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

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ABSTRACT

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.

ANALYSIS

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Background Information

In recent years, clinicians in many manual medicine disciplines have increasingly diagnosed and attempted to treat nerve 'entrapments' – assuming that along the physical course of a nerve, fibrosis in fascia/muscle/connective tissue can compress a nerve or prevent it from 'sliding' back and forth with extremity movements. In theory, such a condition could alter neuron firing (both efferent and afferent) and axonal transport, resulting in a potential myriad of clinical signs and symptoms ranging from pain to sensory disturbance to overt motor dysfunction.

The concept of a 'double crush' syndrome or injury has been around since 1973 (1). In essence, it refers to a nerve that has been compressed or compromised at one location becoming more susceptible to damage at another site along the nerve's course. This theory originated when researchers noted a high prevalence of cervical radiculopathy in patients with carpal tunnel syndrome. 'Double crush' as a clinical hypothesis is still controversial, with one recent clinician survey revealing support/belief in the concept to range greatly (of interest, physiotherapists in this survey were most supportive of this concept, while neurologists were least supportive) (2).

Controversy also exists regarding the potential underlying mechanisms of the 'double crush'. Therefore, the purposes of this Delphi study were:

1. To determine whether experts agree that there can be a possibility of a secondary nerve disorder; and
2. To compile a contemporary list of potential mechanisms to explain the occurrence of dual nerve disorders.

SUMMARY

17 experts from seven countries (Australia - 4, Canada - 1, Denmark - 1, Israel - 1, Sweden - 1, United Kingdom - 1 and the United States of America - 8) completed the first round of the study. 16 completed the entire study. The panel consisted of six clinical researchers, six basic scientists and five university lecturers.

Agreement Among Experts Regarding 'Double Crush'

- 10/17 (59%) of experts either agreed or strongly agreed that the presence of a nerve disorder is a predisposition to the development of a second nerve disorder in the same quadrant. 2/17 (12%) remained undecided, and 5/17 (29%) disagreed. No experts strongly disagreed.
- There was no difference in opinion noted between expert sub-groups (researchers, basic scientists, lecturers).

Potential Mechanisms of Multiple Nerve Injury

- 22 potential mechanisms were listed by the experts.
- 14 of the 22 explained the mechanism of a secondary nerve disorder following a primary nerve disorder (of these, 9 had not been previously proposed in the literature). 4 of the 14 mechanisms were deemed highly plausible (impaired axonal transport, ion channel up or down regulation, inflammation in the dorsal root ganglia, and neuroma incontinuity).
- The remaining 8 mechanisms could be regarded as underlying common drivers. These mechanisms (individually) 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. 5 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.
- The authors noted that mechanisms could certainly co-exist; such combinations were rated as highly plausible.

Discussing Highly Plausible Mechanisms

Impaired Axonal Transport:
In theory, mechanical compression on a nerve may render it more vulnerable to a secondary nerve disorder. As you'll see, there is more research required. To date, animal studies have demonstrated that axonal transport can be impaired at pressure levels commonly seen in human patients. However, additional research suggests that chemical blockage of axonal transport increases mechanosensitivity of axons locally and just proximal to the blockage site, but not distally. To explain this, it has been proposed that dorsal root ganglia and peripheral nerves have separate axonal transport systems, suggesting that altering one system may be insufficient to explain a secondary nerve disorder.

Ion Channel Up or Down-Regulation:
Up-regulation of sodium channels or down-regulation of potassium channels distal or proximal to a primary nerve injury may affect neuron firing thresholds. This mechanism has been suggested as a possible mechanism in chronic pain and central sensitization, but to date most research in this area has been conducted on severe axonal damage, which isn't representative of a 'nerve entrapment' scenario that we might see clinically. However, there is one recent study that demonstrated sodium channel up-regulation in Schwann cell at the site injury in mild compression injuries to nerves (3). More research in this area is required.

