Original article

The double crush syndrome revisited - A Delphi study to reveal current expert views on mechanisms underlying dual nerve disorders

Annina B. Schmid, Michel W. Coppieters*

Centre of Clinical Research Excellence in Spinal Pain, Injury and Health, Division of Physiotherapy, School of Health and Rehabilitation Sciences, The University of Queensland, QLD 4072, St Lucia, Brisbane, Australia

A R T I C L E   I N F O

Article history:
Received 7 January 2011
Received in revised form 7 April 2011
Accepted 9 May 2011

Keywords:
Double crush syndrome
Nerve compression syndromes
Neuropathic pain
Delphi study

A B S T R A C T

A high prevalence of dual nerve disorders is frequently reported. How a secondary nerve disorder may develop following a primary nerve disorder remains largely unknown. Although still frequently cited, most explanatory theories were formulated many years ago. Considering recent advances in neuroscience, it is uncertain whether these theories still reflect current expert opinion. A Delphi study was conducted to update views on potential mechanisms underlying dual nerve disorders. In three rounds, seventeen international experts in the field of peripheral nerve disorders were asked to list possible mechanisms and rate their plausibility. Mechanisms with a median plausibility rating of ≥7 out of 10 were considered highly plausible. The experts identified fourteen mechanisms associated with a first nerve disorder that may predispose to the development of another nerve disorder. Of these fourteen mechanisms, nine have not previously been linked to double crush. Four mechanisms were considered highly plausible (impaired axonal transport, ion channel up or downregulation, inflammation in the dorsal root ganglia and neuroma-in-continuity). Eight additional mechanisms were listed which are not triggered by a primary nerve disorder, but may render the nervous system more vulnerable to multiple nerve disorders, such as systemic diseases and neurotoxic medication. Even though many mechanisms were classified as plausible or highly plausible, overall plausibility ratings varied widely. Experts indicated that a wide range of mechanisms has to be considered to better understand dual nerve disorders. Previously listed theories cannot be discarded, but may be insufficient to explain the high prevalence of dual nerve disorders.

© 2011 Elsevier Ltd. All rights reserved.

1. Introduction

The double crush hypothesis was first formulated in 1973 and states that axons that have been compressed at one site become especially susceptible to damage at another site (Upton and McComas, 1973). The basis for this hypothesis was the high prevalence of cervical radiculopathy observed in patients with carpal tunnel syndrome (CTS) (Table 1). All studies reported a much higher prevalence of cervical radiculopathy in patients with CTS compared to the prevalence of cervical radiculopathy in the general population (<1%) (Radhakrishnan et al., 1994; Salemi et al., 1996).

Even though these epidemiological studies suggest that dual nerve disorders are a clinical entity, controversy still surrounds the double crush hypothesis. A recent international online survey in 528 clinicians revealed that 58% supported the double crush hypothesis; 21% remained undecided and 21% did not support it. The level of acceptance of the hypothesis varied between professions. The majority of physiotherapists (85%) agreed with the double crush hypothesis, half of the hand surgeons (51%) and a minority of neurologists (24%) agreed (Schmid and Coppieters, 2010).

In addition to the controversy on the existence of the double crush syndrome, there is debate on underlying mechanisms. The main point of debate is whether a primary nerve disorder can indeed predispose the nervous system to further injury, or whether the frequent coexistence of nerve disorders is caused by an underlying pathology, such as diabetes or thyroid disease (Wilbourn and Gilliatt, 1997; Morgan and Wilbourn, 1998). Proposed mechanisms associated with a primary nerve disorder which may predispose the nervous system to a secondary nerve disorder are impaired axonal transport (Upton and McComas, 1973; Dahlin, 1991), reduced intraneural microcirculation (Lundborg and Dahlin, 1992; Mackinnon, 1992) and altered nerve elasticity (Osterman, 1991). Axonal transport and intraneural microcirculation have been shown...
to be impaired at the site of nerve compression (Lundborg, 1970; Rydevik et al., 1980; Lundborg et al., 1983; Dahlin et al., 1984).

