value. Full elbow extension is normally expressed as zero degrees, which would result in division by zero to express passive and active extension in patients. To counter this, we defined extension in relation to a fully flexed arm as 145°.

**Motor point stimulation**
Motor point stimulation was performed in the patients and the healthy comparison participants. The latter were included to control for costimulation or volume-conducted activity from adjacent muscles, as well as for putative long-loop reflexes. Misrouting was assessed by stimulating the motor point in one muscle and recording activity in the other, non-stimulated, muscles. Ten muscles were chosen as both stimulation and recording sites. We aimed to sample all roots with an emphasis on the upper brachial plexus, the most commonly affected area in OBPL. The chosen muscles were biceps brachii, deltoid, flexor carpi radialis, brachioradialis, extensor carpi radialis, pronator teres, triceps brachii, latissimus dorsi and the thenar and hypothenar muscles.
Motor points were identified by moving the stimulator of a Medelec Synergy EMG apparatus (Oxford Instruments, Abingdon, Oxfordshire, UK) over the presumed site, stimulating at an intensity of about 8mA and a frequency of one pulse per second, values that are based on the pilot experiments. The point at which maximal muscle contraction occurred was marked on the skin. For some muscles that were paralysed or severely atrophied no contraction was observed. In such cases literature sources and experience were used to identify the putative motor point. After identifying each motor point, two self-adhesive electrodes were placed over that zone, one over the identified point and one 0.5cm distally. These electrode pairs functioned as both stimulation and recording electrodes. Each motor point was then stimulated several times and the responses of the nine other muscles were visualized on the screen. The repetition allowed transient activity to be distinguished from reproducible evoked activity (Fig. S1, online supporting information). Two responses per stimulated motor point from each participant were saved for later comparison and analysis. Responses were acquired using a band pass filter of 10Hz to1kHz and recorded over 50 milliseconds. The procedure resulted in 90 combinations (10 stimulation sites × 9 recording sites). To avoid mistaking direct muscle stimulation for misrouting, only responses that began at least 15ms after the stimulus, during which period no muscle activity, were recorded. For every stimulus–response combination, misrouting was noted as present or absent. Next, the number of comparison participants and patients with present responses for each combination was counted.

For each stimulated muscle we defined a ‘muscle misrouting score’ for each participant by measuring the number of muscles that showed a misrouted response, ranging from 0 (no misrouting) to 9. Adding together the scores for all 10 stimulated muscles resulted in a ‘total misrouting score’ per individual, with a range from 0 to 90 points. Results are presented as median values with the range.

Statistical analysis
IBM SPSS Statistics 20.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The Mann–Whitney U test was used to test for differences between groups in baseline characteristics, motor function tests, and misrouting scores. A significance level of 0.05 was used. In addition, median differences and 95% confidence intervals CIs were calculated with the R statistical program. Correlations between motor function tests and the misrouting scores of the three muscles most affected in OBPL (biceps, deltoid, and brachioradialis) were assessed with Spearman’s correlation coefficient. This resulted in 45 correlations (15 motor function tests × 3 misrouting muscle scores). A Bonferroni corrected significance threshold of 0.001 (0.05/45) was used for the correlations.

Results
Median age (10th–90th centile) was 38 years (range 20–58y) in the OBPL group and 26 years (range 19–56y) in the comparison group (Mann–Whitney U [df=31]=114.0, p=0.43, two-tailed, median difference=–3.00, 95% CI=–16.00 to 5.00). There were five male participants in the OBPL group and eight in the comparison group (χ²=1.46 [df=1, n=33], p=0.23, two-tailed, odds ratio=2.40, 95% CI=0.57 to 10.04). The right hand was affected in 9 out of 17 OBPL cases. There were six left-handed participants in the OBPL group but only 1 among 16 comparison participants (χ²=4.16 [df=1, n=33], p=0.041, two-tailed, odds ratio=0.12; 95% CI=0.01 to 1.17). There were seven OBPL participants with lesion level C5–C6, seven with lesion level C5–C7, and three with either C5–C8 or C5–T1.

Motor function assessment
The results of functional assessment in OBPL are shown in Table I. Median values for passive ROM were the same as for active ROM in OBPL participants. Shoulder abduction was the most impaired, reaching only 67% of normal active abduction, followed by elbow extension at 86%; the range of elbow flexion was normal (100%). Muscle strength was slightly impaired for the biceps muscle (95% of normal value) while strength of the deltoid and triceps muscles was normal (100%). In contrast, the Mallet subscores showed a profound impairment, ranging from 40% to 60% of normal function.

