doi:10.1093/brain/awp050 Brain 2009: 132; 1472–1479 | 1472

BRAIN
A JOURNAL OF NEUROLOGY

Bilateral widespread mechanical pain sensitivity in carpal tunnel syndrome: evidence of central processing in unilateral neuropathy

César Fernández-de-las-Peñas,[1,2,3] Ana Isabel de la Llave-Rincón,[1,2] Josué Fernández-Carnero,[1,2] María Luz Cuadrado,[2,4,5] Lars Arendt-Nielsen[3] and Juan A. Pareja[2,4]

1 Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Madrid, Spain
2 Laboratory of Aesthesiology of Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain
3 Centre for Sensory-Motor Interaction (SMI), Department of Health Science and Technology, Aalborg University, Aalborg, Denmark
4 Department of Neurology of Fundación Hospital Alcorcón and Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain
5 Department of Neurology of Hospital Clínico San Carlos and Universidad Complutense, Madrid, Spain

Correspondence to: César Fernández de las Peñas,
Facultad de Ciencias de la Salud,
Universidad Rey Juan Carlos,
Avenida de Atenas s/n,
28922 Alcorcón, Madrid, Spain
E-mail: cesar.fernandez@urjc.es

The aim of this study was to investigate whether bilateral widespread pressure hypersensitivity exists in patients with unilateral carpal tunnel syndrome. A total of 20 females with carpal tunnel syndrome (aged 22–60 years), and 20 healthy matched females (aged 21–60 years old) were recruited. Pressure pain thresholds were assessed bilaterally over median, ulnar, and radial nerve trunks, the C5–C6 zygapophyseal joint, the carpal tunnel and the tibialis anterior muscle in a blinded design. The results showed that pressure pain threshold levels were significantly decreased bilaterally over the median, ulnar, and radial nerve trunks, the carpal tunnel, the C5–C6 zygapophyseal joint, and the tibialis anterior muscle in patients with unilateral carpal tunnel syndrome as compared to healthy controls (all, $P<0.001$). Pressure pain threshold was negatively correlated to both hand pain intensity and duration of symptoms (all, $P<0.001$). Our findings revealed bilateral widespread pressure hypersensitivity in subjects with carpal tunnel syndrome, which suggest that widespread central sensitization is involved in patients with unilateral carpal tunnel syndrome. The generalized decrease in pressure pain thresholds associated with pain intensity and duration of symptoms supports a role of the peripheral drive to initiate and maintain central sensitization. Nevertheless, both central and peripheral sensitization mechanisms are probably involved at the same time in carpal tunnel syndrome.

Keywords: carpal tunnel syndrome; pressure pain threshold; central sensitization

Introduction

Carpal tunnel syndrome (CTS) is a complex disorder associated with localized compression of the median nerve at the carpal tunnel. It is an important cause of pain, neurologic symptoms and functional limitation of the wrist and hand. It is considered the most common nerve compression disorder of the arm, with reported prevalence rates of 3.8% (95% CI: 3.1–4.6%) for females and 2.7% (95% CI: 2.1–3.4%) for males (Atroshi *et al.*, 1999). A recent study found that the incidence rate of CTS was 1.8/1000 (95% CI: 1.7–2.0) (Bongers *et al.*, 2007). In females the incidence was 2.8 (95% CI: 2.6–3.1) and in males 0.9

Received November 22, 2008. Revised January 31, 2009. Accepted February 3, 2009. Advance Access publication March 31, 2009

(95% CI: 0.8–1.0) showing a female: male ratio of 3:1 (Bongers *et al*., 2007).

Although the aetiology and pathology of CTS is still under debate, there is some evidence involving the whole nociceptive system. Lang *et al*. (1995) suggested that pain intensity in CTS depends on alterations of peripheral and central nervous function. Zannete *et al*. (2006) found that 45% of patients also reported proximal pain, which might be related to central nervous system mechanisms. In addition, the spread of symptoms seen in some patients with CTS could be also related to central processes (Zannete *et al*., 2007). Tecchio *et al*. (2002) and Napadow *et al*. (2006) found cortical remapping in the primary somatosensory cortex S1 in patients with CTS, which was correlated to patients' symptoms, supporting a role of central mechanisms in CTS.

Tucker *et al*. (2007) found bilateral generalized increase in vibration thresholds in patients with CTS which suggests a generalized disturbance of somato-sensory functions rather than the existence of an isolated peripheral neuropathy. Bilateral disturbances of response to vibration stimulus have also been reported in painful musculoskeletal conditions and other unilateral neuropathies reflecting a central nervous system adaptation process to chronic pain (Jensen *et al*., 2002; Greening *et al*., 2003; Laursen *et al*., 2006).

