physioscience-Artikel

Zusatzinformation zum Interview mit Annina B. Schmid
(physiopraxis 6/16)

Schmid AB. Pathophysiology of the Carpal Tunnel Syndrome. physioscience 2015; 11: 2–10
Pathophysiology of the Carpal Tunnel Syndrome
Challenging Common Beliefs

Pathophysiologie des Karpaltunnelsyndroms
Infragestellung verbreiteter Überzeugungen

Author
A. B. Schmid1

Affiliation
Nuffield Department of Clinical Neurosciences, Oxford University, GB-Oxford, School of Health and Rehabilitation Sciences, The University of Queensland, AUS-St. Lucia

Schlüsselwörter
● Karpaltunnelsyndrom
● Entrapment-Neuropathie
● Pathophysiologie
● kleine Nervenfasern
● Demyelinisierung
● Entzündung
● Diagnose

Key words
● carpal tunnel syndrome
● entrapment neuropathy
● pathophysiology
● small nerve fibres
● demyelination
● inflammation
● diagnosis

Abstract
Carpal tunnel syndrome (CTS) is the most common peripheral nerve disorder. Despite its frequency, the exact pathophysiology remains elusive. It is, however, commonly accepted that CTS affects the large nerve fibres, induces non-inflammatory changes and is driven by mechanisms that remain localised to the lesion site. Clinical diagnosis therefore largely relies on local tests for the large fibre domain such as standard electrodiagnostics, vibrometry or von Frey hair testing within the median nerve territory.

In this review, the current beliefs and resulting clinical guidelines are challenged by summarising novel evidence which suggests the presence of hitherto unrecognised pathophysiological mechanisms. A focus is thereby placed on the contribution of small fibre degeneration, the presence of intraneuronal inflammation and remote mechanisms to the pathophysiology of CTS. Since these mechanisms seem to be pertinent to CTS, potential approaches to integrate them in the diagnostic work-up of patients with suspected CTS are suggested.

Future work is, however, required to establish their diagnostic validity as well as impact on management and prognosis of patients with CTS.

Zusammenfassung

Introduction
Carpal tunnel syndrome (CTS) is the most common peripheral neuropathy and affects the median nerve as it travels through the carpal tunnel at the wrist. The lifetime risk of CTS is estimated at about 10 per cent, but increases to over 85 per cent in patients with diabetes [99]. CTS affects men and women during their productive years. The socio-economic burden of CTS is therefore extensive with a reported median of 21 workdays lost in 2009 in the United States of America [10]. To put this in perspective, CTS headed the statis-