Motor point stimulation
In the comparison group, evidence of misrouting was found in only one participant, in whom four stimulated muscles gave rise to misrouted responses
Motor axonal misrouting

The results for both groups are presented in Figure 2. When responses were judged from the stimulation site, misrouted responses in the OBPL group were found for 7 out of 10 stimulated muscles. The muscles that most often gave rise to misrouting were the biceps (n=41), deltoid (n=36), and brachioradialis (n=30) muscles. For the biceps muscle, the 41 misrouted responses represent 27% of all possible instances. Three muscles never gave rise to misrouting: the triceps, latissimus dorsi, and thenar muscles. When judged from the recording point of view, the three muscles over which responses were found most often were the brachioradialis (n=22), triceps brachii (n=22), and the extensor carpi radialis muscle (n=21). Figure 3 shows the muscle misrouting scores, showing in how many cases misrouting was seen following stimulation of a given muscle.

The misrouting score had a median value of 4 (range 0–21) in the total OBPL group and 0 (0–3) in the comparison group. This total score differed significantly between the OBPL and comparison groups (Mann–Whitney U=31.5 [df=28], p<0.001, two-tailed, median difference=−4.00, 95% CI=−7.00 to −1.00); scores per stimulated muscle differed between the groups for the biceps (Mann–Whitney U=38.5 [df=31], p<0.001, two-tailed, median difference=−3.00, 95% CI=−3.00 to −1.00), deltoid (Mann–Whitney U=68.5 [df=31], p=0.003, two-tailed, median difference=−1.00, 95% CI=−4.00 to 0.00), and brachioradialis (Mann–Whitney=72.0 [df=31], p=0.002, two-tailed, median difference=0.00, 95% CI=−3.00 to 0.00) muscles.

Relation between functional assessment and motor point stimulation
Non-parametric Spearman correlations between motor function and motor misrouting within the group of OBPL participants showed no significant correlations at the stipulated level.

Discussion

The main findings of this study were that participants with conservatively treated OBPL displayed considerable functional impairment and motor misrouting; however, this contrasted with good muscle strength. Functional assessment and motor point stimulation will be discussed in further detail below.

Motor function assessment
The strength of the deltoid, biceps, and triceps muscles was excellent; the discrepancy with impaired ROM was large enough to suggest that it was not simply the result of different measurement systems for ROM and strength. The range for active abduction was less broad than for passive abduction, showing that glenohumeral malformation cannot have been the limiting factor. Pronounced muscle weakness also cannot be the explanation, in view of the good strength of the participants. Another mechanism must therefore interfere with motor function, which is most probably co-contraction. In one study, co-contraction explained abduction impairment in OBPL more often than simple weakness in muscle strength. There is the further possibility that central programming may also play a role in this.

Motor point stimulation
Motor misrouting was most often found after stimulation of the biceps, deltoid, and brachioradialis muscles, innervated through the C5 and C6 roots, most often involved in OBPL. It is not likely that the responses were as a result of artefacts, because ‘misrouted’ responses were encountered in only four muscles in only one comparison participant, and in whom additional questioning revealed no known birth or motor problems. These responses concern 4 out of 1440 possible instances (16 comparison participants × 10 stimulated muscles × 9 recorded muscles).

A possible reason for the abundance of misrouting in OBPL is that traction to the brachial plexus in OBPL does not cause a true rupture of nerves as it does in adult brachial plexus traction lesions. In OBPL, a gap between two nerve stumps is very rare; instead, a ‘neuroma in continuity’ is formed. This may inhibit nerve regeneration and form the substrate for misrouting of crossing axons.

There was an intriguing asymmetry in that the pattern of misrouting differed depending on whether a muscle was stimulated or recorded. Stimulation of the triceps did not result in misrouted responses elsewhere but the triceps responded to stimulation elsewhere frequently. In general, muscles responded with misrouted responses more often than they gave rise to them. The first explanation for this is that recording may be more sensitive than stimulation:

relation between functional assessment and motor point stimulation
responses may be recorded regardless of where the active muscle fibres lie in a muscle, but only the few axons that lie near the motor point may be excited by local stimulation. Secondly, a severe lesion of the upper trunk, formed by the C5 and C6 roots, will result in branching of many axons. The deltoid and biceps muscles are innervated by these roots; therefore, misrouted responses in these muscles may stem from branched C5 fibres as well as from branched C6 fibres. For the triceps muscle the situation is different: if its C7 contribution remains intact, those axons will not give rise to motor unit activity elsewhere, but only its C6 contribution can do so.