Despite the controversy surrounding the double crush hypothesis, it is still frequently cited to explain the phenomenon of dual nerve disorders (e.g., Moghtaderi and Izadi, 2008; Smith et al., 2008; Fitzpatrick, 2010). Numerous reviews have summarised the sparse available evidence for potential mechanisms (e.g., Osterman, 1988; Mackinnon, 1992; Simpson and Fern, 1996; Wilbourn and Gilliatt, 1997). These mechanisms have however all been formulated more than 10 years ago. Since then, they have neither been updated nor revised despite substantial advances in neuroscience. Rather than continuing to review potentially outdated mechanisms, other study designs are needed to reveal which mechanisms are currently considered important for the double crush hypothesis, taking into consideration recent advances in neuroscience. A Delphi study was therefore conducted with the following two main aims: (1) to determine whether experts agree that a nerve disorder can be a predisposition for the development of a secondary nerve disorder, and (2) to compile an up-to-date list of plausible mechanisms to explain the occurrence of dual nerve disorders.

2. Methods

A three-round Delphi survey was conducted in a panel of international experts in the field of peripheral nerve disorders. The ‘classical Delphi’ method is used to reach consensus on a controversial topic (Dalkey, 1967). As reaching consensus was not the aim of this study, a ‘policy Delphi’ was conducted. A ‘policy Delphi’ specifically intends to develop alternatives to already existing theories and to examine their acceptability rather than aiming to reach consensus (Turoff, 1970; Loo, 2002). This modification of the Delphi design is therefore a well-suited method to address the aims of this study.

2.1. Expert panel

Fifty experts were invited by mail and email to participate in this study. Invited experts were either clinical researchers who published at least 2 articles specifically on the double crush hypothesis (n = 12), basic scientists with at least 15 articles in the field of peripheral nerve injuries published in international peer-reviewed journals identified via ISI Web of Knowledge (n = 32), and university lecturers with an international reputation in peripheral nerve disorders and neuropathic pain (at least 5 peer-reviewed publications, 1 book chapter and presenting international workshops on neuropathic pain) (n = 6). These a-priori established selection criteria and the number of contacted experts varied among the three subgroups in order to attract the top segment of each category and to correct for the anticipated differences in response rates. All experts remained anonymous towards each other. The institutional ethics committee granted ethical approval.

2.2. Procedure

In the first round, experts rated their level of agreement regarding the statement that a nerve disorder in the upper limb or neck is a predisposition for the development of a secondary nerve disorder in the upper limb or neck. The example which was given was the occurrence of CTS following cervical radiculopathy. A 5-point Likert scale ranging from ‘strongly disagree’ to ‘strongly agree’ was used. In addition, the experts were asked in an open question to list possible mechanisms which may explain the occurrence of a secondary nerve disorder following a primary nerve disorder. Upon receipt of the completed first-round questionnaires, responses were anonymised and two investigators composed a list of mechanisms incorporating every suggestion of the panel. Each mechanism was summarised with a short title followed by a paragraph detailing the proposition. If several experts mentioned the same mechanism, the answers were merged. Since the wording therefore differed from the original answers, all experts were contacted in a second round to verify that their suggestions were still represented in the newly compiled list of mechanisms. (No modification was requested.) In addition, they were given the chance to propose additional mechanisms should they have felt that the list was not complete. (One additional mechanism was added.) The online appendix contains the complete list of mechanisms as compiled in the second round.

In the third round, every expert rated the plausibility of each mechanism on a 10-point Likert scale ranging from 1 (‘not at all plausible’) to 10 (‘highly plausible’) (Brunner et al., 2008). For each mechanism, the authors were given the option to abstain from rating if they felt they did not have sufficient knowledge in that particular field. This option was incorporated to increase the validity of the actual ratings. The questionnaires of each round were trialled in a small sample of researchers and clinicians to increase the chance of correct implementation before they were sent to the participating experts.

