Review

Jorge Menéndez-Cámara, David Cecilia-López, Lorena García-Lamas, Celia Castillo-Fernández, Luis Matesanz-García* and Josué Fernández-Carnero

Misdiagnosis in carpal tunnel syndrome: amyloidosis and other red flags. A narrative review

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Abstract

Introduction: Carpal tunnel syndrome (CTS) involves the entrapment of the median nerve at the wrist. Despite acceptable sensitivity and specificity in diagnostics tests, errors persist, leading to unsuccessful treatments, especially when CTS is an early sign of other conditions.

Content: This review aims to identify red flags that may manifest as CTS or coexist with it, and to describe their clinical presentations.

Summary: A PubMed search (2000–2025) yielded 622 articles, with 24 included in the review. Of these, 12 articles explored CTS and amyloidosis, three with neurological pathologies, three with tumours, two with rheumatic diseases, one with Raynaud's disease, one on CTS in children, and two with other conditions.

Outlook: Many conditions can be mistaken for CTS. Given its high prevalence, healthcare professionals must distinguish these to reduce surgical failures and improve early detection of conditions like cardiac amyloidosis or multiple sclerosis.

Keywords: carpal tunnel syndrome; red flags; diagnosis; clinical reasoning; amyloidosis

***Corresponding author: Luis Matesanz-García**, Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, 28922, Alcorcón, Spain; Cognitive Neuroscience, Pain and Rehabilitation Research Group (NECODOR), Faculty of Health Sciences, Universidad Rey Juan Carlos, Madrid, Spain; CranioSPain Research Group. Centro Superior de Estudios Universitarios La Salle, 28023, Alcorcón, Spain; and Department of Physiotherapy, Centro Superior de Estudios Universitarios La Salle, Universidad Autónoma de Madrid, Madrid, Spain, E-mail: luis.matesanzgarcia@gmail.com. https://orcid.org/0000-0001-5148-6336

Jorge Menéndez-Cámara, Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, Alcorcón, Spain; Cognitive Neuroscience, Pain and Rehabilitation Research Group (NECODOR), Faculty of Health Sciences, Universidad Rey Juan Carlos, Madrid, Spain; and Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Escuela Internacional de Doctorado, Universidad Rey Juan Carlos, Alcorcón, Spain,
E-mail: jorge.menendez@urjc.es

David Cecilia-López, Unit of Elbow-Hand, Service of Traumatology and Orthopedics, Hospital 12 de Octubre, Madrid, Spain; Complutense University of Madrid, Madrid, Spain; Department of Surgery, Hospital Vithas La Milagrosa, Madrid, Spain; and Hospital Viamed Santa Elena, Madrid, Spain, E-mail: dacecilia@hotmail.com

Lorena García-Lamas and Celia Castillo-Fernández, Unit of Elbow-Hand, Service of Traumatology and Orthopedics, Hospital 12 de Octubre, Madrid, Spain

Josué Fernández-Carnero, Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, Alcorcón, Spain; Cognitive Neuroscience, Pain and Rehabilitation Research Group (NECODOR), Faculty of Health Sciences, Universidad Rey Juan Carlos, Madrid, Spain; La Paz Hospital Institute for Health Research, IdiPAZ, Madrid, Spain; and Musculoskeletal Pain and Motor Control Research Group, Faculty of Sport Sciences, Universidad Europea de Madrid, Villaviciosa de Odón, Spain, E-mail: josue.fernandez@urjc.es

Introduction

Carpal tunnel syndrome (CTS) is defined as the compromise of the median nerve as it passes through the wrist, causing symptoms such as paraesthesia, dysesthesia, numbness, and weakness of thenar muscles [1]. Additionally, many cases may present with neuropathic pain [2]. CTS is the most common entrapment neuropathy, affecting up to 1 in 10 people at some point in their lives [1] with a prevalence of around 4 % [3, 4]. It affects more women than men, mainly starting at the fourth decade of life and over 75 years of age, although the general prevalence values can increase up to 84 % in the diabetic population [5–9].

The clinical and economic burden of CTS is significant. According to a retrospective cohort study carried out in Atlanta, the preoperative costs can exceed $800 per patient [10]. Surgery, on the other hand, costs between $2,000–8,000 per patient according to data collected in New York, and over 2000 euros in Europe [11–13]. These figures gain relevance if we take into account that 600,000 surgeries are performed

annually in the USA [14], and that these patients experience more missed days from work than aged and gender-matched population [15].