Inflammation in the Dorsal Root Ganglia:
Animal studies have demonstrated invasion of the DRG by inflammatory cells after peripheral nerve injury. The excitatory cytokines released by these cells could, in theory, change the firing threshold of sensory neurons. Again, the bulk of this research has been conducted on a more severe injury model (in this case, severe compression), so this theory remains speculative pending further research.

Neuroma Incontinuity:
This refers to the failure of regenerating axons to reach their peripheral targets after a nerve injury where the epineurium remains intact. Since regenerating axons are more sensitive to mechanical and thermal stimuli, it is possible that even movement could alter pain sensations generated by healing nerves, even at sites distal to the original injury. More research is required.

Discussing Plausible Mechanisms

Central Sensitization:
Central sensitization involves changes in membrane excitability and increased synaptic efficiency which, in conjunction with reduced inhibition, can lead to reduced pain thresholds, increased pain perception, and spread of pain to non-affected areas. This process, in and of itself, could explain secondary nerve disorders.

Nerve Biomechanics and Altered Movement Patterns:
During movement, peripheral nerves must slide relative to their surrounding and enveloping structures. Changes in longitudinal and transverse nerve motion have been observed in nerve injuries. Altered nerve excursion could increase neural strain distally in the nerve, potentially leading to secondary injury. Such reduction in movement or neural strain has not yet been observed in a research setting, however. Further, it is within reason that painful movement may alter posture and general movement patterns which could alter nerve 'tension' as well – more study is required in this area. To date, only one study has demonstrated an increased prevalence of forward head posture in patients with carpal tunnel syndrome (FHP could, in theory, increase strain on exiting spinal nerves) (4).

Other Potentially Plausible Mechanisms:
Clinicians should keep some other potential mechanisms in mind when considering the 'double crush' phenomenon. First, past pain experiences can lower pain thresholds and influence a patient's sensitivity. In addition, nerve compression could influence microcirculation in nerves themselves, potentially resulting in local edema and reduced blood flow – both of which could affect nerve function. Lastly, we should remember that any of the mechanisms mentioned above could occur together, since many are closely linked. Some experts argue that some of the abovementioned mechanisms would not be sufficient to cause a 'double crush' syndrome, but combinations of factors could negate this argument.

CLINICAL APPLICATION & CONCLUSIONS

This interesting study presented a comprehensive list of potential mechanisms to explain the occurrence of 'double crush syndrome', a secondary nerve disorder following a primary nerve disorder. The identification of previously unmentioned potential 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 collaboration of these 17 experts revealed a large variability in plausibility ratings that supports the authors' initial choice of 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 on this topic is required to further our understanding of this phemomenon.

Study Methods

This was a three-round *Delphi Study* – a design that involves consulting a panel of topic experts to reach consensus on a controversial topic. Specifically, this was a 'policy delphi' – meant to develop alternatives to already existing theories to examine their acceptability, rather than to establish a consensus. Seventeen international experts took part in this project, each having particular expertise in peripheral nerve disorders. In the first round, experts rated their level of agreement regarding the standard 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".

This was accompanied by the example of the occurrence of CTS following cervical radiculopathy. A 5-point Likert scale ranging from 'strongly disagree' to 'strongly agree' was used. Also in this round, the experts were asked in an open question to list possible mechanisms which may explain how a second nerve disorder could occur following a primary nerve disorder.

In the second round, the experts were presented with a list of possible mechanisms to verify that their suggestions were still represented in the newly compiled list of mechanisms (wording would, of course, differ among experts in the first round so the authors had to amalgamate their suggestions).

In addition, they were given the chance to propose additional mechanisms if they felt that the list was not complete (one extra mechanism was added this way). 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'). For each mechanism, the authors could abstain from rating if they felt they did not have sufficient knowledge in that particular field.

STUDY STRENGTHS / WEAKNESSES

Due to the subject at hand, a Delphi study is a logical design to employ. This project included experts from around the world with special knowledge of peripheral nerve disorders, however I feel the absence of clinician experts is notable. The three round design allowed for appropriate feedback and debate amongst participants to clarify points of contention.

Additional References

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