2.3. Statistical evaluation

Plausibility ratings were analysed in SPSS Version 15.0 (SPSS Inc., Chicago, Illinois) by calculating the median and the corresponding interquartile ranges (IQR) for each mechanism. Plausibility ratings were classified according to their median ranking into highly plausible (≥7), plausible (4 to <7) and implausible (<4). A Kruskall–Wallis test was performed on the agreement ratings and the plausibility ratings of each mechanism to evaluate potential differences between the three subgroups of experts.

3. Results

Seventeen experts from seven countries (Australia (n = 4), Canada (n = 1), Denmark (n = 1), Israel (n = 1), Sweden (n = 1), United Kingdom (n = 1) and United States of America (n = 8)) completed the first round of the study. Sixteen experts completed the entire study. The panel consisted of six clinical researchers, six basic scientists and five university lecturers.

### Table 1

<table>
<thead>
<tr>
<th>Publication</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morgan and Wilbourn, 1998</td>
<td>5%</td>
</tr>
<tr>
<td>Kuntzer, 1994</td>
<td>6%</td>
</tr>
<tr>
<td>Yu et al., 1979</td>
<td>11%</td>
</tr>
<tr>
<td>Cassvan et al., 1986</td>
<td>14%</td>
</tr>
<tr>
<td>Pierre-Jerome and Bekkelund, 2003</td>
<td>16–53%</td>
</tr>
<tr>
<td>Osterman, 1988</td>
<td>18%</td>
</tr>
<tr>
<td>Moghtaderi and Izadi, 2008</td>
<td>24%</td>
</tr>
<tr>
<td>Herczeg et al., 1997</td>
<td>33%</td>
</tr>
<tr>
<td>Liveson, 1991</td>
<td>48%</td>
</tr>
<tr>
<td>Upton and McComas, 1973</td>
<td>76%</td>
</tr>
<tr>
<td>Golovchinsky, 1995</td>
<td>94%</td>
</tr>
</tbody>
</table>

The publications are ranked based on prevalence (low to high). Due to a lack of a gold standard to diagnose cervical radiculopathy and carpal tunnel syndrome, different diagnostic methods have been employed which may be responsible for the variation in prevalence values.
Fifty-nine percent of the experts either agreed or strongly agreed that the presence of a nerve disorder is a predisposition for the development of a secondary nerve disorder in the same quadrant; 12% remained undecided and 29% disagreed. None of the experts strongly disagreed. There was no difference in agreement ratings between expert subgroups (Kruskall–Wallis \( p = 0.61 \)).

The experts listed 22 potential mechanisms to explain the occurrence of dual nerve disorders (Figs. 1 and 2). Fourteen mechanisms explained the occurrence of a primary nerve disorder (Fig. 1). Of these mechanisms, nine have not previously been suggested in relation to dual nerve disorders. Four mechanisms reached a median of \( \geq 7 \) and were therefore considered highly plausible (impaired axonal transport, ion channel up or downregulation, inflammation in the dorsal root ganglia and neuroma-in-continuity). Seven mechanisms were categorised as plausible (median \( >4 \) to \( <7 \)), whereas three mechanisms were considered implausible (median \( \leq 4 \) (Fig. 1).

The remaining eight mechanisms (Fig. 2) could be regarded as underlying common drivers. These mechanisms by themselves may predispose to multiple nerve disorders in contrast to processes that are associated with a first nerve disorder subsequently leading to a secondary nerve disorder. Five of these mechanisms were considered highly plausible (systemic factors, neurotoxic medication, age, lifestyle and the fact that these disorders are common). The remaining three mechanisms were considered plausible (Fig. 2).

The experts pointed out that mechanisms are likely to occur together. A combination of mechanisms was rated as highly plausible (median = 9.5; IQR = 1.8). For most of the other mechanisms there was a large variability in plausibility ratings between experts as evidenced by the relatively large interquartile ranges.