Given its prevalence, it is easy to assume that those patients presenting for consultation with signs and symptoms in the wrist and hand region compatible with CTS do indeed have CTS. In many cases this will be true, but in another percentage of patients we would be incurring in a diagnostic error derived from a confirmation bias, applying in the best case a treatment with little or no effect on the patient, and in the worst case avoiding a red flag [16]. In these cases, the symptoms may be due to pathologies without nerve involvement or where the nerve is affected but the aetiology is other than compression (CTS of atypical presentation) [17, 18]. In the latter case, surgery for CTS may relieve the symptoms but only temporarily, thus postponing a correct diagnosis [18].

Why clinical presentation matters

Diagnostic errors can cause up to 10 % of adverse events in hospital practices [19] and are associated with greater morbidity than other types of medical errors [20]. Among the causes of a diagnostic error are cognitive errors, derived from a poor anamnesis, lack of knowledge of the professional or a poor clinical reasoning process [21].

Currently there is no gold standard for CTS diagnosis [22] so its prevalence can fluctuate between 3.8 and 2.7 % depending on whether it is confirmed by orthopaedic or neurophysiological tests [5]. Although clinical presentation, orthopaedic test and nerve conduction studies (NCS) have acceptable values of sensitivity and specificity [23–25], diagnostic errors persist. Consequently, it has been reported that some patients undergo unsuccessful decompression surgeries, particularly when CTS serves as an early manifestation of an underlying conditions rather than being of idiopathic nature [26–28].

Red flags are not always easy to detect in patients with diagnosis of CTS. Sometimes they may manifest as a CTS with an unusual clinical presentation, but at times they become apparent only years after the initial diagnosis, thus making our diagnosis challenging [29, 30]. Therefore, it is crucial for professionals to conduct a thorough anamnesis and have a strong understanding of semiology to integrate all the data gathered from the assessment into different clinical hypotheses [31].

Clinical presentation of carpal tunnel syndrome

Symptoms have a progressive onset with sensations of numbness, intermittent paraesthesia or dysesthesias, mainly in the first three fingers. These sensations are predominantly nocturnal and may be associated with sustained positions but resolve rapidly with movements of the hand (Flick's sign). Gradually, the symptoms may progress to more continuous paraesthesia's or dysesthesias, pain, especially nocturnal pain, and loss of strength of the abductor pollicis brevis of the thumb, potentially leading to thenar atrophy in more severe cases [1, 22, 32, 33].

The main symptoms are those associated with negative signs resulting from involvement of small and large fibres [34]. Patients describe it as numbness, tingling, cramping in the first three fingers, mainly the thumb, loss of grip strength or difficulty in grasping objects. Negative signs follow the innervation pattern, so loss of sensation in the thenar eminence is unusual as it is innervated by the palmar cutaneous branch of the median nerve, which originates proximal to the carpal tunnel [35].

Most of the CTS patients report pain of mild intensity, varying between 1.2 and 5.6 out of 10 on the VAS scale [36], Besides, it isn´t always of neuropathic origin. According to neuropathic pain questionnaires such as the DN4 or NPSI, about 80 % of patients present pain with neuropathic characteristics, but approximately 20 % have nociceptive pain [2, 36, 37].

Pain is not limited to the median innervation area; about 40 % of patients present extraterritorial symptoms [2, 37, 38]. While this has been correlated with greater neurophysiological compromise, quantitative sensory test (QST) measurements suggest that extraterritorial symptoms are better explained by central or inflammatory mechanisms than from nerve involvement itself. [39, 40]. Figure 1.

Regarding orthopaedic tests, the most prominent are provocation tests such as Phalen's test, Tinel's sign, Carpal Compression Test, and Hand Elevation Test, and tests related to sensory measures such as Semmes-Weinstein monofilaments and two-point discrimination [23, 24, 41]. Other tests described include Durkan's test, reversed Phalen test and scratch-collapse test [3]. It should be noted that their sensitivity, specificity, and likelihood ratios values vary between studies and depending on whether they are compared with healthy individuals or patients with negative electromyography [33].