1 Annina Schmid is funded by a Neil Hamilton Fairley Fellowship by the National Health and Medical Research Council (NHMRC) Australia.
tics whereas the loss of workdays caused by low back pain was almost three times lower (8 days; [10]. Despite ample literature on CTS (currently > 8500 articles indexed on PubMed), our understanding of the aetiology and pathomechanisms of CTS remains limited [7]. It is commonly accepted that there is a link between CTS and elevated carpal tunnel pressure [34, 56, 81, 88, 109]. In order to maintain adequate microcirculation of the median nerve, a specific pressure gradient is required in the carpal tunnel [101]. This gradient should be characterised by the highest pressure in the arteries followed by the capillaries, the nerve fascicles, the veins and the lowest pressure in the carpal tunnel. If the pressure in the carpal tunnel increases above venous pressure, obstruction of venous return with subsequent circulatory slowing and intra-neural oedema formation would result. Several studies have investigated the pressure within the carpal tunnel in patients with CTS compared to healthy people. Whereas the pressure in healthy people in a neutral wrist position is usually below 15 mmHg, it can rise to around 30–40 mmHg in wrist flexion and extension [34, 57]. In patients with CTS, however, mean pressures of over 30 mmHg have been reported in a relaxed neutral wrist position [19, 34, 55]. These pressures rise even higher in end of range wrist positions with values up to 250 mmHg in wrist extension [34, 97]. The elevated pressures, which can be well above arterial blood pressure, reverse the normal pressure gradient within the carpal tunnel. This may lead to a circulatory disturbance within the median nerve. The factors that induce the identified increase in carpal tunnel pressure remain controversial. They would, however, involve an increase in carpal tunnel content (e.g. additional lumbrical muscle belly [4, 77]), synoval fibrosis [27], a decrease in size of the carpal canal (e.g. congenitally [73, 98]), arthritic changes [7] or a combination of both [7]. The pathomechanisms suggested to be responsible for symptoms in CTS are linked to the elevated carpal tunnel pressure. The most commonly proposed mechanisms are transient ischaemia or actual mechanical deformation of the median nerve. Mechanical deformation finds its main support in animal studies, which identified mechanical neural damage at the edges of nerve compression [32, 80]. This mainly included changes to the myelin sheath such as myelin invagination and shortening of the internodes (the myelinated segments of the axons; [32, 80]). Actual mechanical neural deformation is also apparent by the typical hourglass shape of the median nerve that can be found in patients with CTS [3]. In contrast, transient ischaemia as a mechanism is supported especially in mild CTS by the immediate relief of sensory symptoms when shaking the hand which presumably increases blood circulation. Furthermore, an immediate improvement in neural blood flow after transverse carpal ligament transection [96] and the immediate relief of symptoms after surgery in some patients suggests predominance of transient ischaemic over structural changes [110]. Presumably, the relative contribution of ischaemia or actual mechanical deformation with resulting structural changes is a matter of disease severity or progression. The downstream mechanisms of increased pressure and resulting intraneural ischaemia or mechanical deformation are believed to (1) affect the large nerve fibres, (2) induce non-inflammatory changes and (3) remain localised to the lesion site. Recent evidence, however, challenges these common beliefs and suggests that we have to substantially revise our understanding of the pathomechanisms involved in CTS.

Below I will summarise the current literature on the pathophysiology of CTS and how it challenges these commonly accepted assumptions. Furthermore, clinical implications of these novel research discoveries regarding the pathophysiology of CTS are discussed.

CTS – A pure large nerve fibre syndrome?

CTS is commonly believed to predominantly affect the large diameter nerve fibres, which consist of axons as well as their myelinating Schwann cells. Indeed, animal models mimicking mild chronic nerve compression lead to a breakdown of the myelin sheath at the compression site [61, 79, 93]. Remyelination occurs, but remains incomplete if the compression on the nerve persists [37]. In humans, the presence of demyelination has been confirmed over a century ago in a case study in which nerve biopsies were evaluated post-mortem in a patient with bilateral isolated thenar atrophies [31]. Upon histological examination, the median nerve appeared swollen proximal to the carpal ligament with extensive intra-fascicular fibrosis and complete demyelination beneath the carpal ligament. In addition to demyelination, the structural and functional integrity of the large axons can be compromised in CTS, leading to deafferentation of target tissues. In humans, damage to large axons (and not only their myelin sheath) is evident in severe stages of the disease by the focal thenar atrophy that suggests motor deafferentation. Results from animal models also suggest that acute peripheral nerve injury leads to a predominant loss of large axons [5, 13, 18]. These models include, however, extensive nerve injuries such as the chronic constriction injury (tying ligations around a nerve) or nerve crush (acute and severe compression with tweezers), which do not reflect the rather mild nature and slow onset of CTS. Other authors have used animal models of acute graded compression to investigate its effect on large fibre function [21]. From these studies it is apparent that the conduction velocity of large myelinated fibres is blocked after approximately 20 minutes of compression with a compression chamber (200 mmHg) whereas the same degree of compression did not markedly change the conduction velocity of the unmyelinated axons even if applied over 2 hours [21]. Due to these studies, it is commonly accepted that the large axons are less resistant to compression than unmyelinated axons. Given the predominance of reports on large fibre dysfunction after nerve compression, it is not surprising, that clinical diagnosis of compression neuropathies relies on tests for the large fibre domain. The guidelines on the diagnosis of CTS for instance only mention tests for the large fibres such as standard electrodiagnostic testing, evaluation of touch sensitivity with Semmes Weinstein filaments, texture discrimination as well as vibrometry [1]. Standard electrodiagnostic tests are still considered the “gold standard” of diagnosing CTS by many. They measure the ability of the large myelinated fibres (A-beta and motor fibres) to conduct electrical impulses. Standard protocols include sensory and motor nerve action potential latencies and amplitudes (Fig. 1). Since these recordings are done with surface electrodes over skin, compound action potentials of all axons within the stimulated nerve trunk are recorded rather than single action potentials of individual axons. By dividing the distance over which the action potentials were recorded by the respective latencies, nerve conduction velocities can be determined.
The characteristic slowing of nerve conduction velocity upon electrodiagnostic testing in patients with CTS is commonly interpreted as a sign of demyelination [64]. In contrast, a decrease in amplitudes has been interpreted as a sign of axonal loss assuming that fewer axons are firing upon stimulation [64]. However, a decrease in compound action potential amplitudes may also be caused by demyelination of some fibres [64]. The comparably slower conduction velocity of the demyelinated compared to spared fibres could lead to a temporal dispersion of action potentials resulting in smaller amplitudes. It therefore remains subject of debate whether the changes seen upon electrodiagnostic testing are indeed due to axonal loss or rather to demyelination or ischaemia [12, 48].