In addition to vibration thresholds, other quantitative sensory tests, e.g. pressure pain thresholds (Chesterton *et al*., 2003; Rolke *et al*., 2005) have been previously used for investigating the nociceptive systems in different chronic pain conditions, e.g. whiplash (Sterling *et al*., 2002), fibromyalgia (Desmeules *et al*., 2003), repetitive strain injury (Greening and Lynn, 1998), chronic tension type headache (Fernández-de-las-Peñas *et al*., 2007), low back pain (O'Neill *et al*., 2007), and osteoarthritis (Bajaj *et al*., 2001). These studies evaluated pressure pain threshold levels in deep tissues, particularly muscles and joints. Furthermore, pressure algometry has been used to investigate pressure sensitivity over nerve trunks in patients with whiplash associated disorders (Sterling *et al*., 2003; Scott *et al*., 2005) or chronic tension type headache (Fernández-de-las-Peñas *et al*., 2008). Generalized sensitization indicated by lower pressure pain threshold levels over median, radial and ulnar trunks was found in patients with whiplash as sign of hyper-excitability of the central nervous system (Sterling *et al*., 2002, 2003). To the best of the authors' knowledge, no published studies have previously investigated pressure pain sensitivity over nerve trunks and the presence of generalized deep tissue pressure hyperalgesia in patients with CTS. The aim of the present study was to investigate whether widespread pressure pain hyperalgesia is a feature of patients with unilateral CTS.

Materials and Methods

Subjects

Consecutive patients diagnosed with CTS, by an experienced neurophysiologist from the Neurology Department of Fundación Hospital Alcorcón were screened for eligibility criteria. The inclusion criteria included both clinical and electrophysiological signs of CTS (Chan *et al*., 2007). The patients should present with pain and paresthesia within the median nerve distribution. The Katz hand diagram was used to assess categorization of CTS symptoms (Katz *et al*., 1990). Furthermore, patients should present, upon the physical examination, at least two of four of the following clinical findings: nocturnal paresthesia, positive Tinel sign, positive Phalen sign or self-perceived hand strength deficits. Symptoms should have persisted for at least 6 months and be strictly unilateral. It has been found that patients with CTS can present with sub-clinical or 'non-discomfort' CTS in the 'unaffected' hand (Padua *et al*., 1998). In order to exclude these two clinical pictures, we asked for any symptom or discomfort (paresthesia) in both hands. Clinical examination should be negative in one hand.

In addition, the electro-diagnosis study should reveal deficits of sensory and motor nerve conduction following the recommendations of the American Association of Electrodiagnosis, the American Academy of Neurology, and the American Academy of Physical Medicine and Rehabilitation (AAEM 1999, 2002) for the diagnosis of mild to moderate CTS. Specifically, the findings from the electro-diagnosis study of the median nerve that were needed to confirm the diagnosis of CTS included: (i) median nerve distal sensory latency of the index finger (>3.60 ms); and/or (ii) median nerve distal motor latency (>4.20 ms). Sensory and motor conduction studies of the radial and ulnar nerves were done to rule out radial or ulnar nerve involvement.

Patients were excluded if they exhibited any of the following criteria: (i) older than 65 years of age; (ii) previous treatment interventions with surgery and/or steroid injections; (iii) multiple diagnoses of the upper extremity (shoulder pathology, cervical radiculopathy, whiplash cervical, previous cervical surgery); (iv) history of wrist or arm trauma; (v) history suggesting underlying causes of CTS (e.g. diabetes mellitus, thyroid disease); (vi) pregnancy; (vii) bilateral symptoms; (viii) history of musculoskeletal medical conditions (e.g. rheumatoid arthritis, reflex sympathetic dysfunction, fibromyalgia); (ix) if the patient was actively involved with or seeking litigation at the time of the study; and (x) presence of a score greater of 8 points in the Beck Depression Inventory.

Finally, healthy control subjects were recruited from volunteers who responded to a local announcement and were excluded if they exhibited a history of upper extremity or neck pain, fractures or any neurological disorder. This study was supervised by the Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos. The project was approved by the local human research committee (FHA-URJC 029). All subjects signed an informed consent prior to their inclusion.

