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HOT TOPICS IN PAIN AND HEADACHE (N ROSEN, SECTION EDITOR)

Recent Advances in the Understanding and Management of Carpal Tunnel Syndrome: a Comprehensive Review

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Abstract

Purpose of Review Carpal tunnel syndrome (CTS) is an entrapment neuropathy that involves the compression of the median nerve at the wrist and is considered the most common of all focal entrapment mononeuropathies. CTS makes up 90% of all entrapment neuropathies diagnosed in the USA and affects millions of Americans.

Recent Findings Age and gender likely play a role in the development of CTS, but additional studies may further elucidate these associations. Of known associated risk factors, diabetes mellitus seems to have the greatest association with CTS. One of the most commonly reported symptoms in CTS is a "pins-and-needles" sensation in the first three fingers and nocturnal burning pain that is relieved with activity upon waking. Treatment for CTS is variable depending on the severity of symptoms.

Summary Conservative management of CTS is usually considered first-line therapy. In cases of severe sensory or motor deficit, injection therapy or ultimately surgery may then be considered. Still CTS is often difficult to treat and may be reoccurring. Novel treatment modalities such as laser and shockwave therapy have demonstrated variable efficacy though further studies are needed to assess for safety and effect. Given the unknown and potentially complex etiology of CTS, further studies are needed to explore combinations of diagnostic and therapeutic modalities.

Keywords Carpal tunnel syndrome · Entrapment neuropathy · Chronic pain management · Endoscopic release · Injection therapy

Introduction

Entrapment neuropathies, disorders of peripheral nerves defined by damage and compression to a nerve as it passes through a narrow space, top the list of most frequently encountered mononeuropathies [1, 2]. Carpal tunnel syndrome (CTS), first described in 1863 by Sir James Paget, is an entrapment neuropathy where the median nerve is compressed at the wrist and is the most common of all focal entrapment mononeuropathies [3]. The median nerve can become entrapped in several other locations in the arm and forearm as well, but these entrapment neuropathies occur at a much lower frequency [3]. As a whole, CTS makes up 90% of all entrapment neuropathies diagnosed in the USA and affects millions of Americans [3].

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Epidemiology

It is reported that one in five ambulatory clinic visits in the USA is for CTS and that lifetime risk for the condition is estimated around 10% [1, 3]. The incidence of CTS is approximately 1 in 1000 individuals in the general population [4, 5]. The gender distribution of CTS diagnoses is somewhat difficult to ascertain [1]. While the condition is thought to have a predilection for females, this assumption may be based on patients who self-refer to neurophysiological labs or clinic and thus would be biased [1]. In reality, CTS could likely be

more or less equally distributed between the two sexes [6]. A postal survey of 3000 individuals randomly selected from the general population of southern Sweden found that the male to female ratio of CTS prevalence was approximately 1:1.4 [1]. It is notable, however, that in this study, the prevalence of CTS in individuals aged 65–74 years was almost four times higher in women than in men [1]. Thus, it is possible that age and gender play a role in the development of CTS, but further studies are needed to elucidate this association.

Risk Factors

Although the precise etiology of CTS is unknown, the condition is largely assumed to be either idiopathic or multifactorial. Suspected risk factors for the development of CTS include obesity, diabetes mellitus (both type 1 and type 2), hypothyroidism, menopause, arthritis, age, and pregnancy [1, 3, 7]. Of all of these risk factors, diabetes seems to have the greatest association with CTS with a prevalence rate of 30% in patients with diabetic neuropathy and 14% in those without neuropathic symptoms [7]. It is suspected that since menopause, hypothyroidism, and pregnancy are all considered risk factors, hormonal changes may be linked to the development of CTS, but to date, there is no confirmatory evidence of this association [6]. Mechanical risk factors include inflammation, thickening, arthritic deformity, bony irregularities, or tenosynovial proliferation in the carpal tunnel that result in the stretching, tethering, and subsequent compression of the median nerve [3, 5]. Another notable mechanical risk factor is wrist shape [5]. Square wrists, defined by a dorsal-volar distance to medial-lateral distance ratio greater than 0.7, are at increased risk of developing CTS [5]. This observation may explain bilateral cases of CTS as well as positive family history of the condition [5]. The overlap between the aforementioned suspected risk factors and these mechanical risk factors is still being investigated [1]. While it is hypothesized that pregnancy increases risk of CTS mainly via edema, there is no specific mechanism by which diabetes or obesity increase risk of CTS [1].