Despite the frequent use of electrodiagnostic testing, there are several shortcomings to be considered. First, even though electrodiagnostic testing is commonly used to decide whether surgery is indicated [107], no universally accepted standardised procedure or classification is in place to determine the severity of electrodiagnostic changes [2, 6]. Furthermore, its correlation with patients’ symptoms or function deficits remains controversial. Even though some authors report a good association between electrophysiological findings and symptoms [24, 113], several authors found no correlation between electrodiagnostic findings and CTS related symptoms or function even when taking confound-

ing factors such as age, gender and psychological factors into account [16, 54].

Another limitation is that electrodiagnostic testing is designed to pick up loss of function. Whereas numbness is common in patients with CTS, paraesthesia and pain are even more frequent and occur in 84.6 and 88.4 per cent of affected limbs respectively [78]. Pain and paraesthesia represent gain of function and are mediated by axonal hyperexcitability or ectopic activity somewhere along the nociceptive pathways, which cannot be detected by standard electrodiagnostic testing. Most importantly, it should not be forgotten that electrodiagnostic testing can only evaluate the large diameter myelinated fibres (e.g. A-beta and motor fibres) and does not provide any information about the function of small myelinated (e.g. A-delta fibres) or unmyelinated (e.g. C) fibres.

In contrast to common beliefs that CTS predominantly affects the large fibre population, there are recent indications that the small fibres may be affected before electrodiagnostic evidence for large fibre dysfunction can be found [103]. For instance, thermal detection thresholds upon quantitative sensory testing are elevated in patients with symptoms indicative of CTS but normal electrodiagnostic tests [103]. Since thermal detection thresholds are mediated by small myelinated and unmyelinated nerve fibres, this finding suggests an early dysfunction of these small fibres. We have recently confirmed that mild chronic nerve compression in animals induces a predominant structural loss of small axons whereas large axons were demyelinated but otherwise spared [93]. This was apparent by the preferential upregulation of markers of axonal damage in small diameter dorsal root ganglia neurones, a shift towards a loss of small dorsal root ganglia neurones as well as the presence of varicose peripheral afferents expressing calcitonin gene related peptide (a marker for peptidergic small diameter axons). When translating these findings to patients with CTS, we not only identified a dysfunction of small diameter nerve fibres upon quantitative sensory testing, but also a clear structural loss of intraepidermal nerve fibres in skin biopsies taken in the median nerve innervated territory of the affected hand (Fig. 2; [94]). Since only thinly myelinated and unmyelinated fibres pierce the epidermis, these findings confirm not only a dysfunction, but also structural degeneration of small axons. In contrast, large sensory axons as evaluated by the density of Meissner corpuscles (mechanoceptors innervated by A-beta fibres) and dermal myelinated nerve bundles seemed preserved [94]. These data suggest that the diagnostic work-up of patients with suspected CTS should not remain restricted to large fibre tests. The evaluation of small fibre involvement may be especially important in those 10 – 25 per cent of patients with symptoms indicative of CTS but negative electrodiagnostic tests [50, 112]. Indeed, our preliminary data suggest that this cohort of patients has a preferential degeneration of small fibres [94].