As for nerve conduction studies, although their utility has been questioned [42], a recent review article by Jeremy Bland highlighted their importance as they can provide objective values related to the severity and progression of the pathology, and because they are useful in the clinical reasoning process to help rule out or confirm other clinical conditions [43]. It is suspected that up to 7 % of nerve

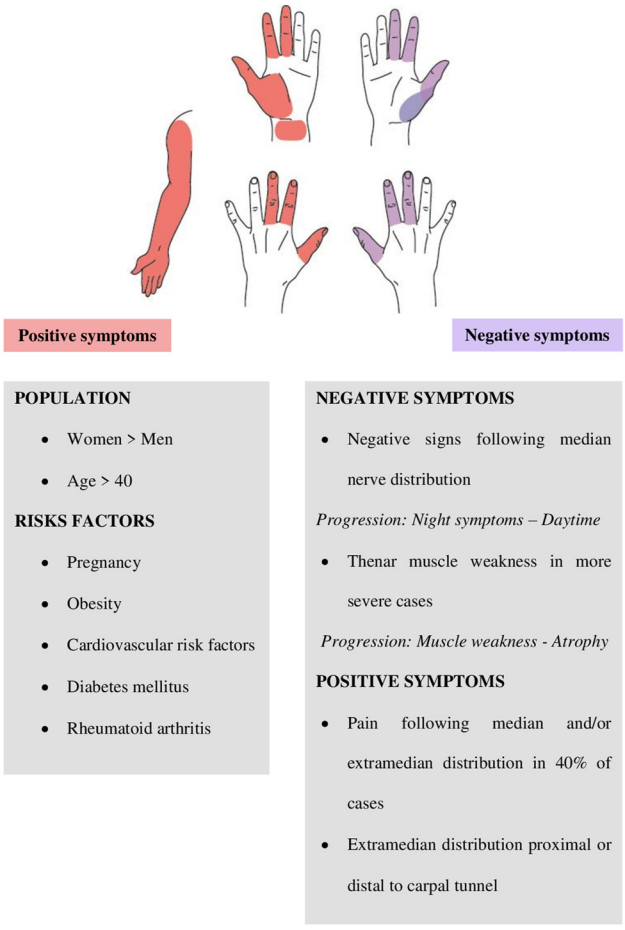

Figure 1: Carpal tunnel syndrome classical clinical presentation, both negative and positive symptoms.

conduction studies conducted in patients with suspected CTS show an alternative diagnosis [44].

When performing a differential diagnosis in a patient with carpal tunnel syndrome (CTS), most clinical conditions to rule out are related to musculoskeletal pathology such as cervical radiculopathy, entrapment neuropathies of the median nerve in mechanical interfaces at the elbow like Struthers' ligament, lacertus fibrosus or pronator teres syndrome, trapeziometacarpal osteoarthritis or de Quervain's tenosynovitis. However, physiotherapists and physicians should consider various red flags, most of which are of rheumatological or neurological nature [27].

Objectives

The aim of this narrative review is to gather information about those red flags that may manifest as a CTS with an unusual clinical presentation or coexist with CTS, and to describe the clinical presentation of each one of them so that physical therapists and other professionals can correctly refer to the appropriate healthcare professional when needed.

Materials and methods

A literature search was performed in PubMed database using the search terms ("Carpal tunnel syndrome" [Mesh] OR "Carpal tunnel" OR "median nerve" OR "median nerve entrapment" OR "entrapment neuropathy" OR "entrapment neuropathies") AND ("red flag" OR "differential diagnosis" OR "misdiagnosis" OR "clinical reasoning").

The search was filtered for articles published between 2000 and 2025, yielding a total of 622 articles, of which 517 were excluded in a first reading by title and abstract, excluding articles that did not discuss carpal tunnel syndrome or its red flags. Of the remaining 105 articles, 74 were excluded because they were case reports, 6 because they did not address diagnosis or red flags in CTS, and 1 was a book chapter. A total of 24 articles were included for the review (Flow chart is shown in Figure 2).

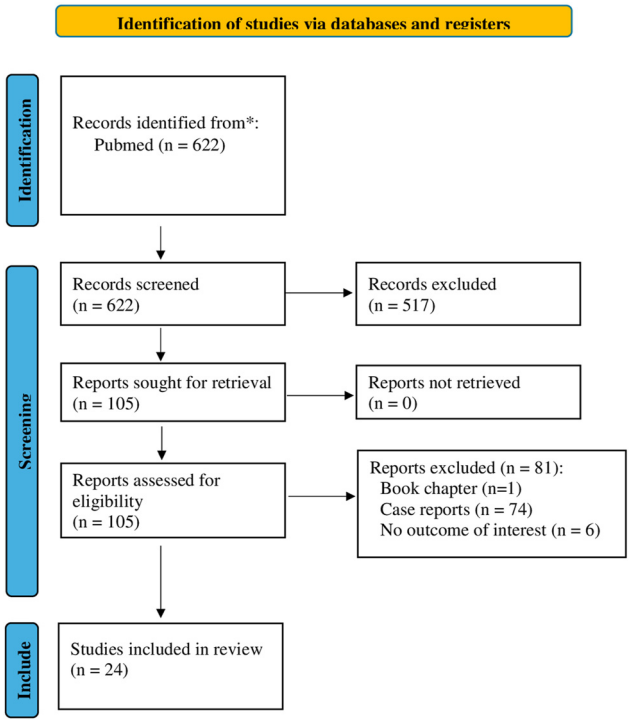

Figure 2: PRISMA flow diagram of study identification, screeing, eligibility assessment, and inclusion.