Anatomy and Pathophysiology

The carpal tunnel is a shallow, U-shaped osteofibrous canal bordered on three sides by the carpal bones and on the fourth by the flexor retinaculum [1, 3, 4]. Thus, the floor of the tunnel is formed by the carpal bones while the roof is formed by the flexor retinaculum, giving the tunnel fairly inelastic borders [4, 5]. The carpal tunnel measures approximately 20 mm at its narrowest point at the level of the hook of the hamate and 25 mm at its widest point at the Kaplan cardinal line [3, 4]. Ten total structures—the nine flexor tendons and the median nerve—travel from the forearm to the hand through the tunnel [3]. The median nerve is formed by fascicles from the medial and lateral cords of the brachial plexus, and, upon reaching the elbow, it innervates the pronator teres, palmaris longus, flexor carpi radialis, and flexor digitorum superficialis [3].

The terminal branches of the median nerve include several proper digital sensory nerves and one motor nerve [3]. Sensation is supplied to the most radial 3.5 fingers, the thenar musculature, and the lumbricals of the index and middle fingers [4]. In most individuals, the ulnar half of the fourth finger, the fifth finger, and the palmar and dorsal surfaces of the ulnar side of the hand are innervated by the ulnar nerve [5]. The palmar cutaneous branch of the median nerve runs superficial to the flexor retinaculum and is not affected by CTS [4]. Since this branch provides sensation laterally to the volar base of the thumb and medially to the radial side of the palm, these features can be used to distinguish CTS from more proximal median neuropathy [4]. The motor nerve is referred to as the recurrent (thenar) branch of the median nerve because it turns around in the palm and goes on to innervate muscles within the thenar eminence [3]. It is the effect of compression on these terminal branches that results in the symptoms of CTS [3].

The short segment of the median nerve, or the portion of the nerve that travels in the carpal tunnel between the distal wrist flexion crease and the proximal metaphysis, is considered to be at highest risk of injury [3]. When the wrist is in neutral position, pressure within the carpal tunnel normally is approximately 2.5 mmHg and, in a healthy individual, will not exceed 5 mmHg [3, 4]. This pressure increases when the wrist is flexed or extended [3]. When the pressure within the compartment reaches 20 to 30 mmHg, epineural blood flow to the median nerve has the potential to become impaired, resulting in epineural perfusion and ultimately ischemia [3, 4]. In some patients with CTS, pressures as high as 100 mmHg during flexion or extension have been observed [5]. High pressure, extended duration, and resulting arterial and venous ischemia can lead to the development of pathology in the median nerve that begins with sensory demyelination, followed by motor demyelination, and eventually sensory and motor axon loss [3].

Microscopic changes of the median nerve have been shown to occur in a dose-dependent manner, with increased time periods of high pressure resulting in more permanent damage [4]. Histomorphologically, non-inflammatory fibrosis in the sub-synovial connective tissue (SSCT), especially that surrounding the flexor tendons, is considered the hallmark of the development and progression of CTS [7, 8]. The SSCT refers to the multilayered structure that contains all of the tissues between the visceral synovial sheath, flexor tendons, and median nerve within the carpal tunnel [7]. It is thought that through specific differential finger movements, the SSCT is damaged and undergoes fibrosis, accumulating interstitial fluid and leading to a buildup of carpal tunnel pressure and restriction of the median nerve [8]. There is an association between SSCT fibrosis in CST patients and the expression of growth factors such as transforming growth factor