Taken together, recent evidence confirms that patients with CTS have involvement of large fibers as apparent by prolonged nerve conduction velocities and decreased sensory and motor compound action potentials [82], as well as the presence of elevated vibration [58, 92, 106] and mechanical detection thresholds to von Frey hairs [8, 94]. Since structural integrity of large axons seems largely preserved at least in mild stages of the disease [94], these changes may be caused by demyelination rather than major axonal loss of large fibres. In contrast though, small diameter nerve fibres seem to degenerate independent from electrodiagnostic test severity [94] and may be an explanation for classic
CTS symptoms in the absence of electrodiagnostic test abnormalities. Therefore, clinicians should consider including tests for the small fibre domain in the diagnostic work-up of patients with CTS, rather than exclusively relying on large fibre tests.

**CTS – Is it non-inflammatory?**

The second commonly accepted assumption concerning CTS is that it is a non-inflammatory condition [7]. This assumption is mainly based on the absence of inflammatory markers in the synovial sheets of tendons [27, 33] and blood serum [33] of patients with CTS. It should, however, be noted that the absence of a systemic elevation of inflammatory markers does not necessarily exclude localised or low-grade inflammatory changes.

Indeed, patients with CTS exhibit some patterns indicative of an inflammatory condition. The typical nocturnal symptoms are classically ascribed to a physiological decrease of blood pressure which inverts the pressure gradient required to maintain adequate neural blood circulation in patients with CTS. However, night symptoms and perturbed sleep are also common in inflammatory diseases [47, 59]. Potentially, the changes in metabolic activity ensuing from maintained nocturnal ischemia cause accumulation of oedema and inflammatory cells. Since inflammatory mediators released by inflammatory cells lower the firing threshold of nearby neurons [68], inflammation is a plausible explanation for nocturnal ectopic axonal firing, which is perceived by patients as paraesthesia and pain.

A strong indication that local inflammation is an important part of the pathophysiology of CTS is the beneficial effect of steroid injections, which are used as a first line treatment. Steroids are potent suppressors of an inflammatory response and are more effective than placebo in reducing symptoms in patients with CTS in the short term (up to 1 month; [44, 65]). Besides steroids, non-steroidal anti-inflammatory drugs (NSAID) are sometimes used in the treatment of CTS [83]. The available evidence for their efficacy is, however, sparse and most trials do not adhere to basic methodological principles of randomised controlled trials [15]. Since inflammation has not been identified in synovial tissue or systemically in blood serum, the beneficial effect of steroid injections may be attributed to inflammation within other tissues inside the carpal tunnel. It is well known that experimental acute and severe nerve injuries induce a localised inflammation within the injured nerve trunk [40, 43, 68, 70, 71]. Recently, we demonstrated that even a mild and chronically developing experimental nerve compression is sufficient to induce intraneuronal inflammation [93]. This was apparent by the recruitment and activation of inflammatory cells to the lesion site including macrophages (Fig. 3), dendritic cells as well as T-lymphocytes. In addition to the endoneurium, immune cells also infiltrated the epineurium of the compressed nerve. Such inflammation of the neural connective tissue may be responsible for the sensitisation of nervi nervorum within the epineurium [9], which may contribute to the pain experience in patients with CTS.