Differential diagnosis of red flags

Of the 24 articles included, 12 explore the relationship of CTS with amyloidosis [26, 45–55], three with neurological pathologies [18, 27, 56], three with tumours [57–59], two with rheumatic pathology [60, 61], one with Raynaud's disease [62], one about CTS in children [63] and two with various pathologies [16, 29] (Supplementary material Table 1).

Therefore, the sections that we are going to discuss are the following:

– Amyloidosis:

As highlighted by the journal *The Journal of Bone & Joint Surgery* in its latest editorial 'What's New in Hand Surgery', amyloidosis is the main red flag to consider in patients with carpal tunnel syndrome [64]. The diagnosis of amyloidosis encompasses a heterogeneous group of diseases characterized by abnormal deposits of amyloid protein in various tissues, forming fibrous bands that can eventually affect organ function. It can be hereditary, nonhereditary, localized or systemic, and the different types of amyloidosis can present different organ involvement and prognosis [65].

CTS is more prevalent in cases of cardiac amyloidosis, whether by transthyretin (ATTR), both hereditary and wild type (ATTRv or ATTRwt), or by light chain amyloidosis (AL). On one hand, the risk of amyloidosis has been estimated to be threefold higher in patients with CTS compared to general population [66]. In a retrospective review of 185 patients undergoing carpal tunnel release surgery, 29 % had amyloidosis, and of these, 80 % had the TTR type [26]. The prevalence of ATTR in CTS population varies between studies, ranging from 8.5 to 18.5 %, and can reach up to 33 % if the sample has bilateral CTS [48, 52, 54]. On the other hand, in patients diagnosed with ATTR the incidence of CTS reaches 20 % compared to 4 % in the general population [67], with some studies raising the number up to 46 % [68].

One difficulty for patients with amyloidosis is the delay in diagnosis as non-cardiac manifestations such as CTS precede the diagnosis by years. AL may present a diagnostic delay of 2 years [69], and this delay increases to 5 or 6 years in ATTR [30, 70]. This means that during this time they receive inadequate treatments, therefore worsening their prognosis [45].

Furthermore, CTS is just one of the symptoms, so recognising other possible manifestations can be useful for correct differential diagnosis. Common clinical manifestations in ATTR include cardiac manifestations (heart failure, arrhythmias, pacemakers…), neurological manifestations (CIDP, toxic neuropathy, alcoholic neuropathy, vascular neuropathy), and musculoskeletal manifestations (CTS, rotator cuff tear, long head of biceps tendon rupture, spinal stenosis, and trigger finger) [46], with CTS being the most common non-cardiac manifestation, present in 20–60 % of cases [30, 47, 49, 70]. However, it is important to bear in mind that the CTS that these patients present with, even if it manifests itself years before the actual diagnosis, is real, and therefore surgery in these cases can alleviate the symptoms.

Clinical manifestations that may raise suspicion of amyloidosis are male gender, age >50 years in men or >60 in women, bilateral CTS, trigger finger, biceps tendon rupture, lumbar stenosis, rotator cuff involvement, failure of carpal tunnel release surgery, hearing impairment, and cardiac involvement [46, 47, 49–54, 69]. Nevertheless, ATTRv has been associated with an increased odds ratio of these clinical manifestations only in population over 60 years [55].

Prospective studies evaluating the sensitivity and specificity of these characteristics to detect amyloidosis in patients with CTS are still lacking [47]. However, implementing a screening program with these variables could reduce the number of surgery failures and reduce the diagnostic delay, thus improving the prognosis of patients [45].

– Neurologic pathologies:

– Multiple sclerosis:

  Multiple sclerosis (MS) is a demyelinating autoimmune disease that affects the central nervous system, both motor and sensory pathways [71]. Diagnostic error is still common and there is still no gold standard test or pathognomonic sign, so the diagnosis is based on clinical, imaging and laboratory tests [72, 73].

  Around 85–90 % of patients present with disease progression characterized by remissions and relapses (RRMS), i.e. a period of neurological dysfunction followed by periods of remission of symptoms, while 10–15 % present with an eminently progressive clinical picture (PPMS). The intermittent phenotype affects three times more young women than men, starting around the age of 30 [74]; however, the more progressive phenotype usually begins in the fourth decade without sex distinction and can be more easily masked with CTS [75].