Pressure pain threshold assessment

Pressure pain threshold (PPT) is defined as the minimal amount of pressure where a sense of pressure first changes to pain (Fischer, 1990). An electronic algometer (Somedic AB, Farsta, Sweden) was used to measure PPT levels. The algometer consists of a 1 cm^2 rubber-tipped plunger mounted on a force transducer. The pressure was applied approximately at a rate of 30 kPa/s, with the algometer placed perpendicular to the application point. Participants were instructed to press switch when the sensation changed from pressure to pain. The mean of three trials (intra-examiner reliability) was calculated and used for main analysis. A 30 s resting period was allowed between each measure. The reliability of pressure algometry has been found to be high [ICC = 0.91 (95% CI: 0.82–0.97)] (Chesterson *et al*., 2007).

Self-reported measures

A 10 cm Numerical Pain Rating Scale (Jensen *et al*., 1999) (NPRS; 0 = no pain, 10 = maximum pain) was used to assess the pain status: (a) current level of hand pain; (b) worst level of hand pain experienced in the preceding 24 h; and (c) lowest level of pain experienced in the preceding 24 h. Patients were asked to draw the distribution of their hand pain on an anatomical map (Katz and Stirrat, 1990). The pain area was calculated with a digitizer (ACECAD D9000, Taiwan). Furthermore, the Spanish version (Rosales *et al*., 2002) of the Boston Carpal Tunnel Questionnaire (Levine *et al*., 1993) (BCTQ), a self-report measure of related functional limitation and symptom severity, was also used. This questionnaire evaluates two domains: (i) the functional status scale assesses ability to perform 8 common hand-related tasks; and (ii) the symptom severity scale includes 11 items assessing hand pain severity, numbness, and weakness at night and during the day. Each question is answered on a 5-point scale (1 = no complaint; 5 = very severe complaint) with higher scores indicating greater severity. The BCTQ has established responsiveness, validity, and reliability (Bessette *et al*., 1998).

Sample size determination

The sample size determination was done with an appropriate software (Tamaño de la Muestra, 1.1©, Spain). The determinations were based on detecting significant differences of 20% on pressure pain threshold levels over each point between both groups (Prushansky *et al*., 2004) with an alpha level of 0.05, and a desired power of 80%. This generated a sample size of at least 16 participants per group.

Study protocol

The study protocol was the same for patients and controls. All examinations were performed in a quiet, draught-free, temperature and humidity controlled laboratory (24°C ± 1°C, relative humidity 25–35%). All participants had abstained from any kind of exercise since the previous day. Those who smoked were asked not to do so from two days before the study. None of the CTS patients were being treated with drugs with actions on the cardiovascular system, haemostasis or blood flow. Participants were not allowed to take analgesics or muscle relaxants through the 72 h prior to the examination. Participants attended a 10 min session for familiarization with pressure pain threshold assessment. Pressure pain threshold levels were measured bilaterally over the median, ulnar and radial nerve, the articular pillar of C5–C6 zygapophyseal joint, the carpal tunnel, and the tibialis anterior muscle by an assessor blinded to the subjects' condition and with 6 years of experience using the algometer. The order of assessment was randomized between participants.

Peripheral nerve trunks nerves were identified by manual palpation and marked with a wax pencil as follows: the median nerve was located in the cubital fossa medial to and immediately adjacent to the tendon of biceps; the ulnar nerve was located in the groove between the medial epicondyle and the olecranon, and the radial nerve was marked where it passes through the lateral inter-muscular septum between the medial and lateral heads of triceps to enter the mid to lower third of the humerus. These anatomical sites have been described in previous studies (Sterling *et al*., 2002, 2003). The articular pillar of C5–C6 zygapophyseal joint was chosen by its segmental relationship with the median nerve. The carpal tunnel area was evaluated because it is the symptom area. Finally, the tibialis anterior was chosen as a distant site, halfway between the most superior attachment to the tibia and its tendon in the upper one third of the muscle belly. This area has been used as a remote site in previous studies conducted on whiplash (Sterling *et al*., 2003; Scott *et al*., 2005), fibromyalgia (Desmeules *et al*., 2003), chronic tension type headache (Ashina *et al*., 2006) and low back pain (O'Neill *et al*., 2007).

Statistical analysis

Data were analysed with the SPSS statistical package (14.0 Version). Results are expressed as mean ± SD and 95% CI. The Kolmogorov–Smirnov test was used to analyse the normal distribution of the variables ($P > 0.05$). Quantitative data without a normal distribution (i.e. pain history, pain area, current level of pain, less and worst level of pain in the preceding 24 h) were analysed with non-parametric tests, whereas data with a normal distribution (PPT) were analysed with parametric tests. The intra-class correlation coefficient (ICC) was used to assess the intra-examiner reliability of pressure pain threshold levels over each point. Demographic characteristics of both study groups were compared using unpaired Student's *t*-test and χ^2 tests of independence. A two-way ANOVA test was used to evaluate the differences in pressure pain threshold levels assessed over each point (median, radial, or ulnar nerves, carpal tunnel, C5–C6 joint or tibialis anterior) with side (affected/unaffected or dominant/non-dominant) as within-subject factor and group (patients or controls) as between-subject factor. *Post-hoc* comparisons were done with the Bonferroni test. Finally, the Spearman's rho (r_s) test was used to analyse the association between pressure pain threshold data, the clinical variables relating to symptoms and the scales of the BCTQ. The statistical analysis was conducted at a 95% confidence level, and a $P < 0.05$ was considered statistically significant.