Unfortunately, proving the presence of neural inflammation in patients with CTS is highly challenging since a histological evaluation of median nerve tissue is not possible for obvious reasons. People have, however, used indirect methods to assess neural inflammation. One example is the use of magnetic resonance imaging, which demonstrates increased signal intensity of the median nerve on T2 weighted images [20, 41]. Since increased signal on T2 weighted images suggests an increased fluid content, this has been interpreted as the presence of oedema, which can be a correlate of inflammation [49].

In summary, an inflammatory reaction in CTS cannot be excluded although the available evidence in humans is weak and indirect. Future studies are required to elucidate a potential role of inflammation in the pathophysiology of CTS.

---

**Fig. 2 a, b** Patients with CTS have a reduced intraepidermal nerve fibre density (adjusted from Schmid et al. [94]). a The figures depict sections through skin taken from the ventrolateral aspect of the proximal phalanx of the index finger. The left panel represents a skin of a healthy control participant and the right panel a patient with CTS of same age and gender. The dermal-epidermal border is marked with a white dotted line. Whereas fibres in the subepidermal plexus (arrow heads) are present in the patient with CTS (arrow heads), there is a clear reduction in fibres piercing into the epidermis (arrows), suggesting degeneration of small fibres. b The graph confirms a significant reduction of intraepidermal nerve fibre density in patients with CTS compared to age and gender matched healthy controls (p < 0.0001). Calibration equals 100µm.
CTS – Driven by local mechanisms only?

The pathophysiology of CTS is considered to be driven by focal mechanisms at the lesion site. Indeed, the textbooks describe that symptoms are classically restricted to the median innervation territory of the hands. Clinically, the majority of patients with CTS, however, report symptoms outside the median innervation territory (up to 70 per cent; [111]). In addition to extraterritorial symptoms in the hands, patients with CTS have a high prevalence of widespread pain in the elbow, shoulder and neck region [17, 72, 86]. In addition to these widespread symptoms, signs have also been identified in a non-anatomical manner. For instance, a subgroup of patients with CTS have widespread thermal and mechanical hyperalgesia which can be found over the ulnar and radial area of the hand as well as the elbow, neck or even the tibialis anterior [23, 28, 29, 114]. These widespread signs and symptoms cannot solely be attributed to focal pathomechanisms. It has been hypothesised that extraterritorial symptoms may be caused by transmission of the elevated carpal tunnel pressure to Guyon’s canal [35]. Whereas such transmission of pressure may account for symptoms in the ulnar nerve distribution, it cannot explain the frequent occurrence of symptoms in the radial nerve territory or proximal to the carpal tunnel. Alternatively, spread of symptoms may be attributed to secondary musculoskeletal changes due to pain related alterations in movement patterns or posture. As an example, patients with CTS have been found to have increased forward head posture compared to healthy people [22], which may explain coexisting neck pain. Such alterations in posture are, however, unlikely to explain many widespread findings such as thermal or mechanical hyperalgesia over the tibialis anterior muscle [23].

Widespread symptoms in other neuropathic pain conditions are commonly attributed to the presence of spinal or supraspinal mechanisms [51]. Whereas the widespread distribution of hyperalgesia is in accordance with the presence of central sensitisation at a spinal level [114], recent literature has also identified morphological and functional changes at a cortical level as determined with (functional) magnetic resonance imaging [25, 45, 74 – 76, 104, 105]. For instance, patients with CTS present with a more extended [74 – 76] or restricted [25] somatosensory representation of the fingers innervated by the median nerve. The nature of reorganisation (extension versus restriction) may depend on the predominance of paraesthesia or pain. Whereas CTS patients with paraesthesia as a predominant symptom seem to have an extended representation of their fingers in their somatosensory cortex, those patients with pain present with a more restricted representation [104]. Not surprisingly, the extent of the reorganisation in the primary somatosensory cortex correlates with the functional deficit [63]. In addition to function cortical changes, a recent study also identified a decrease of grey matter volume in patients with CTS [62]. The mechanism underlying such morphological cortical alterations remains, however, elusive and may include changes to neuronal (e.g. deafferentation, dendritic spine remodelling) or glial cell architecture [62].