  In terms of symptomatology, MS as a systemic disease presents symptoms in more than one region and eminently of a demyelinating nature. Common neurological symptoms are visual involvement (neuritis, double vision, nystagmus), trigeminal neuralgia or signs of partial myelopathy such as asymmetric limb weakness or positive Lhermitte's sign [71]. If the patient presents with negative signs in the hand such as loss of strength and/or sensibility, it is important to consider that compressive neuropathies have a progressive increase in symptomatology, and they do not usually

show an intermittent progression. Furthermore, in CTS negative signs such as loss of strength or atrophy don't manifest as the first symptoms as these imply a more advanced stage. Finally, symptoms onset usually does not begin before the fourth decade of life except for CTS due to pregnancy.

However, there are no reliable data on how many patients with MS have a coexisting CTS, or in how many of them MS has been misdiagnosed in the early stages as CTS. Given these data, and taking into account the demyelinating nature of the disease, surgery would only be indicated in those cases where it has been demonstrated that CTS is present and coexists with MS.

– Amyotrophic lateral sclerosis:

Amyotrophic lateral sclerosis (ALS) is an idiopathic neurodegenerative disease primarily affecting motor pathways, but it can progress to cognitive symptoms such as dementia and emotional lability. There are several phenotypes within ALS, each with a distinct symptomatology onset. The most common presentation (70 %) begins with limb symptoms indicative of both upper and lower motor neuron injury, although it can also begin with bulbar involvement (25 %) where initial symptoms include speech and swallowing difficulties [76].

Medical evaluation and nerve conduction studies are essential for diagnosis [76], although there are clinical indications that can make us suspect progressive motor involvement and the presence of signs of upper motor neuron lesions such as hyperreflexia, pathological reflexes such as Babinski, spasticity or altered coordination of movement, and lower motor neuron signs such as weakness or atrophy [77].

While the incidence of ALS in Europe is not very high, 2–16 individuals per 100,000 population [76], a recent study surveying members of the American Association for Hand Surgery concluded that 11 % of surgeons had performed nerve decompression surgeries on patients later diagnosed with ALS [18]. Another study reviewed the medical records of 33 ALS patients and found that 43 % were initially misdiagnosed, and orthopaedic surgeons were among the specialists these patients initially sought out with their symptoms [78]. Lastly, another retrospective study concluded that out of 260 patients, 34 had undergone surgical interventions for conditions that later proved to be initial symptoms of ALS, including five surgeries for carpal tunnel syndrome (CTS) [28]. As with MS, we do not have reliable data on how many patients have ALS coexisting with CTS. However, these data may indicate that in these patients, surgery would not be indicated, as the cause of their symptoms is not due to nerve entrapment. Besides, subjecting patients to surgery could delay an accurate diagnosis.

Key points for differential diagnosis include assessing signs compatible with upper motor neuron involvement as they are not typical of peripheral neuropathy. It is also uncommon for ALS patients to have sensory symptoms common in CTS such as paraesthesia's, but they will exhibit other symptoms such as weakness, atrophy, and fasciculations. Finally, multifocal involvement and the presence of bulbar symptoms (speech impairment or lingual atrophy) should also be considered [79].

– Other neurological pathologies:

Two reviewed articles emphasized the importance of neurological diseases in the differential diagnosis of upper limb entrapment neuropathies.

One reported 12 cases of patients initially diagnosed with CTS later identified as neurological pathologies. Among the pathologies there were four cases of upper motor neuron disease, two cases of multiple sclerosis, two cases of cervical pathology and peripheral neuropathy, one case of syringomyelia and another unresolved case. The authors concluded that misdiagnosis is often associated with atypical clinical or electrodiagnostic features and that surgery may not be beneficial when CTS coexists with another neurological disorder that is the main cause of hand symptoms [27].

The other included study is a narrative review of less common different neurological conditions such as Charcot-Marie-Tooth disease, multifocal motor neuropathy, or hereditary neuropathy with pressure paralysis. This review emphasizes the importance of thorough history taking and physical examination, mainly based on the location and progression of symptoms, to reach a correct diagnosis before subjecting patients to surgery [56].

– Polyneuropathy:

While our literature search, due to the search terms used, did not yield specific articles discussing the relationship between CTS and polyneuropathies, given the high prevalence of conditions like diabetic neuropathy, we have decided to include polyneuropathies among the possible differential diagnoses.

