NEUROPATHIC PAIN IN POST-BURN HYPERTROPHIC SCARS: A PSYCHOPHYSICAL AND NEUROPHYSIOLOGICAL STUDY

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ABSTRACT

Introduction. Pain complicates hypertrophic post-burn pathologic scars (PPS) **Methods**. To investigate the possible neuropathic origin of pain, 13 patients with painful-PPS involving at least one hand underwent clinical examination including the Douleur Neuropathique en 4 questions (DN4) questionnaire, median, ulnar and radial nerve conduction studies (NCS), cold (CDT) and heat-induced pain thresholds evaluation by quantitative sensory testing, and cutaneous silent period (CSP) of the abductor pollicis brevis. Controls were 9 patients with non painful-PPS, 52 healthy subjects, and 28 patients with carpal tunnel syndrome (CTS). **Results.** All patients with painful-PPS had possible neuropathic pain (DN4 score ≥ 4). NCS signs of CTS were similarly present in PPS subjects with or without pain. Hands with painful-PPS had lower CDT and CSP duration, more frequent cold and heat pain hypesthesia and thermal allodynia than controls. **Discussion.** In PPS, possible neuropathic pain is associated with psychophysical and neurophysiological abnormalities suggestive of small fiber damage.

Key words: neuropathic pain, burns, post-burn scars, quantitative sensory testing, cutaneous silent period

INTRODUCTION

Post-burn pathologic scars (PPS) may commonly complicate the healing of burn wounds in up to 77% of patients. PPS encompass different type of scars, i.e. hypertrophic, contracture and atrophic, but hypertrophy is the most frequent presentation.[1] Pain is a frequent and often severe accompanying symptom of hypertrophic PPS, and it has been hypothesized that pain may be of neuropathic origin.[2]

The grading of certainty for the diagnosis of neuropathic pain labels it as definite if clinical and laboratory evaluations demonstrate the presence of both a neuroanatomically plausible distribution of pain itself, and the evidence of a lesion of the somatosensory system.[3] In patients with burns, entrapment neuropathies are frequent.[4] In hypertrophic PPS there is a moderate-to-severe reduction of skin nerve fiber density.[5,6] Therefore, patients with PPS are at increased risk of both small- and large-fiber sensory nerve damage, which may be the basis for the development of neuropathic pain**.** Standardized screening tools may allow for identification of patients with possible neuropathic pain. Therefore, they are recommended as standardized case identification tools in research studies.[7] The Douleur Neuropathique en 4 questions (DN4) questionnaire is a validated clinician-administered 10-item pain questionnaire that indicates the presence of neuropathic pain for scores ≥ to 4.[7-9] This questionnaire consists of a patient interview (seven items related to symtoms) and a standardized clinical examination (consisting of search for pinprick and touch hypesthesia and allodynia to brush).[8] The DN4 in Italian translation has been adopted to identify patients with neuropathic pain associated with carpal tunnel syndrome (CTS).[9]

In this study, patients with PPS involving at least one hand were screened by the DN4 questionnaire for the presence/absence of possible neuropathic pain in the PPS on the hands. Then, they underwent psychophysical and neurophysiological evaluation to assess for damage to either large or small peripheral sensory nerve fibers in the PPS site. Large fibers were evaluated by routine nerve conduction studies (NCS). Quantitative sensory testing (QST) and the cutaneous silent period (CSP) were performed to assess the function of small fibers. In fact, both QST and CSP are non-invasive

tools that are frequently abnormal in patients with small fiber neuropathy.[10-13] QST measures the function of small fibers by assessing temperature thresholds.[10,11] CSP is a transient suppression of EMG activity that occurs during sustained muscle contraction and after electrical stimulation delivered to the fingers.[12-18] CSP is mediated mainly by Aδ afferents.[13-15,17]

The aim of this study was to investigate the possible neuropathic origin of the pain in PPS by examining clinical features and by investigating the function of both small and large fibers to search for a lesion of the somatosensory system. The latter provides at the same time a pathophysiological basis for pain.

METHODS

Patients.

One hundred-twenty patients with PPS followed by the Burn Center of our hospital were screened for inclusion in the study. Diagnosis of hypertrophic PPS was made, as previously described,[1] on a clinical basis by two expert plastic surgeons (MS and DR), taking into account color, thickness, width, pigmentation, contour, degree of vascular congestion, vascularity, shape, height, texture, consistency and extensibility of the scar. Ancillary laboratory evaluation included ultrasound and videocapillaroscopy studies. An example of a hypertrophic PPS involving the hand is provided in Figure 1.