Another explanation for the frequent occurrence of widespread symptoms is the presence of remote neuroinflammation. It is well known that acute and extensive experimental nerve injury not only induce an activation of immune cells locally, but also in associated dorsal root ganglia, the spinal cord or even higher cortical and subcortical centres [26, 43, 69]. These remote inflammatory responses include the activation of macrophages, T-cells as well as glial cells (e.g. astrocytes and microglia in the spinal cord and brain; satellite glial cells in the dorsal root ganglia). This response is proposed to be triggered by a retrograde signal in injured sensory axons or their Schwann cells [42].

We recently showed that even mild chronic nerve compression is sufficient to induce a neuroimmune reaction in the dorsal root ganglia, where the cell bodies of the compressed axons are located (Fig. 4; [93]). The presence of neuroinflammation at this level may explain extraterritorial symptoms and signs in patients with CTS for the following reason. The dorsal root ganglia are densely packed with cell bodies of neurones originating from different sites in the periphery and projecting into different spinal pathways. For instance, a dorsal root ganglion at the cervical level C7 contains sensory axons projecting from the median, radial, axillary as well as occasionally from the ulnar nerve. Inflammatory mediators released by immune cells attracted to the C7 dorsal root ganglia by a peripheral median nerve injury may therefore lead to hyperexcitability and spontaneous discharge not only of injured neurones originating in the median nerve, but also of intact neurones nearby, which project from other territories. Therefore, remote neuroinflammation in the dorsal root ganglia C7 may explain the occurrence of symptoms as well as hyperalgesia not only in the median nerve territory, but also in the axillary, musculocutaneous, radial or even ulnar innervation territories. Widespread pain and the high prevalence of coexisting disorders in patients with CTS may therefore be attributed to the presence of such remote inflammatory reactions.

Clinicians should be aware that patients with CTS have a high frequency of extraterritorial symptoms. This knowledge should not only be incorporated in the subjective examination, but the presence of remote sensory changes that may be indicative of central
sensitisation, altered cortical representation or remote immune-inflammatory mechanisms should also be carefully evaluated.

Clinical implications

The sections above have summarised recent evidence suggesting that the pathomechanisms of CTS involves both large and small fibre dysfunction, a potential inflammatory component and remote mechanisms accounting for extraterritorial spread of symptoms. The impact of these novel findings on diagnostic work-up, management and prognosis of patients with CTS has not yet been scientifically evaluated. Therefore, this part of the review relies on inferences made from experimental models or other conditions with similar pathomechanisms.

Diagnosis

The diagnostic work-up for CTS relies on large fibre dysfunction as apparent by the current clinical guidelines [1]. Electrodiagnostic tests, vibrometry and von Frey hair testing all evaluate the function of the large myelinated fibres. The presence of thenar muscle atrophy and weakness (e.g. pinch strength) in later stages of the disease point towards actual degeneration of motor axons. However, since small fibres seem to be affected early in the disease process [94, 103], clinical evaluation of small fibre function should not be omitted in patients with CTS. Clinical tests for the small fibre domain include thermal detection thresholds (quantitative sensory testing; [89]), sympathetic reflex testing [111] and evaluation of skin biopsies [52]. These tests remain challenging in daily practice due to expensive equipment and time consuming procedures. However, pinprick testing provides a feasible and cheap alternative to investigate a dysfunction of the small myelinated (A-delta) fibres.

Loss of pinprick sensitivity has previously been shown to be associated with loss of intraepidermal nerve fibre density in patients with small fibre neuropathy [108]. This test can be performed in a similar way to light touch testing and only takes a couple of minutes to perform. First, patients are shown how a sharp prick (e.g. with toothpick, neurotip) should feel by gently pricking over a healthy skin area (e.g. chest, cheek). Thereafter, pinprick will be tested in a circular manner around the extremities (in the case of CTS around the upper arms and forearms) as well as by testing each finger separately (palm and dorsum). The patients are instructed to tell the tester whether the pinpricks feel similarly as sharp as on the unaffected territory and to indicate if the sensation increases/decreases. Territories with affected pinprick sensation are then mapped out.