Polyneuropathies encompass a wide range of clinical entities with different aetiologies and clinical presentations. Common aetiologies include diabetic neuropathy, viral-associated neuropathies (SARS-CoV-2), toxic-induced neuropathies (chemotherapy-induced neuropathy), and autoimmune conditions such as chronic or acute inflammatory demyelinating polyneuropathy (Guillain–Barré) [80–83].

CTS may manifest as an initial phase of a polyneuropathy [43], so the patient may not report symptoms in other areas, thus complicating the diagnosis, or it may manifest in combination with symptoms in other regions, like the "glove and stocking" distribution typical of polyneuropathy, thereby facilitating evaluation [84]. However, we should keep in mind that carpal tunnel syndrome can coexist with polyneuropathy (mainly in diabetic patients) and that not all bilateral CTS cases indicate polyneuropathy. Some studies report that up to 87 % of CTS patients present bilateral symptoms, the risk increases as the disease progresses [85, 86], and this can be influenced by genetic [87], mechanical factors [33], or be a "double crush syndrome". In these cases, surgery would be indicated.

Therefore, in cases of bilateral CTS, a comprehensive evaluation in collaboration with other professionals is necessary. For unilateral symptoms, we should delve into the medical history regarding diabetes, infections, cancer treatments, and alcohol consumption.

Focusing on *diabetic neuropathy*, it is defined as the presence of signs and symptoms related to peripheral nerve dysfunction in diabetic patients after ruling out other aetiologies. The symptoms presented resemble those of CTS, with tingling, numbness, pain, and weakness. However, these symptoms usually start in the lower limbs and subsequently extend to the upper limbs, resulting in the characteristic "glove and stocking" distribution [88, 89].

Half of diabetic patients will develop neuropathy, and 50 % of them will be asymptomatic [90], so it would be advisable to perform a somatosensory examination including the lower limbs to rule out polyneuropathy [91]. Additionally, it should be noted that the vast majority of patients with diabetic neuropathy do not have an official diagnosis, so the medical history may not be sufficient to rule it out [92].

The differential diagnosis in these cases is further complicated by the fact that diabetes is considered a risk factor for CTS [33]. That is, we may encounter a diabetic patient with a genuine CTS, diagnosed clinically and by electrodiagnostic tests, without associated polyneuropathy. In the case of a patient with genuine CTS with associated polyneuropathy or a patient with polyneuropathy but without CTS, the onset and distribution of symptoms will help in diagnosis.

Regarding the possible coexistence or not of these clinical conditions, it is estimated that around 10–20 % of patients with CTS have diabetes [93, 94]. On the other hand, in patients with a previous diagnosis of diabetic polyneuropathy, the incidence of CTS ranges from 5 to 15 %, depending on gender and type of diabetes [95].

Another polyneuropathy to consider is *small fibre neuropathy* (SFN). This term encompasses neuropathies with predominant involvement of Aδ and C fibres, so other pathologies such as diabetic or amyloid neuropathies (which may progress to large or mixed fibre neuropathies) are included within it [96, 97]. It is estimated to have a prevalence of 53 cases per 100,000 [98].

SFN has a heterogeneous clinical presentation, which may manifest as polyneuropathy or focal mononeuropathy. However, the most common presentation is polyneuropathy with a glove and stocking distribution, similar to diabetic neuropathy, followed by ganglionopathy [99, 100]. SFN can be excluded if the patient has signs or symptoms consistent with large fibre involvement such as impaired vibration detection or positive electrodiagnostic studies [97]. Therefore, a thorough sensory evaluation of the patient, both at the hand and distal levels, can guide us toward a correct diagnosis.

– Inflammatory arthropathy:

Inflammatory arthropathies are a group of autoimmune conditions among which we can find some common ones like rheumatoid arthritis [101].

In the review by Muramatsu et al. [60], they studied the relationship between rheumatoid arthritis (RA) and the presence of upper limb neuropathies. CTS was the most prevalent neuropathy in their department, with RA present in 1 out of 10 CTS surgeries. The authors highlight that orthopaedic testing may be limited due to RA-associated symptoms such as loss of range of motion, and they conclude that in some cases, CTS-like symptoms may improve with antirheumatic treatment without the need for surgical intervention, so assessing the presence of RA in patients with CTS may be relevant for their management.

The other article extracted from the literature search analyses the relationship between chondrocalcinosis and CTS [61]. Chondrocalcinosis, or Calcium Pyrophosphate Dihydrate Deposition Disease (CPDD), is an arthropathy associated with calcium deposits and can affect the wrist. In this retrospective study, the authors report that CTS was the initial presentation in 14 % of cases; however, radiological findings varied, so surgical treatment is not always CTS surgery as arthrodesis surgeries were necessary in some cases.