The experts could abstain from rating when they felt a particular mechanism was outside of their area of expertise, but on average, there were only 1.5 abstentions per mechanism. There was no difference in plausibility ratings among the three subgroups of experts for any mechanism (Kruskall–Wallis all \( p > 0.05 \)).

4. Discussion

Fifty-nine percent of the experts either agreed or strongly agreed that the presence of a nerve disorder is a predisposition for the development of a secondary nerve disorder in the same quadrant. Although the majority of experts supported this view, the fact that 29% of experts disagreed indicates that controversy still surrounds the double crush hypothesis. Interestingly, the level of agreement among experts was comparable with the agreement among clinicians (Schmid and Coppieters, 2010).

Experts who did not support the statement that a primary nerve disorder predisposes to a secondary nerve disorder were not excluded from continuing in the study. One reason for this was that when asked to list mechanisms to explain dual nerve disorders, experts could also list mechanisms which may cause dual or multiple nerve disorders, such as systemic diseases. In other words, mechanisms associated with underlying pathologies that can cause multiple nerve injuries could be listed in addition to mechanisms associated with a primary nerve disorder that lead to a secondary nerve disorder.

Eight mechanisms which could be regarded as common drivers for dual or multiple nerve injuries were listed. There is high level evidence that systemic factors such as diabetes or thyroid disease (Briemberg, 2009), and neurotoxic medication such as cancer drugs (Peltier and Russell, 2006) lead to polyneuropathies. These mechanisms are however independent of a primary nerve disorder and do therefore not reflect the initially described double crush hypothesis where one nerve disorder predisposes the nervous system to the development of a secondary nerve disorder (Upton and McComas, 1973). In this discussion, we will therefore focus on the mechanisms associated with a first nerve disorder which may trigger a secondary nerve disorder.

Fig. 1. Suggested mechanisms associated with a nerve disorder that may predispose to the generation of a secondary nerve disorder. Median and interquartile ranges (IQR) of the plausibility ratings, the number of experts who abstained from rating and whether mechanisms have previously been linked to the double crush hypothesis are listed for each mechanism. DRG: dorsal root ganglia.
All mechanisms previously linked to the double crush hypothesis were still listed, indicating that these mechanisms cannot be dismissed. The nine newly proposed mechanisms suggest however that the traditionally advocated mechanisms may be insufficient to explain how a nerve disorder may render the nervous system more vulnerable for the development of a secondary nerve disorder.

To prevent the introduction of bias, all experts were invited to rate each mechanism regardless of their level of agreement with the double crush hypothesis. Although approximately one third of the experts disagreed with the double crush hypothesis and had the choice to rate the mechanisms related to a primary nerve disorder as ‘not at all plausible’, only 3 mechanisms were considered implausible. Considering the low abstention rate (1.5 experts per mechanism) experts were reluctant to dismiss the suggested mechanisms. Below we will briefly discuss the mechanisms that were rated as highly plausible or plausible.

### 4.1. Highly plausible mechanisms

#### 4.1.1. Axonal transport

Animal studies revealed that axonal transport is impaired at pressure levels commonly observed in patients (Dahlin and Lundborg, 1990; Rempel et al., 1997). Chemical blockade of axonal transport increases the mechanosensitivity of axons locally and just proximal to the blocking site, but not distally (Dilley and Bove, 2008). It has however been proposed that the peripheral nerve and the dorsal root have separate axonal transport systems (Morgan and Wilbourn, 1998), suggesting that impaired axonal transport in one system may be insufficient to explain the coexistence of cervical radiculopathy and CTS. Similarly, impaired axonal transport by itself cannot explain the combination of CTS and ulnar neuropathy as different nerves have separate transport systems (Morgan and Wilbourn, 1998). It remains to be investigated whether compromised axonal transport due to mechanical compression is sufficient to render the nerve more vulnerable at remote sites.