Results

Demographic and clinical data of the patients

One hundred and fifteen patients with CTS were screened for possible eligibility criteria between March 2007 and January 2008. Finally, a total of 20 females presenting with unilateral CTS, aged 22–60 years old (mean: 43 ± 11 years) satisfied all the eligibility criteria and agreed to participate. The reasons for exclusion were the following: bilateral symptoms ($n = 60$), fibromyalgia ($n = 9$), whiplash syndrome ($n = 7$), previous surgery ($n = 7$), pregnancy ($n = 4$), diabetes ($n = 4$) and age above 65 ($n = 4$). In addition, 20 matched healthy females without upper extremity symptoms, aged 21–60 (mean: 41 ± 8 years) were also included. All participants were right-hand dominant. Fourteen patients (70%) had their right hand affected and the remaining six (30%) had the left hand. Fourteen (70%) patients showed a classic pattern of CTS and the remaining six (30%) patients showed a pattern of probable CTS according to the Katz diagram. The mean duration of hand pain was 3.7 ± 2.2 years (95% CI: 1.8–5.5) and the pain area on the affected hand was 42.3 ± 6.1 cm^2 (95% CI: 35.2–49.1). The mean current level of hand pain was 4.9 ± 1.3 (95% CI: 4.3–5.5), the worst level of pain experienced in the preceding 24 h was 7.3 ± 0.9 (95% CI: 6.9–7.8), whereas the lowest level of hand pain in the preceding 24 h was 2.1 ± 1.3 (95% CI: 1.5–2.7). The BCTQ functional status

scale score was 2.8 ± 0.6 (95% CI: 2.4–3.1) and the BCTQ symptom severity scale score was 2.9 ± 0.4 (95% CI: 2.8–3.2).

Significant positive correlations between duration of pain history and current level of hand pain ($r_s = 0.87$; $P < 0.001$), worst level of pain experienced in the preceding 24 h ($r_s = 0.85$; $P < 0.001$), and lowest level of pain experienced in the preceding 24 h ($r_s = 0.81$; $P < 0.001$) were found. A significant negative correlation between duration of pain symptoms and hand pain area ($r_s = –0.58$; $P = 0.002$) was also found: the longer the pain symptoms, the smaller the hand pain area. No significant correlation between either scale (functional status or symptom severity) of the BCTQ and clinical pain features was found.

Pressure pain sensitivity over peripheral nerve trunks

The intra-examiner repeatability of pressure pain threshold readings for the three nerves ranged from 0.9 to 0.94 for the affected side and from 0.91 to 0.93 for the unaffected arm suggesting high repeatability of pressure pain threshold data. The standard error of measurement (SEM) ranged from 6.0 to 6.6 kPa for the affected side and from 5.3 to 5.9 kPa for the unaffected arm.

The ANOVA revealed significant differences between both groups, but not between sides, for pressure pain threshold levels over the median (group: $F = 119.3$; $P < 0.001$; side: $F = 0.07$; $P = 0.812$, Fig. 1), radial (group: $F = 134.2$; $P < 0.001$; side: $F = 1.4$; $P = 0.283$) and ulnar (group: $F = 142.2$; $P < 0.001$; side: $F = 1.7$; $P = 0.192$) nerves. No significant interaction between side and group for pressure pain threshold levels over the median ($F = 0.02$; $P = 0.868$), radial ($F = 2.1$; $P = 0.137$) or ulnar ($F = 1.8$; $P = 0.197$) nerves was found. Over each nerve, patients showed bilateral lower pressure pain threshold levels than healthy controls ($P < 0.001$). Table 1 summarizes pressure pain threshold assessed over median, ulnar or radial nerves for both sides within each study group.