Clinically, loss of pinprick sensitivity in the territory of the affected nerve suggests loss of function of small fibres (e.g. degeneration or demyelination) whereas increased sensitivity suggests gain of function such as axonal hyperexcitability. The latter may have several underlying reasons including peripheral sensitisation, intraneural inflammation (see below) or ion channel changes. Currently, no direct methods are available to determine intraneural inflammation in patients. Magnetic resonance imaging is, however, used to indirectly visualise intraneural oedema as a correlate of inflammation by investigating signal intensities of affected nerves on T2 weighted images [20]. Mostly though, magnetic resonance images are not available for patients with CTS. Considering that intraneural inflammation and the ensuing secretion of inflammatory mediators lowers the firing threshold of axons, patients would presumably exhibit symptoms and signs representing gain of function. Symptoms may include pain and paraesthesia as well as nocturnal symptoms that may not completely disappear upon shaking the hands (c.f. ischaemia).

Characteristic signs of gain of function would include thermal or mechanical hyperalgesia upon quantitative sensory testing or mechanical hypersensitivity evoked by neural provocation tests. Neural provocation tests for patients with CTS may include neurodynamic tests (e.g. upper limb neurodynamic tests), nerve palpation as well as Tinel’s and Phalen’s signs. Whereas positive signs and symptoms may indeed be caused by neural inflammation, they may also be attributed to other mechanisms such as ischaemia, ion channel changes or peripheral (or central) sensitisation which often coexist with intraneural inflammation. The presence of remote mechanisms can clinically be evaluated by testing for gain of function outside the affected innervation territories. In a subgroup of patients with CTS for instance, the presence of extraterritorial thermal or mechanical hyperalgesia upon quantitative sensory testing (e.g. over radial nerve territory, elbow or neck) has been interpreted as a sign of central sensitisation [28, 114]. If quantitative sensory testing equipment is not available, clinicians may use palpation to identify widespread mechanical hyperalgesia and heat/cold pain thresholds may be tested with hot water tubes or ice blocks respectively. The latter has been shown to be useful in patients with whiplash-associated disorders, in whom a value over 5 on a numerical pain rating scale after 10 seconds of ice application had a high likelihood to identify cold hyperalgesia [66]. Whether this cut-off applies to other body sites and other diagnoses remains to be evaluated.
Impaired two-point-discrimination and left/right judgement have been suggested as clinical correlates for altered cortical re-organisation. The left/right judgement task is a test in which patients are shown pictures of body parts such as hands in different positions and are asked to identify to which side of the body these parts belong to [84]. These tasks use similar brain substrates as imagined and executed movements [46, 67, 85, 100, 102]. Accurate left/right judgement is therefore suggested to depend on the integrity of the body’s representation in cortical and subcortical somatosensory and motor areas [30, 95].

Patients with CTS have previously been shown to have a focused deficit in the accuracy of recognising their affected hand compared to healthy people [91], which implies the presence of cortical changes. The validity of the left/right judgement task to detect cortical reorganisation, however, has not been evaluated. Two-point-discrimination has also been shown to be impaired in patients with CTS [60] and is a reliable (at least for intratrester reliability) and inexpensive test to perform in clinics [14]. However, impaired two-point-discrimination may not only be caused by cortical reorganisation, but axonal degeneration leading to a reduction of skin receptor density would most certainly contribute. Therefore, caution is warranted when interpreting the findings of two-point-discrimination in conditions where axonal degeneration might be present.

Management and prognosis

So far it remains unknown whether the relative contribution of small axon degeneration, inflammation and remote mechanisms impact on the management or prognosis of patients with CTS. The combined knowledge from basic science evidence and other clinical conditions suggests, however, that these factors are highly likely to influence patients’ response to management and prognosis. For instance, animal models demonstrate only slow and often incomplete regeneration of small fibres whereas large fibre regeneration is faster [36, 38]. Preliminary evidence in humans also implies that experimental ablation of small fibres in skin with high doses of capsaicin only recovers slowly and incompletely even after many months [87]. Whether the slow regeneration capacity of small fibres may worsen the surgical or conservative management prognosis of those patients with CTS who have an accompanying small fibre degeneration remains to be established.