(TGF-β), vascular endothelial growth factor (VEGF), and interleukins [7]. It has also been suggested that TGF-β second messengers (Smads), downstream fibrotic mediators, increased production of collagen types I–IV, and decreased expression of matrix metalloproteases are all implicated in the pathophysiology of CTS via fibrosis of the SSCT [7]. The role of these factors in the etiology of CTS may help explain why the administration of platelet-rich plasma has proven to be a viable therapy for the condition [7].

Clinical Presentation

Symptoms

Although CTS may arise spontaneously, most patients recall their symptoms developing and worsening over months, years, or decades [3]. A commonly reported symptoms is a "pins-and-needles" sensation in the first three fingers (thumb, index, middle, and half of the ring) and nocturnal burning pain that is relieved by shaking of the hand upon waking [3, 5]. Although both distribution of symptoms to the fingers and awareness of this distribution vary, most patients report concentration of symptoms to the index and middle fingers and sparing of the fifth finger due to its ulnar innervation [5]. As the condition progresses, patients often experience intermittent pain and numbness that arise during daytime activities like driving, lifting, or using the computer [3]. It is notable that while the link between computer use and CTS has been popularized in recent years, the association remains controversial. Evidence suggests that computer use is, at most, a minor risk factor that can be attributed to mechanical stress of the median nerve due to contact with surrounding tendons [1].

While symptoms do vary, patients subjectively describe the sensation of CTS and overwhelmingly have a response of "pain" both distal and proximal to the site of compression rather than other sensory abnormalities like tingling or numbness [1, 5]. For some, this pain eventually becomes constant, and patients begin to report swelling of the affected hand, motor control difficulties, and in some cases of late disease, weakness due to thenar atrophy [3]. In late stages of severe disease, visible atrophy or shrinking of the thenar eminence muscles may also be observed [7]. It is noteworthy, however, that due to anatomical variation, neurologic symptoms do not always follow the exact distribution of median nerve innervation [3]. Consequently, many patients develop symptoms in all of the fingers and the entirety of the hand, forearm, arm, or shoulder [3].

Physical Findings

Since pain is a common symptom of CTS, it is often helpful to visually compare the affected and unaffected hands to determine if strength and sensory limitations can be tied to pain or muscle loss [3]. Two-point discrimination and pinprick testing are often also used to elicit sensory deficits in the median distribution and are sometimes only noted through direct comparison to the unaffected hand [5].

Specialized physical exam maneuvers such as Tinel's and Phalen's tests are designed to apply stress to the median nerve at the wrist in order to elicit CTS symptoms [3]. A positive Tinel sign is elicited when symptoms are evoked by percussion of the median nerve while a positive Phalen sign is marked by symptoms upon 1 min of forced compressive wrist posture, hyperextension or hyperflexion [1, 5]. Although the sensitivity and specificity of these tests are variable, they are efficient and are often coupled with clinical history and other physical exam findings to diagnose CTS with reasonable certainty in ambulatory clinic settings [1, 3]. Beyond the use of Tinel's and Phalen's maneuvers, it is thought that the strength of the abductor pollicis brevis muscle can provide information about the extent of functional impairment in CTS [1]. The abductor pollicis brevis can be tested clinically by asking the patient to place the thumb perpendicular to the plane of the hand and to resist attempts to push the thumb into the plane of the hand [5]. While it is thought that hand dynamometry may be more reliable than clinical examination, it is not commonly implemented due to limitations imposed by time and limited equipment [1].