Generally, in cases of inflammatory arthropathies, the main symptom is usually pain, especially polyarticular pain. It should be noted that autoimmune diseases such as rheumatological conditions may be present even when dealing with a true case of CTS, and these should be considered as a risk factor to inform about prognosis [33]. In an observational study conducted by Agarwal et al. [102] they assessed

the presence of neuropathies in patients with rheumatoid arthritis and reported that CTS was present in 10 % of patients. Additionally, 20 % complained of paraesthesia's, even though one in three did not have neuropathy.

Therefore, like patients with diabetes, we may encounter CTS with inflammatory arthropathy, or we may have to differentiate between them, although in this case, it will be easier.

- Other red flags:
- Raynaud's phenomenon:
  Raynaud's phenomenon is a pathology that affects micro-vascularization mainly in the fingers and toes. Whether primary or secondary in origin, it is characterized mainly by changes in finger coloration resulting from small vessel involvement. The main symptoms are sensitivity or pain to cold, changes in coloration during the vasospastic episode, and may be accompanied by tingling and functional impairment [103]. In the evaluation, the professional should assess the coloration of the fingers, as well as possible alterations in peripheral pulse [17, 104].
  A recent narrative review analysed the relationship between this phenomenon and carpal tunnel syndrome (CTS), concluding that there appears to be a relationship between these two clinical conditions, although it is not yet possible to establish a causal or temporal link between them. The prevalence of Raynaud"s phenomenon is higher among patients with CTS than in controls, although is still low (<1 %) [105], and the incidence of CTS in patients previously diagnosed with Raynaud's phenomenon is <5 % [106]. This association is further evidenced by the fact that in some cases, CTS surgery seems to help reduce Raynaud's symptoms [62].
- Tumours:
  In the literature search, two observational studies [57, 59], one review [58], and more than 30 case reports that analysed the relationship between different types of tumours and the diagnosis of CTS were found.
  Tumours affecting the peripheral nerve are uncommon, mostly benign, and extraneural. A recent narrative review on this topic found that congenital fibrolipomatous hamartoma was the most common tumour followed by schwannoma, but there is a wide variety of histopathology in these conditions [107, 108]. In most cases, surgery is the main therapeutic option.
  There is still not enough literature to establish an epidemiological profile with clear symptoms; however, among the reviewed cases, there seems to be no distinction in prevalence between men and women, and the age of presentation is around 30 years, below the typical age of CTS presentation. Among the most common clinical findings are the presence of a palpable soft mass, enlargement of the volar forearm, wrist, or hand, and paraesthesia's [58, 59].
- Paediatric CTS:
  Unlike the usual sociodemographic profile, cases of CTS in paediatric populations have also been reported. This population group is not common, and these cases are usually due to red flags such as congenital anomalies, susceptibility to hereditary pressure paralysis, mucopolysaccharidosis, or other low-prevalence neurological diseases [63, 109]. Potulska-Chromik et al. [63] conducted a retrospective study of 11 cases of CTS in children and determined that in six of them, it was due to a congenital anomaly, two due to mucopolysaccharidosis, and the rest due to various causes. They also determined that the most common symptoms, unlike the usual clinical presentation, were clumsiness in the hand and hypoplasia of the thenar eminence, above sensory disturbances. Therefore, in a case of paediatric CTS, it will always be advisable to refer.
- Space-occupying lesions:

In their observational study, Onen et al. [29] analysed the importance of magnetic resonance imaging in cases with unusual clinical presentations. They studied 55 cases with suspected CTS and found 71 pathologies, most related to space-occupying lesions such as bone or ganglion cysts. In their conclusions, they highlight that most cases of CTS can be diagnosed clinically and electromyographically, but imaging tests may be necessary in cases with doubtful clinical presentation such as young age, male sex, recurrent and unilateral symptoms, and lack of predisposing factors. They also argue that pathologies causing nerve damage to influence the type of surgery indicated, so a correct diagnosis can reduce the percentage of surgical failures.

Nevertheless, despite clinical presentation, while performing surgery it's recommended to routinely check the carpal tunnel to rule out any space-occupying lesions.

Conclusions and clinical implications

There are numerous red flags that can be mistaken for carpal tunnel syndrome. In most cases patients will have a genuine CTS, however, given CTS's high prevalence, healthcare professionals such as physical therapists and physicians should be aware of the differences in the clinical presentations of each of them (summed up in Table 1), with the aim of reducing diagnostic errors, diagnostic delay and selecting

more efficiently which patients require complementary medical tests. This could reduce the number of surgical failures and improve the prognosis of patients diagnosed with cardiac amyloidosis or multiple sclerosis through early detection.