Given the potential deleterious effects on axonal firing [68] and development of remote changes [43], local intraneural inflammation should be addressed as early as possible. Interventions that may reduce inflammation include cortisone injections (at least in the short term; [65]), but therapeutic interventions such as nerve and tendon gliding exercises may as well reduce intraneural swelling as apparent by the reduction of nerve signal intensity on T2 weighted magnetic resonance images following one week of exercises [90]. Whether the presence of intraneural inflammation may predict management outcome remains to be investigated.

In conditions other than CTS, it is well accepted that the presence of central changes requires a distinct management approach [53]. This may include graded motor imagery, neuroscience education, or cognitive behavioural therapy among several other methods, which are beyond the scope of this review. The benefit of these interventions for patients with CTS in whom symptoms are maintained by remote mechanisms needs to be evaluated. It should, however, not be forgotten that numerous central processes including cortical changes are triggered and can be maintained by peripheral input [39]. Therefore, addressing the underlying cause and normalising the potential abberant afferent input into the central nervous system remains an important part when attempting to modulate central changes.

Conclusions

This review highlights the recent evidence concerning the pathophysiology of CTS. The likely contribution of small nerve fibre dysfunction, inflammatory changes as well as the presence of remote mechanisms to the clinical presentation of CTS challenge common beliefs and current diagnostic guidelines. Future work is required to establish the validity and clinical value of adding tests for these parameters in the diagnostic work-up for patients with CTS. Furthermore, their impact on patient management and prognosis will need to be determined.

Literatur

3 Arons JA, Collins N, Arons MS. Results of treatment of carpal tunnel syndrome with associated hourglass deformity of the median nerve. J Hand Surg Am 1999; 24: 1192–1195
5 Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain 1988; 33: 87–107
6 Bland JD. A neurophysiological grading scale for carpal tunnel syndrome. Muscle Nerve 2000; 23: 1280–1283
8 Borg K, Lindblom U. Diagnostic value of quantitative sensory testing (QST) in carpal tunnel syndrome. Acta Neurol Scand 1988; 78: 537–541
12 Cappelen-Smith C, Lin CS, Burke D. Activity-dependent hyperpolarization and impulse conduction in motor axons in patients with carpal tunnel syndrome. Brain 2003; 126: 1001–1008
Invited Review


19 Coppiters MW, Schmid AB, Kuhler PA et al. Description, reliability and validity of a novel method to measure carpal tunnel pressure in patients with carpal tunnel syndrome. Man Ther 2012; 17: 589 – 592

20 Cudlip SA, Howe FA, Clifton A et al. Magnetic resonance neurography studies of the median nerve before and after carpal tunnel decompression. J Neurosurg 2002; 96: 1046 – 1051


41 Horch RE, Allmann KH, Laubenberger J et al. Median nerve compression can be detected by magnetic resonance imaging of the carpal tunnel. Neurosurgery 1997; 41: 76 – 82; discussion: 83


46 Jeannard M. Mental imagery in the motor context. Neuropsychologia 1995; 33: 1419 – 1432


48 Kiernan MC, Moghosoros I, Burke D. Conduction block in carpal tunnel syndrome. Brain 1999; 122 (5): 933 – 941

49 Kleinert E, Hamb B, Hildebrandt G et al. Diagnosis and staging of carpal tunnel syndrome: comparison of magnetic resonance imaging and intra-operative findings. Acta Neurochir (Wien) 1996; 138: 228 – 233


Schmid AB. Pathophysiology of the ... physioscience 2015; 11: 2 – 10
Schmid AB. Pathophysiology of the… physiotherapy 2015; 11: 2–10