#### 4.1.2. Ion channel up or downregulation

Ion channel upregulation (e.g., sodium-channels) and downregulation (e.g., potassium-channels) distal as well as proximal to the primary nerve injury may lower the firing threshold of neurons. There is growing evidence for upregulation of specific sodium-channels locally as well as in the dorsal root ganglia, dorsal horn and the thalamus (Dib-Hajj et al., 1999; Hains et al., 2004; Zhao et al., 2006). These sodium-channels rapidly recover from inactivation and are excitable by depolarisations below the action potential threshold (Waxman et al., 2000). This characteristic allows action potential generation at higher frequencies which has been associated with the development and maintenance of neuropathic pain (Waxman et al., 2000; Hains et al., 2004). However, these experiments use nerve injury models which involve major axonal loss. There is one recent study that demonstrated sodium-channel upregulation in Schwann cells at the site of injury in mild nerve compression injuries (Frieboes et al., 2010). Future studies need to investigate whether such changes are present at distant sites to the injury.

#### 4.1.3. Immune-inflammation of the dorsal root ganglia

Animal studies demonstrated an invasion of immune cells in the dorsal root ganglia (DRG) following peripheral nerve injury (Hu et al., 2007). Excitatory cytokines released by these immune cells may lower the firing threshold of sensory neurones (Moalem and Tracey, 2006). Since cell bodies of intact and injured neurones lie in very close proximity in the DRG, immune-inflammation at this site may affect intact axons originating from a site distant to the injury. Even though there is growing evidence for such immune-inflammation, a limitation is that these experiments were carried out in the chronic constriction injury model (Bennett and Xie, 1988). This model leads to extensive axonal loss (Hu et al., 2007) and may not reflect human neuropathies, often characterised by minimal fibre loss (Mackinnon and Dellon, 1986).

#### 4.1.4. Neuroma-in-continuity

If the epineurium remains intact after peripheral nerve injury, regenerating axons sprout along the nerve trunk. These axonal sprouts may fail to reach their peripheral targets, forming so called neuroma-in-continuity (Mavrogenis et al., 2008). Regenerating axons are more sensitive to mechanical and thermal stimuli (Janig et al., 2009) and exhibit ectopic activity (Gorodetskaya et al., 2003). The experts suggested that otherwise pain free stimuli such as movement may now be sufficient to excite these regenerating axons even at distant sites from the injury.

### 4.2. Plausible mechanisms

#### 4.2.1. Central sensitisation

Central sensitisation involves changes in membrane excitability and increased synaptic efficacy which, together with reduced inhibition, may lead to reduced pain thresholds, intensified pain perception and spread of pain to non-affected areas (Ji et al., 2003; Latremoliere and Woolf, 2009). A state of central sensitisation may therefore explain the occurrence of a secondary (normally subclinical) nerve disorder.
4.2.2. Nerve biomechanics and altered movement patterns

During movement, peripheral nerves glide relative to their surrounding tissues (Dilley et al., 2003; Coppieters et al., 2006). Changes in longitudinal (Hough et al., 2007) and transverse (Greening et al., 1999; Erel et al., 2003) nerve movement have been demonstrated in nerve disorders. Impaired nerve excursion at one site may increase neural strain at distant sites and therefore increase the risk for secondary nerve disorders (Osterman, 1991). Reduced nerve movement or increased strain distant to a compression site have however not yet been demonstrated.

The experts further suggested that altered movement patterns may arise from pain and motor or sensory deficits following a nerve disorder. This may put excessive strain on the nervous system distant to the affected site. One of the few studies that investigated this demonstrated an increased forward head posture in patients with CTS (De-la-Llave-Rincon et al., 2009) which may affect the spinal nerves as they exit the cervical spine.

4.2.3. Cognitive, psychological or psychosocial factors

It is well known that past pain experiences (Rollman et al., 2004), hypervigilance or fear can lower pain thresholds (Vlaeyen and Linton, 2000). A patient’s awareness and sensitivity to a neuropathy may be increased when having experienced similar symptoms elsewhere.

4.2.4. Immune-inflammation of the peripheral nerve and spinal cord

As discussed above, immune-inflammation at different sites in the nervous system may lower the firing thresholds of sensory neurones (Moalem and Tracey, 2006). Peripheral nerve injury models have been shown to induce immune-inflammatory reactions locally as well as in the spinal cord (Eriksson et al., 1993; Zhang and De Koninck, 2006; Hu et al., 2007).