However, there are currently no high-quality prospective studies analysing the effectiveness of a screening algorithm based on clinical presentation to detect these red flags in these patients, so this could be a future line of research.

Table 1: Summary of the red flags to be considered in the differential diagnosis of carpal tunnel syndrome and their clinical presentation. CTS: carpal tunnel syndrome, MRI: magnetic resonance imaging, RA: rheumatoid arthritis, SSCT: subsynovial connective tissue, T1D/T2D: Type 1/Type 2 diabetes.

Red flags	Key findings	Prevalence of CTS	Differences from CTS
Amyloidosis	Male gender>50 Bilateral symptoms of CTS History of: – Trigger finger – Biceps tendon rupture – Lumbar stenosis – Rotator cuff rupture – Hearing impairment – Cardiac symptoms	Patients with CTS – ATTR in ~8.5–18.5 % Patients with amyloidosis (ATTR) – CTS in ~20 % Both can coexist	Based on clinical history – Male>female – Combined with neurological or cardiac manifestations Diagnosis confirmation: – Genetic testing – Biopsy: SSCT
Multiple sclerosis	Remissions and relapses (RRMS) > progressive (PPMS) Symptoms: – Multifocal – Visual: Neuritis, nystagmus, double vision – Partial myelopathy: Sensory symptoms, Lhermitte's symptom, asymmetric limb weakness, incontinence, erectile dysfunction	No reliable data on the prevalence of MS in patients diagnosed with CTS Unlikely to coexist	Based on clinical history: – 30 years>40–75 years – RRMS>progressive – Multifocal: Visual or trigeminal nerves – Early negative signs Diagnosis confirmation: – Clinical history – Laboratory test – MRI
Amyotrophic lateral sclerosis	Multifocal: – Limb-onset 70 % – Bulbar-onset 25 % – Trunk or respiratory onset 5 % Upper motor neuron symptoms – Hyperreflexia, spasticity – Lower motor neuron symptoms – Fasciculations, weakness, wasting Paraesthesia's not common	No reliable data on the prevalence of ALS in patients diagnosed with CTS Unlikely to coexist	Based on clinical history: – Multifocal – Upper motor neuron symptoms – Paraesthesia's not common Diagnosis confirmation: – Clinical history – Nerve conduction studies – MRI
Polyneuropathy	Multifocal – Length-dependent polyneuropathy > non-length-dependent polyneuropathy – Glove and stocking distribution – Autonomic neuropathy Negative and positive signs Can coexist with CTS	Patients with CTS – Diabetes in ~10–20 % – Patients with polyneuropathy – CTS in ~6.8 % males and 13.5 % females with T1D – CTS in ~5 % males and 10 % females with T2D Both can coexist	Based on clinical history: – Multifocal – Feet>hands – Loss of ankle reflexes in diabetic neuropathy Diagnosis confirmation: – Nerve conduction studies – Skin biopsy
Inflammatory arthropathy	Pain>paraesthesia's Multifocal Improvement of symptoms with antirheumatic treatment in some cases Can coexist with CTS	Patients with CTS – RA in ~10 % No reliable data on the incidence of CTS in patients with inflammatory arthropathy Both can coexist	Based on clinical history: – False positive orthopaedic test for CTS – Pain>paraesthesia's Diagnosis confirmation: – Laboratory test – X-ray
Raynaud´s phenomenon	Sensitivity to cold Changes in finger coloration Episodic Multifocal: Thumbs, toes, nose and ears Can coexist with CTS	Patients with CTS – Raynaud´s phenomenon in<1 % Patients with Raynaud´s phenomenon – CTS in<5 % Both can coexist	Based on clinical history: – Digital colour changes – Aggravating factors: Cold – Multifocal Diagnosis confirmation: – Clinical history – Laboratory testing – Nailfold capillaroscopy

Table 1: (continued)

Red flags	Key findings	Prevalence of CTS	Differences from CTS
Tumours	Benign>malignant ~ 30 years Related to soft tissues Paraesthesia's are common	No reliable data on the prevalence of tumours in patients diagnosed with CTS Unlikely to coexist	Based on clinical history: – 30 years>40–75 years – Palpable soft mass – Faster progression of symptoms – Enlargement of volar forearm, wrist or palm Diagnosis confirmation: – MRI
Paediatric population	Clumsiness Hypoplasia of thenar eminence	No reliable data on the prevalence of congenital anomalies in paediatric patients diagnosed with CTS Unlikely to coexist	Always refer for medical screening Diagnosis confirmation: – MRI

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