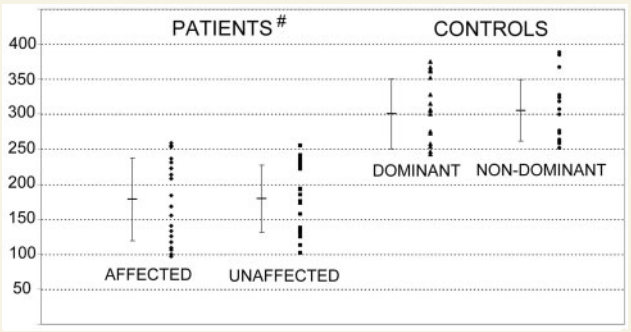

Figure 1 Pressure pain threshold levels (kPa) over the median nerve in patients with CTS and healthy controls. The horizontal bar represents the mean value and the error bars the SD. # indicates significant difference in PPT between patients and controls.

Pressure pain sensitivity over symptomatic and non-symptomatic points

The intra-examiner repeatability of pressure pain threshold readings over the C5–C6 zygapophyseal joint, the carpal tunnel and tibialis anterior muscle was 0.9, 0.88 and 0.92, respectively for the affected arm or 0.92, 0.9 and 0.94 for the unaffected side. The SEM was 4.5, 6.1 and 5.2 kPa for the affected arm or 4.1, 5.9 and 5.1 kPa for the unaffected side.

The ANOVA revealed significant differences between both groups, but not between sides, for pressure pain threshold levels over the carpal tunnel (group: $F = 127.8$; $P < 0.001$; side: $F = 0.4$; $P = 0.526$), C5–C6 zygapophyseal joint (group: $F = 85.6$; $P < 0.001$; side: $F = 0.02$; $P = 0.804$; Fig. 2) and the tibialis anterior muscle (group: $F = 86.7$; $P < 0.001$; side: $F = 1.3$; $P = 0.291$; Fig. 3). No significant interaction between side and group was found either (C5–C6 zygapophyseal joint $F = 0.02$; $P = 0.956$, carpal tunnel $F = 1.7$; $P = 0.199$ and tibialis anterior muscle $F = 0.4$; $P = 0.533$). Patients showed bilateral lower pressure pain threshold levels in both the symptomatic region and non-symptomatic points than controls ($P < 0.001$). Table 2 summarizes pressure pain threshold levels assessed over the carpal tunnel, the C5–C6 zygapophyseal joint and the tibialis anterior muscle for both sides within each study group.

Pressure sensitivity and clinical features in patients with CTS

Finally, significant negative correlations between duration of pain symptoms and pressure pain threshold levels over both median

Table 1 Differences in pressure pain thresholds (PPT) over median, ulnar and radial nerves between patients with unilateral CTS and healthy controls

	Median nerve[a]	Ulnar nerve[a]	Radial nerve[a]
Patients with CTS			
Affected side	178.4 ± 42.5 (95% CI: 155.7–200.9)	257.2 ± 34.2 (95% CI: 236.2–278.1)	190.9 ± 34.2 (95% CI: 168.8–205.7)
Non-affected side	179.5 ± 38.9 (95% CI: 156.8–202.1)	288.7 ± 33.8 (95% CI: 267.7–309.6)	227.8 ± 31.1 (95% CI: 205.7–249.9)
Healthy controls			
Dominant side	300.4 ± 44.8 (95% CI: 277.8–323.1)	400.2 ± 39.7 (95% CI: 379.3–421.2)	343.0 ± 43.5 (95% CI: 320.9–365.1)
Non-dominant side	305.3 ± 41.2 (95% CI: 282.7–327.9)	396.4 ± 33.3 (95% CI: 375.5–417.4)	332.8 ± 40.2 (95% CI: 310.7–354.9)

Values (kPa) are expressed as mean ± SD (95% CI).
a Significant differences between patients and controls (two-way ANOVA test).

nerves (both sides, $r_s = -0.57$; $P < 0.001$), both C5–C6 zygapophyseal joint (both sides, $r_s = -0.44$; $P = 0.007$), both carpal tunnel (affected $r_s = -0.7$; $P < 0.001$, unaffected side $r_s = -0.55$; $P < 0.001$) and both tibialis anterior muscles (affected $r_s = -0.49$; $P = 0.004$, unaffected side $r_s = -0.56$; $P < 0.001$) were found. In such way, the longer the duration of pain history, the lower the bilateral pressure pain threshold levels.

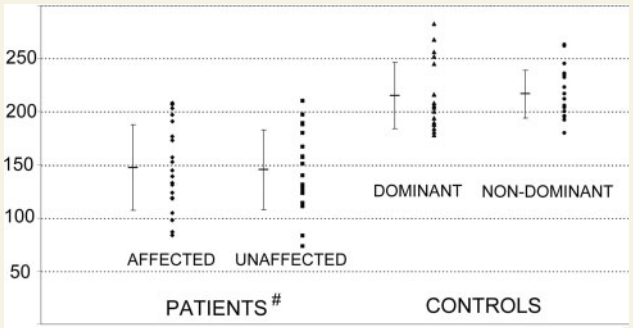

Figure 2 Pressure pain threshold levels (kPa) over the C5–C6 zygapophyseal joint in subjects with CTS and healthy controls. The horizontal bar represents the mean value and the error bars the SD. # indicates significant difference in PPT between patients and controls.