Diagnosis and Differential

The most effective diagnostic tool for CTS has been subject to debate in recent literature. While both traditionalists and contemporary thinkers agree that a diagnosis can be made based on clinical symptoms, traditionalists argue that electrodiagnostic testing (EDX), also known as nerve conduction studies (NCS), is the gold standard for confirming a CTS diagnosis [9]. They further claim that other provocative tests like Tinel's and Phalen's are not reliable and that ultrasound cannot be used to make a diagnosis of CTS [9]. EDX assesses peripheral nerve injury by measuring the effect of electrical current as opposed to looking directly at underlying pathophysiology [9]. Peripheral nerve damage can include myelin injury and disruption or even axonal death and Schwann cell loss [9]. Even amongst those who agree that EDX is a necessity for diagnosing CTS, there is disagreement on the single best technique for administering electrical impulses [9].

On the other hand, different groups have claimed that these nerve conduction studies may be an "unnecessary evil" that puts most patients through undue stress for little, if any, clinical benefit [10]. The Sonoo group further challenges EDX as a gold standard, arguing that it should not be considered the gold standard given the abundance of false negatives and positives [10]. In accordance with the recommendation of the American Academy of Orthopedic Surgeons, Sonoo et al.

and Fowler et al. concede that EDX has utility for those individuals with severe CTS who might require surgery, but challenge EDX's utility in more moderate cases of CTS [11]. While a numerical scoring system such as CTS-6 can be useful for diagnosing CTS, a confirmatory ultrasound of the median nerve has been proposed as a cost- and time-effective alternative to EDX [11]. In a separate publication, the Fowler group looked at a 19-study meta-analysis with over 3000 patients diagnosed with CTS by EDX or the clinical scoring system CTS-6 [12]. Kwon et al. and Deniz et al. independently compared sensitivity and specificity findings between their ultrasound-diagnosed patients and used Fowler et al.'s EDX-diagnosed patients as a reference standard; they found that while the sensitivity and specificity of ultrasound were slightly lower than those of EDX, in almost all cases, these differences were insignificant [12]. This observation raises the question of whether EDX should be used as the reference standard if there is not an agreed-upon gold standard test for CTS diagnosis. The American Academy of Orthopedic Surgeons has claimed that agreeing upon and establishing a reference standard are the most important goals for research surrounding the diagnosis of CTS [10].

According to the AAEM practice parameters, EDX had a specificity presented in the 97–99% range; in recent years, the false-positive rate has hovered closer to 20% [10]. These false positives are hypothesized to arise from incorrect diagnoses of median neuropathy at the wrist (MNW) that is asymptomatic and does not require further treatment. This distinction is important and frequently overlooked in most publications—MNW occurs at the transverse carpal ligament while CTS is a collection of symptoms that can occur in the absence of MNW [10].

The Fowler and Sonoo groups do not question the overall utility of EDX, rather its use as a first-line diagnostic tool for all patients suspected of having CTS. The groups understand the limitations of ultrasound, specifically that it cannot be used to determine the severity of CTS. However, they ask that EDX purists also recognize its benefits, including the fact that EDX administration with an experienced technician takes 30 min while ultrasound takes only 90 s [11]. Furthermore, patient comfort should be considered and repeated shocks should not be administered if deemed unnecessary. That being said, in more complex CTS cases where surgery or comorbidities must be considered, EDX and even needle EMG are preferred to localize a lesion and to determine an underlying cause [10].