4.2.5. Impaired microcirculation

Nerve compression affects intraneural microcirculation resulting in intra- and extraneural oedema (Rydevik et al., 1981; Lundborg et al., 1983). Whereas reduced microcirculation may be compensated at distant sites by vascular anastomoses (Ogata and Naito, 1986; Maki et al., 1997), the absence of a lymphatic in the endoneurium (Powell and Myers, 1986) may challenge the evacuation of intraneural oedema. If ongoing, intraneural oedema may lead to fibrotic changes (Mackinnon, 2002). It remains unclear whether these changes can affect the nerve at distant sites.

4.3. Combination of mechanisms

The view that dual nerve disorders are caused by a combination of mechanisms was almost invariably rated as highly plausible. Indeed, several of the suggested mechanisms are closely linked. Immune-inflammation for example may increase the mechanosensitivity of neurones (Grossmann et al., 2009) or lead to fibrotic changes with subsequent impairment in nerve biomechanics. Likewise, ongoing input from peripheral neurones may excite the central nervous system and maintain a state of central sensitisation. A combination of mechanisms may also counter the criticism that impaired axonal transport by itself is insufficient to explain dual nerve disorders. Axonal transport obstruction has been shown to lead to morphological changes of the cell body and to glial cell activation in the spinal cord (Colburn and DeLeo, 1999), which may explain the coexistence of ulnar and median neuropathies.

4.4. Considerations

Whereas the expert retention rate was high with only one expert’s opinion lost in round three, a possible limitation of this study is the low participation rate among basic scientists (19%). Although a low response rate might influence generalisability, we believe our expert panel (see acknowledgement) is representative for the leaders in this field. The panel size is in accordance with previous recommendations (Ludwig, 1997).

Categorisation of the plausibility ratings (highly plausible, plausible and implausible) was based on scales used for defining expert agreement in other Delphi studies (Gould et al., 2010). Even though this subdivision is arbitrary, over 50% of experts needed to rate a mechanism $\geq 7$ or $\leq 4$ for it to be considered highly plausible or implausible. Considering the international standing of the experts, we believe that these boundaries accurately reflect the plausibility of the proposed mechanisms. It has however to be taken into consideration that the plausibility ratings for most mechanisms varied substantially. We believe that the paucity of research rather than the heterogeneity of the expert panel was responsible for the variability. This view is supported by the comparable plausibility ratings among the three subgroups of experts. The variance in plausibility ratings highlights the need for future experimental studies to evaluate the validity of the suggested mechanisms.

This study resulted in a comprehensive list of potential mechanisms to explain the occurrence of a secondary nerve disorder following a primary nerve disorder. The identification of many new mechanisms shines fresh light on the double crush hypothesis and assists in the development of a research agenda to further understand dual nerve disorders. The large variability in plausibility ratings supports our initial choice for a policy Delphi study to reveal current opinion on mechanisms and rate their acceptance, rather than conducting a classical Delphi to reach consensus. More research in this domain is needed before reaching consensus on underlying mechanisms can be attempted.

Acknowledgements

The authors would like to thank the expert panel for their time and effort in making this study possible (Prof Marshall Devor, Prof Ze’ev Seltzer, Prof Troels Jens, Prof Adrian Upton, Prof Elspeth McLachlan, Dr Michael Thacker, Prof Robert Myers, Prof Lars Dahlín, Dr Toby Hall, A/Prof Geoffrey Bove, Prof A Lee Osterman, Dr David Butler, Prof A Lee Dellon, Mr Max Zuszman, Prof Lawrence Hurst, Dr Wayne Massey and Dr James Richardson). Furthermore, we are grateful to Prof Lucas Bachmann and A/Prof Warren Laffan for their valuable contribution to the methodology of this study.

Appendix. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.math.2011.05.005.

References