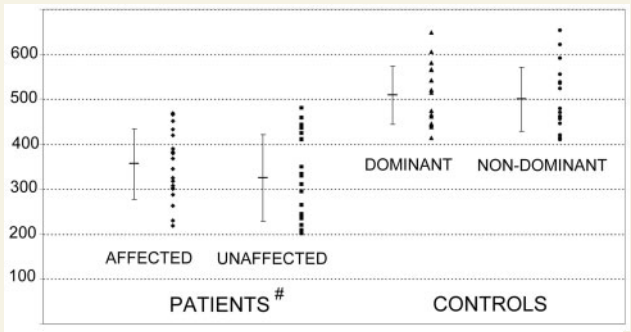

Figure 3 Pressure pain threshold levels (kPa) over the tibialis anterior muscle in CTS and healthy controls. The horizontal bar represents the mean value and the error bars the SD. # indicates significant difference in PPT between patients and controls.

In addition, current level of pain intensity was also negatively correlated with bilateral pressure pain threshold levels over the median nerve (both sides, $r_s = -0.58$; $P < 0.001$), the ulnar nerve (affected side $r_s = -0.63$; $P < 0.001$; unaffected side $r_s = -0.51$; $P < 0.001$), C5–C6 zygapophyseal joint (both sides, $r_s = -0.45$; $P < 0.001$), carpal tunnel (both sides, $r_s = -0.58$; $P < 0.001$) and tibialis anterior muscle (both sides $r_s = -0.52$; $P < 0.001$). In such a way, the greater the pain intensity, the lower the bilateral pressure pain threshold levels.

Discussion

The main finding of the present study was a bilateral and widespread decrease in pressure pain thresholds (PPT) in unilateral CTS when compared to healthy controls. These findings suggest that there is central sensitization in patients with unilateral CTS. Furthermore, the generalized decrease in pressure pain threshold levels was associated with hand pain intensity and duration of symptoms history, supporting a role of the peripheral drive to initiate and maintain central widespread sensitization. Otherwise, central sensitization may modulate local pain perception in CTS. Both peripheral and central mechanisms are probably involved in CTS.

Central sensitization in patients with CTS

In this study, pressure pain threshold was significantly decreased bilaterally over the median, ulnar, and radial nerve in patients with CTS as compared to healthy controls which suggests a generalized sensitization of neural tissues in this pain condition. This result is in accord with previous studies conducted in chronic whiplash showing a bilateral decreased pressure pain threshold levels over peripheral nerves (Sterling *et al*., 2002, 2003), a sign of hyperexcitability of the central nervous system (Zusman, 1992). In a sensitized state, antidromic discharges originating from the central nervous system might sensitize peripheral nerve trunks (Daemen *et al*., 1998) assuming that the nerve trunk stimulation by-passes the peripheral receptors. Over time, this might affect the physical condition of the nerve trunk and would lower the threshold of the nociceptive fibres of the *nervi nervorum*. Furthermore, low-threshold Aβ-fibre afferences input in states of central sensitization

Table 2 Differences in pressure pain thresholds (PPT) over C5–C6 zygapophyseal joint, carpal tunnel and tibialis anterior muscle between patients with unilateral CTS and healthy controls

	C5–C6 zygapophyseal joint[a]	Carpal tunnel[a]	Tibialis anterior muscle[a]
Patients with CTS			
Affected side	147.5 ± 30.4 (95% CI: 132.4–162.4)	345.5 ± 43.1 (95% CI: 312.9–378.1)	356.1 ± 48.5 (95% CI: 321.1–391.1)
Non-affected side	145.2 ± 27.6 (95% CI: 130.2–160.2)	362.4 ± 42.9 (95% CI: 329.8–394.9)	324.8 ± 55.8 (95% CI: 289.8–359.8)
Healthy Controls			
Dominant side	215.2 ± 31.1 (95% CI: 200.2–230.2)	557.9 ± 53.8 (95% CI: 525.2–590.4)	508.7 ± 64.6 (95% CI: 473.7–543.7)
Non-dominant side	216.7 ± 22.6 (95% CI: 201.7–231.7)	520.1 ± 52.9 (95% CI: 487.5–552.7)	499.5 ± 61.8 (95% CI: 464.5–534.4)

Values (kPa) are expressed as mean ± SD (95% CI).
a Significant differences between patients and controls (two-way ANOVA test).

could depolarize nociceptive second order neurones, and this may enhance pain perception (Hoheisel *et al*., 1993). Nevertheless, we do not exactly know what is causing the pain to nerve pressure.