The inclusion criteria for this study were: 1) a PPS that involved both the dorsum and the palmar surface of at least one hand; 2) complaint of pain at the site of PPS. Patients were screened for the presence of possible neuropathic pain by the DN4 questionnaire, which defines the occurrence of possible neuropathc pain for scores ≥ 4.[7,8] Patients who had PPS involving at least one hand but did not suffer from pain were also included in the study as a control group, to better elucidate the clinical and neurophysiological features of PPS that were associated with pain.

All patients underwent a standardized clinical assessment[19] that included Medical Research Council scale score of six muscles of each arm and four of each leg, and pinprick, touch, vibration and position sense assessment in the upper and lower limbs. Vibration sense impairment was quantified using a graduated 128 Hz Rydel-Seifer tuning fork.[19] Allodynia to brush was also evaluated at the PPS site as part of the DN4 questionnaire.[8] Itch intensity was measured by an 11-point Likert scale (0=no itch, 10=worst possible itch).[7] Severe itch was defined for scores that were ≥ 6. The Visual Analog Scale (VAS) to evaluate the intensity of pain, Beck Depression Index and Mini Mental State Examination were also performed. Exclusion criteria were: age lower than 14 years and higher than 80 years; severe depression defined as a Beck Depression Index score of more than 30; Mini Mental State examination score below 26**;** inability to complete the QST examination with sufficient accuracy (see below); concurrent treatment with neuroleptics, antiepileptics, benzodiazepines or

antidepressants; history of alcohol and/or illicit drug abuse; family history of inherited neurological disease; past history or clinical or laboratory evidence of cervical radiculopathy, myelopathy, polyneuropathy, or other neurological diseases; history of diabetes and/or other known causes of autoimmune, metabolic, or toxic peripheral neuropathies. Normative data for QST and CSP were obtained from 52 (22 men, 30 women; age 41.1 ± 13.4 years) and 22 (7 men, 15 women, age: 41.2 ± 17.2 years) healthy subjects, respectively for a total of 104 and 44 hands. As burn patients have an increased susceptibility to focal mononeuropathies,[4] the results of the NCS, CSP and QST evaluations were compared to those obtained in 28 consecutive patients with CTS who were evaluated routinely in our EMG laboratory (7 men, 21 women, age 49.9 ± 14.4 years). The diagnosis of CTS was based on the clinical and neurophysiological criteria set by the American Academy of Neurology and the American Association of Electrodiagnostic Medicine.[20-21] CTS was bilateral in 16 patients and unilateral in 12, for a total of 44 hands considered in the analysis. The study was approved by the local ethics committee, and both patients and controls gave their informed consent to the performance of laboratory evaluations.

Neurophysiological assessment.

Patients underwent bilateral motor NCS of median and ulnar nerves and antidromic sensory NCS of median, radial and ulnar nerves according to standard techniques.[19] Needle EMG examination was performed, when necessary, to evaluate the degree of denervation or to rule out cervical radiculopathy. NCS were performed with a commercially available electrodiagnostic machine (Viking Quest, Carefusion, Madison,Wisconsin). Comparison of both antidromic median and ulnar sensory latency to the fourth digit was performed bilaterally in patients with PPS and in subjects with clinical suspicion of CTS who had normal motor and sensory conduction of the median nerve.[21,22] A median sensory latency at least 0.5 ms greater than the ulnar latency at the fourth digit was considered suggestive of CTS.[22] Severity of NCS abnormalities suggestive of CTS were graded as minimal, mild, moderate, severe and extreme.[23]

The CSP of the abductor pollicis brevis muscle was recorded with surface electrodes in a bipolar belly-tendon montage after electrical stimulation of the index finger.[18] The patients and controls performed an isometric contraction at maximum force against resistance, and they were provided with audio feedback to maintain constant contraction. Stimulation was delivered through ring electrodes with the cathode placed at the proximal interphalangeal joint of the second digit. The CSP was obtained after stimulation at an intensity 8 times the perception threshold for electric shock.[14] This threshold was evaluated separately in each hand by slowly increasing the intensity of stimulation delivered at 1 Hz, until the subjects perceived a sensation of non-painful electric shock. EMG activity was rectified and averaged over 8 trials in each hand. The onset and offset of the CSP were defined by visual inspection as the beginning of an abrupt decrease and recovery of EMG activity, as previously described.[18]

Quantitative sensory testing.