The differential diagnoses of CTS can be broken down into four major categories: brain, cervical spine, musculoskeletal, and neurologic [9]. Complications related to the brain can be either due to demyelinating disease or cerebral insult, including tumor, lesion, or stroke [9]. The cervical spine similarly only has two major differentials: spinal cord injury that could be traumatic or due to the presence of a tumor and cervical disc disease such as spondylosis, stenosis, or radiculopathy [9]. The disease most commonly confused with CTS is cervical radiculopathy that can be differentiated via needle EMG [6]. The musculoskeletal complications are more numerous and include inflammatory processes such as arthropathies, tendonitis, epicondylitis, and compartment syndrome. Further, there can be obstructive inclusions such as hand or ganglion tumors. Myofascial pain syndrome must also be considered in the musculoskeletal differential of CTS. Lastly, neurological issues are the most diverse causes of CTS. Issues range from brachial plexopathy, including Parsonage-Turner and thoracic outlet syndromes, to various infections that could also cause CTS symptoms. Motor neuron diseases, demyelinating diseases, ischemic monomelic neuropathy, and compression neuropathy can affect the radial nerve and cause CTS symptoms. Polyneuropathy and complex regional pain syndrome are more involved diagnoses that can elicit CTS symptoms as well [9]. The wide range of causes for CTS symptoms helps explain the current lack of a single gold standard diagnostic tool [9]. Thus, remembering that CTS is a clinical diagnosis with many causes is paramount to understanding the vast array of causes and subsequent treatments for the relief of symptoms.

Therapeutic Modalities

Treatments for CTS are variable and depend on the severity of the syndrome. Classically, non-deficit CTS has been managed conservatively with immobilization or injections. When non-deficit CTS is resistant to treatment, more aggressive treatment is necessary. Similarly, when CTS presents with a deficit or in a severe acute form, surgical management may be pursued [13].

Conservative Management

Conservative management of CTS is usually considered first-line therapy unless a patient presents with a severe sensory or motor deficit. Conservative management can encompass any or all of the following interventions. First, immobilization of the wrist via a rigid splint is the most common initial therapy and avoids extreme motion by forcing the wrist into a neutral position with the goal of decreasing edema and nerve friction. Less commonly, a softer, more pliable brace is used. The trade-off for more movement is heightened risk of edema and compression. In coordination with these therapies, oral supplements have shown promise in case studies. To further help reduce edema, oral diuretics have marginal efficacy. Vitamin B6 is a coenzyme in neural function and has the potential to help patients with undiagnosed neuropathy. Oral steroids and NSAIDs can help relieve symptoms but not treat the underlying CTS. Lastly, certain physical exercises have been hypothesized to reduce pressure and improve venous return by increasing tendon and median nerve gliding. They

have shown to have marginal therapeutic effect on a patient-by-patient basis and should be considered based on each patient's preference [14].

In a large systematic review, multiple traits were heavily associated with lack of responsiveness to conservative management and called for both the patient and physician to rethink the treatment strategy and consider more aggressive avenues. These included symptom duration, thenar wasting, and a positive Phalen test [15••].

Surgical

In a large systematic review that included over a hundred studies, surgical interventions were compared with conservative management and corticosteroid injections. While corticosteroids usually provided more immediate relief than surgical procedures or conservative interventions, the benefit of injections diminishes over time; surgical relief provides the most effective outcomes in the medium and long term [16]. The procedure involves an incision in the transverse carpal ligament to enlarge the carpal tunnel. The surgery takes approximately 10 min and, with approximately 600,000 completed per year, is considered a common procedure in the field of surgery [17]. Previously, the surgery was performed completely open, but it is now carried out using either a mini-open or endoscopic approach. The mini-open technique cuts the roof of the carpal tunnel while the endoscopic technique is camera driven and increases the size of the tunnel internally. Given the technical simplicity of the procedure, efforts to reduce costs have begun to transfer the surgery out of the operating room and into a procedure room with field sterility. Studies have shown that this transfer is associated with a massive reduction in cost without compromising infection rates, patient satisfaction scores, or postoperative pain control [17].

The procedure to release compression carries with it an inherent risk and potential for complications. The carpal tunnel itself contains four FDP tendons and four FDS tendons as well as the FPL tendon and the median nerve. Damage of any of these components during surgery can lead to motor or sensory deficits [18]. Injury to the median nerve, the most superficial and most damaged structure in the carpal tunnel, can occur when the incision is made in the transverse carpal ligament. Other surrounding structures such as the thenar branch, common digital nerves, and ulnar nerve are rarely damaged but can also lead to motor and sensory deficits [18]. Further, if the surrounding vessels such as the ulnar artery and the superficial palmar arch are nicked, the field will pool with blood. These vessels must be repaired to prevent ischemic injury [18]. Postoperatively, issues include infection of the incision site, pain, and tendon issues as well as weakness under pressure or during grasping motions. Most of these complications are associated with scar tissue and resolve spontaneously within a few months [18].