Consistent with a significant decrease in pressure pain threshold bilaterally over peripheral nerves, a significant bilateral decrease in pressure pain threshold over the C5–C6 zygapophyseal joint (segmental point), the carpal tunnel (symptomatic point) and tibialis anterior muscle (distant point) was also present in CTS patients when compared with healthy controls. A significant decrease in pressure pain threshold bilaterally over C5–C6 zygapophyseal joint may represent the existence of segmental sensitization of the nociceptive system in CTS, whereas a significant bilateral decrease in pressure pain threshold over the tibialis anterior muscle may indicate multi-segmental sensory sensitization or sensitization of the central nervous system in patients with CTS. Therefore, a bilateral decrease in pressure pain threshold levels over peripheral nerve trunks, C5–C6 zygapophyseal joint, carpal tunnel and tibialis anterior muscle strongly argues for the hypothesis that central sensitization mechanisms are involved in the pathogenesis of a unilateral neuropathy such as CTS. In agreement with this hypothesis, Tucker *et al*. (2007) found bilateral generalized increase in vibration thresholds in patients with CTS, suggesting a relevant role of central sensitization. In addition, central mechanisms could be responsible of the proximal pain (Zanette *et al*., 2006) or spread symptomatology (Zanette *et al*., 2007) reported by patients with CTS. Otherwise, functional neuroimaging has demonstrated cortical remapping of the primary somatosensory cortex S1 in CTS, with the extent of cortical hand somatotopy being correlated with the patients' symptoms (Tecchio *et al*., 2002; Napadow *et al*., 2006). The current study provides further evidence for central sensitization processes in CTS.

Nevertheless, since hyper-excitability of the central nervous system is a dynamic condition influenced by multiple factors including the activity of peripheral nociceptive inputs (Herren-Gerber *et al*., 2004), it may be hypothesized that the existence of peripheral nociceptive barrage from nerve tissues, particularly the median nerve, may contribute to this sensitization process.

Peripheral nociception driving to initiate or maintain central sensitization

The involvement of segmental and/or central sensitization mechanisms has been reported in many local pain syndromes, e.g. whiplash (Sterling *et al*., 2002), repetitive strain injury (Greening and Lynn, 1998), chronic tension type headache (Fernández-de-las-Peñas *et al*., 2007), low back pain (O'Neill *et al*., 2007), osteoarthritis (Bajaj *et al*., 2001) and unilateral shoulder pain (Ge *et al*., 2008). These evidences agree with findings in animal models where unilateral localized musculoskeletal pain causes sensitization of contra-lateral segments (Sluka *et al*., 2001). The existence of sensitization mechanisms in local pain syndromes suggests that sustained peripheral noxious input to the central nervous system plays a role in the initiation and maintenance of central sensitization. Gracely *et al*. (1992) reported that the hyperalgesia and allodynia ceased when a neuroma was blocked in patients with painful neuropathy. They proposed a model of neuropathic pain in which ongoing nociceptive afferent input from a peripheral focus dynamically maintains altered central processing (Gracely *et al*., 1992).

In the current study, pressure pain threshold over the median nerve, the C5–C6 zygapophyseal joint, the carpal tunnel and the tibialis anterior muscle were negatively associated with hand pain intensity and duration of pain symptoms. These results support a role of peripheral sensitization mechanisms in the initiation and maintenance of central sensitization. In fact, increased recruitment of central neurons by peripheral nociceptive stimulation (Hoheisel *et al*., 1993), enhanced spatial summation (Price *et al*., 1989), and spatial referral, i.e. tonic nociceptive input from local tissue can result in pain of remote areas and increase pain intensity (Staud, 2007) have been suggested to be the potential peripheral mechanisms.

Nerve trunk associated pain has usually been ascribed to increased activity in mechanically sensitized nociceptors within the *nervi nervorum* (nerves that innervate the connective tissue layers of the nerve itself) (Sunderland, 1978; Asbury and Fields, 1984). It seems that nerve endings of the *nervi nervorum* may be sensitized by different noxious stimuli. Mechanical, thermal or chemical stimuli can lead to an increased synthesis and release of algogenic substances in the periphery, resulting in a neurogenic inflammation (Bove and Light, 1997; Watkins and Maier, 2004). The sensitization of nerve nociceptors may trigger spontaneous discharges in the sensory nerve fibres (Sunderland, 1991), resulting in ectopic discharges in the dorsal root ganglion (Bridges *et al*., 2001; Hansson, 2003). This ectopic activity may cause changes in the dorsal horn receptive fields and contribute to the central hyper-excitability (Malan *et al*., 2000; Chacur *et al*., 2001).