**Function and misrouting**
A relation between a functional impairment and the degree of misrouting has been suggested. After nerve surgery, misrouting is thought to contribute to a lack of functional recovery. However, we did not find such a correlation in patients in our study who had not undergone surgery, the strongest significance being 0.04 for the relation between biceps strength and biceps misrouting. There are several possible reasons for the absence of a relation between functional impairment and degree of misrouting. Firstly, we assessed misrouting qualitatively; however, the functional consequences of misrouting may depend on the quantitative degree of misrouting. Secondly, the limited variation of the variables in this population precluded statistical significance. Thirdly, the Bonferroni correction together with limited group size may have made it unlikely that there was significance.

**Limitations and perspective**
Possible drawbacks of this study are that no criterion standard exists for the assessment of the severity of the nerve lesion in OBPL, although assessment in this study was done systematically by an experienced neurosurgeon. Mallet subscores and aggregate scores showed poor recovery of function; the maximum score of 5 was never assigned and the scale in practice starts at the value of 2. A limitation of the motor point stimulation test is that it results in a qualitative estimate of the presence or absence of misrouting in a muscle pair, but cannot determine what proportion of muscle fibres in a muscle are innervated by axons that do not belong there.

**Conclusion**
The presence of widespread motor misrouting together with motor functional impairment in conservatively treated OBPL, not explained through weakness, suggests that misrouting in OBPL deserves to be studied further.

**Acknowledgements**
We thank our colleagues from the Department of Rehabilitation for their help with gathering OBPL participants for the study and the technicians at the department of Clinical Neurophysiology for their help with the motor point studies.
Chapter 4

References

Table 1: Functional motor assessments

<table>
<thead>
<tr>
<th></th>
<th>Normal values*</th>
<th>Obstetric brachial plexus lesion measurements, median (10th–90th centile)</th>
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<td>Flexion elbow</td>
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<td>Extension elbow</td>
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The normal values and obstetric brachial plexus lesion measurements are shown for three clinical assessments: range of motion, muscle strength, and Mallet score. ‘Normal values for range of motion were taken from reference works.\textsuperscript{18,19} The column ‘percentage of normal’ shows the median value of the obstetric brachial plexus lesion measurement as a percentage of the corresponding normal value.

Figure 1: Schematic drawing of motor misrouting in obstetric brachial plexus lesions. Regenerating axons tend to branch, and the various branches may end up in different muscles. The reinnervated muscle fibres may lie in an agonist of the intended muscle, an antagonist, or a muscle with another function (deltoid instead of biceps, shown here). Roth’s method\textsuperscript{9–11} for measuring misrouting in obstetric brachial plexus lesions is based on the principle that stimulating any part of a neuron will excite all its branches: stimulating nerve endings in one muscle and recording a response in another muscle establishes the presence of a branched motor neuron.
Figure 2: Motor misrouting in obstetric brachial plexus lesion participants. The horizontal axis shows the 10 muscles when used as stimulation sites, and the vertical axis shows their use as recording sites. Each node contains the number of patients with misrouting for that stimulus–response combination (maximum 17). The radius of the circle corresponds to the number of participants. Values below the columns indicate the number of recorded responses per stimulated muscle, and percentages denote the number in relation to the maximum number of recorded responses 153 (9 muscles × 17 participants). Values to the right of the rows indicate the number of cases with misrouting per recording site.

Figure 3: Motor muscle misrouting scores of participants with OBPL. Stimulation sites are shown on the horizontal axis. The vertical axis shows the subscore of number of misrouted responses. The numbers near the circles indicate how many participants reached that score. For instance, there were seven participants in whom stimulation of the biceps muscle resulted in misrouted responses in three other muscles. This is also visualized with a circle with a radius corresponding to the number of participants with the corresponding subscore. The maximum value is 17, except for the flexor carpi radialis and pronator teres, for which the values of one participant are missing.
Figure S1: Representative case of biceps motor point stimulation and simultaneous recording in the other nine muscles. Two consecutive measurements in an obstetric brachial plexus lesion subject are overlaid showing reproducibility of the responses. The responses in channel two and eight (from top to bottom) have a duration of approximately 15 and 20 ms, presumably formed by summation of separate motor unit potentials.