While many patients feel immediate relief, the symptoms of some patients can persist. Failure of initial carpal tunnel release is between 7 and 25%; complications are bad enough that 5 to 12% of patients require further revision surgery [18]. These revisions may be necessary due to incomplete release, the need for further compression, or incorrect diagnosis [18]. In patients who have persistent systems, corticosteroids can be injected to provide short-term relief. Response to these corticosteroids is also a good predictor of whether or not subsequent surgery would provide any utility [19].

Minimally Invasive Procedure

Endoscopic Release

Endoscopic compression release originated in 1989. Multiple endoscopic approaches for the treatment of CTS have been put forth since then but over time, the approach named after Agee et al. has been shown to be associated with the most favorable outcomes. A single incision is made 0.5–1.0 cm proximal to the wrist flexion crease that follows the deep surface of flexor retinaculum to the distal fat pad. Sectioning of the flexor retinaculum is begun distally [13]. The risk of damage to surrounding neurovascular bundles is less than 1%, and the procedure is performed in coordination with a radiologist as an ultrasound-guided release [20]. Unfortunately, confirmation of a successful surgery is not possible via the palmar carpal ligament because it is not under pressure and therefore does not spring apart after the release is complete [20]. A systematic review found that endoscopic release is similarly safe to an open procedure, carrying no greater risks while also being associated with less time off of work and removal from daily activities [21]. The same group showed in a subsequent systematic review of over 2500 procedures that endoscopic release was as effective at relieving symptoms and completely or partially restoring functional status as the open technique [22].

Injection Therapy

Corticosteroid Corticosteroid injection relies on the anti-inflammatory effects of steroids to help relieve symptoms of carpal tunnel syndrome. Corticosteroid injections have been shown to have similar Boston Carpal Tunnel Questionnaire (BCTQ) score reductions when compared with splinting. The injections are also associated with higher subjective patient satisfaction scores and decreased quantities of administered painkillers than the splinting group [23]. Further, when comparing a combination of the two conservative treatments against injections alone, the individuals randomized into the combination group showed even greater improvements as determined by the BCTQ as well as improved nerve function and reduction of symptoms [24•]. Usually, combined with a

local anesthetic, the injection target is the flexor crest of the wrist on the ulnar side of the palmar tendon [14]. In recent years and with the improvement of ultrasound, instead of using anatomical landmarks, it has been shown that using ultrasound-guided injection leads to significant symptom reduction 1 month postoperatively [25].

Platelet-Rich Plasma Alternatively, platelet-rich plasma (PRP) injections contain concentrated platelets and several growth factors that can help alleviate symptoms. The mechanisms include growth, angiogenesis, and axon regeneration that could promote median nerve regeneration. PRP has shown efficacy in a range of applications from dentistry to orthopedics and from neurosurgery to cosmetics [26]. A systematic review of five studies that included three RCTs, one case-control, and one case report suggest that PRP injections improved symptoms of patients who had mild CTS [27]. This improvement was measured using the BCTQ and significant reductions were observed in multiple studies of symptom severity [27]. However, this finding was not unanimous and, in some cases, did not provide an increased benefit when added to a treatment plan that included a conservative wrist splint [28••]. Given the dearth of currently published literature on this topic, there is opportunity for further study of PRP injections for the treatment of CTS.