In such instances, the initial painful condition, such as neurogenic inflammation via the *nervi nervorum* sensitized by the compression of the median nerve in the carpal tunnel (Hall and Elvey, 1999), may act as a trigger for the chronification through gradual sensitization of nociceptive pathways in CTS. This is also supported by another study showing that the degree of sensitization in patients with chronic musculoskeletal pain is related to the severity of the musculoskeletal pain disorder (Carli *et al*., 2002). Tecchio *et al*. (2002) reported a positive correlation between cortical S1 reorganization and pain intensity in patients with CTS; hence we cannot rule out that central mechanisms may also play a significant role.

Unfortunately no prospective studies have been conducted following the degree of sensitization in patients with CTS over time or after surgery. There is one study where patients with painful osteoarthritis and deep-tissue hyperalgesia were evaluated before and 6–14 months after successful hip replacement (Kosek and Ordeberg, 2000). The sensitization process was normalized after the operation when the patients were pain-free, supporting the notion that the continuous afferent barrage is needed to maintain the sensitization (Kosek and Ordeberg, 2000). Nevertheless, other peripheral nociceptive afferences can be also involved in this process in CTS.

Limitations

Population-based epidemiological studies with greater sample size are needed to permit a more generalized interpretation of these results. Furthermore, pressure pain sensitivity can be influenced by depression or anxiety, although this is unlikely since, in the present study, CTS patients in a state of depression were excluded (>8 points in the Beck Depression Inventory). Tucker *et al*. (2007) reported bilateral generalized increase in vibration thresholds, whereas this study found bilateral widespread increase in mechanical pain sensitivity in subjects with CTS. It would be interesting to investigate other somato-sensory tests, e.g. stimulus response function or bilateral thermal sensitivity, to confirm the presence of central sensitization in patients with unilateral CTS. In addition, we only included patients with mild to moderate CTS and with strictly unilateral symptoms. Nevertheless, Padua *et al*. (1998) found that most unilateral cases are likely to become bilateral with time. Our findings could explain why patients with unilateral CTS may develop bilateral symptoms, since this process might be related to a central processing rather than an exclusive bilateral neuropathy. In the present study, from a total of 115 patients with CTS, only 20 (16%) females suffered from strictly unilateral symptoms, which agree with Padua *et al*. (1998) who found an incidence of bilateral clinical CTS of 87%.

Finally, Ylinen *et al*. (2007) have suggested that, although the repeatability of pressure pain threshold assessment allows the use of pressure algometry for research purposes, caution is advised when interpreting the results in clinical practice. This assumption was based on their findings related to the variation on individual level for pressure pain thresholds in the cervical spine. These authors proposed that differences between pressure pain threshold levels should reach 20 N/cm^2 to be considered as relevant (Ylinen *et al*., 2007). Conversely, Prushansky *et al*. (2004) have established that differences between 20% and 25% are required to indicate a true change in pressure pain threshold. Our results are in line with those previously reported by Prushansky *et al*. (2004), but did not reach the level of 20% established by Ylinen *et al*. (2007). This finding may be related to the fact that we used the same algometer as Prushansky *et al*. (2004), whereas Ylinen *et al*. (2007) used a different device. Furthermore, these studies investigated pressure pain thresholds over the cervical region, whereas only 1 point included in the current study was located in this region (C5–C6 zygapophyseal joint). No study has previously analysed differences for pressure pain threshold values in peripheral nerve trunks, carpal tunnel or tibialis anterior muscle to be considered relevant. Additionally, in the current study we obtained good to excellent intra-examiner reliabilities of our measurements and SEMs between 4.1 kPa and 6.3 kPa, suggesting that differences between groups can be considered as real.

Conclusions

This is the first study to reveal that a widespread mechanical hyperalgesia is observed in patients with unilateral CTS, which may suggest that central sensitization is involved. Additionally, the generalized hyperalgesia was associated with hand pain intensity and duration of symptoms, supporting a role of the peripheral inputs. Nevertheless, both central and peripheral sensitization mechanisms are likely to be involved at the same time in CTS.

Funding

Universidad Rey Juan Carlos and Comunidad de Madrid (reference CCG08-URJC/BIO-3469).

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