Alternative Therapy

Laser Therapy

The goal of low-level laser therapy is to transfer energy through a beam to reduce inflammatory response in a target tissue. By the induction of the production of endorphins, serotonin, and other mediators, the goal is to reduce edema and even promote axonal regeneration [14]. A meta-analysis was performed using data from seven clinical trials with 270 wrists in the treatment group and 261 wrists in the control group. Statistically significant improvements were found in the low-level laser treatment group for hand grip, visual analog scale, and sensory nerve action potential 3 months post treatment of mild CTS [29]. Unfortunately, no statistically significant differences were found in other clinical parameters or nerve conduction studies, and, when pooling the data, the laser variables (i.e., power, frequency, and wavelength) were not always exactly consistent [29]. Although this meta-analysis produced some promising results, a further randomized controlled trial under consistent parameters must be carried out to make definitive conclusions.

Shock Wave Therapy

Extracorporeal shock wave therapy is a relatively new treatment that has been used since the turn of the century for inflammatory musculoskeletal disorders and peripheral neuropathies. The mini-shock waves induce axonal regeneration through various pathways and have also showed efficacy in reducing chronic neuropathic pain [30]. The waves themselves can be administered in a focused or radial pattern. Radial waves have the advantage of dispersing throughout an entire area, albeit at lesser magnitude; meaning they do not require exact localization of entrapment. In initial studies, radial shock wave therapy was administered to no significant effect in comparison with the control group that was just administered a splint [30].

Since it was hypothesized that shock wave therapy would be dose-dependent, further study tested multiple dosages of shock waves. The study was set up for patients to be randomized to receive three treatments, one treatment, or no treatments. The group that received three treatments over 14 weeks showed significant reduction in their BCTQ score with patients that had moderate CTS showing a greater absolute reduction than those with mild CTS [31]. In summary, multiple shock wave sessions were required to produce a significant result in comparison with the placebo or single-session groups, indicating that the effects of shock waves most likely have a cumulative nature [31].

Conclusion

CTS, first described in 1863 by Sir James Paget, is the most commonly diagnosed compression entrapment peripheral neuropathy in the USA [7]. The condition typically presents with primary symptoms of pain, numbness, and paresthesia in the first 3.5 fingers, but may be associated with complications that develop over time, including weakness of the hand, decreased fine motor skills, clumsiness, and visible thenar atrophy. In its most basic form, the mechanism for CTS, though not fully understood, involves buildup of pressure in the carpal tunnel due to edema and fibrosis of the SSCT with subsequent compression of the median nerve. Recent studies have shown that growth factors such as TGF-β and VEGF may be implicated in the progressive fibrosis of the SSCT and may serve as viable therapeutic targets. Most cases of CTS are idiopathic, but risk factors are thought to include age and pregnancy as well as conditions such as diabetes, hypothyroidism, and arthritis. The direct mechanisms by which these risk factors predispose patients to CTS are currently unknown.

CTS has traditionally been diagnosed through the combination of clinical history and physical exam maneuvers such as Tinel's test and Phalen's test, but the advent of new technology has led to controversy surrounding the gold standard for diagnosis. Some camps believe that the variable sensitivities and specificities of provocative maneuvers make them unreliable and that techniques such as EDX, ultrasound, or a

combination of the two should be favored for their ability to look more directly at underlying pathophysiology. Like diagnostic methods, treatments for CTS are variable and depend on the severity of the syndrome and preferences of the patient and the physician. Conservative treatment is usually considered first-line therapy for patients who present with non-deficit CTS, but treatment is generally escalated to surgical intervention when a patient presents with or progresses to severe sensory or motor deficits. Given the unknown and potentially complex etiology of CTS, future studies should continue to explore combinations of existing and potentially new diagnostic techniques to determine a universally accepted gold standard for diagnosis.

Compliance with Ethical Standards

Conflict of Interest Ivan Urits, Kyle Gress, Karina Charipova, Vwaire Orhurhu, and Omar Viswanath declare no conflict of interest. Alan D. Kaye discloses that he is on the Speakers Bureau for Depomed, Inc., and Merck.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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