QST was performed to evaluate the thresholds for both cold- and heat-induced pain sensation. The evaluation of cold- and heat-induced pain sensation, the sites of QST evaluation, and the algorithms were chosen in order to estimate the function of small fibers (C and Aδ)[24] with sufficient accuracy and to keep the time needed sufficiently short to avoid subject fatigue. In patients with PPS and healthy controls, the QST evaluation was performed on the dorsal radial surface of the hand and on the palmar surface of the index finger. In patients with CTS the evaluation was performed on the palmar surface of the index finger. QST was performed with a commercially available thermal stimulation device (Medoc TSA II, Durham, North Carolina).

Heat-induced pain threshold (HPT) was evaluated by the method of limits.[24] Stimulation started at 32° C and increased by a rate of 1° C per second until the subject perceived a change from heat sensation to pain, or the temperature of the probe reached 50°C. Five trials on each site were averaged to evaluate the HPT. Cold detection threshold (CDT) was evaluated by a staircase method with null stimulations.[24,25] Briefly, three ranges of steps of cooling are presented, beginning with a

gross 3° C decrease of temperature. Stimulation started at 32° C. In this reaction-time-independent evaluation, the subject was asked to define whether he/she had perceived the cooling step. Threshold was evaluated by a computerized algorithm. QST was considered insufficiently accurate if subjects failed to identify at least two of five null stimuli during CDT evaluation. Hypesthesia for cold and heat-induced pain was defined if CDT was lower and HPT higher than the minimal and maximal cut-off values for the site, respectively. Thermal allodynia was defined if HPT was lower than the minimal cut off value for the site. A similar definition for loss or gain of function was previously reported.[10,26]

Statistical analysis.

The normality of the quantitative parameters distribution was analyzed using the Kolmogorov-Smirnov test. The parameters that were non-normally distributed were log-transformed in order to be analyzed using the parametric methods of inferential analysis. Cut-off values of the non-parametrically distributed variables were calculated as mean ± 2 SD of the log transformed data, and the results were retransformed into the original units. A similar approach to define the reference cut-off of the QST has been previously reported.[26, 27]

Analyzing neurophysiological data from patients with bilateral CTS may overstate a statistical significance if the comparison was made only by hand.[28] Since both PPS and CTS were frequently bilateral in our series, in order to avoid this bias, we performed the statistical analysis both by hands and by patients according to the suggestions of Padua et al.[28] The differences among the groups of hands/patients (with painful-PPS, with non painful-PPS, healthy and with CTS) were analyzed using the one-way ANOVA with the Bonferroni *post hoc* test. A multivariate ANOVA test was used to adjust the results for sex and age. Correlations were analyzed by estimating the parametric r-Pearson correlation coefficient separately for each group of hands. Continuous data were expressed as mean ± SD. Categoric data were compared using the Chi-square test or the Fisher exact test when appropriate. Statistical analysis was carried out using the Statistical Package for the Social Sciences

software version 9.0 (SPSS Inc., Chicago, IL, USA). In all the analyses, P-values<0.05 were considered to be statistically significant.

RESULTS

Clinical features

Thirteen patients (10 men, 3 women; age 48.6 ± 8.8 years) satisfied both criteria, and, therefore, in all of them, the pain at the site of PPS had a possible neuropathic origin. An additional 9 patients had only PPS in the hands but did not complain of pain in any part of their bodies (5 men, 4 women, age 41.7 ± 16.7 years). All patients with PPS, both painful and non-painful, had suffered from deep-partial or full-thickness burns involving 16-45% of body surface area. Painful-PPS were bilateral in 4 patients and unilateral in 9. Eight patients with unilateral painful-PPS had non painful-PPS affecting the contralateral hand. In patients with only non-painful-PPS, these were bilateral in 6 and unilateral in 3 patients. A total of 39 hands with PPS were evaluated, 17 with painful PPS and 22 with non-painful PPS.

In patients with PPS and pain, the DN4 score was 7 ± 1.9 (range 4-9), and the VAS score was 5.6 ± 1.8 (range 3.5-9). The pain was located on the dorsum of the hand in all patients and also on the palmar surface of hands and fingers in 7 patients. Pain was continuous in 12 patients, paroxysmal in the remaining one. Severe itch was present in 6 patients (11-point Likert score range 6 to 9). Tactile and pinprick hypesthesia were detected at the site of painful-PPS, but not in the remaining part of the body surface in all patients. Allodynia to brush was present at the site of painful-PPS in 7 hands. Clinical and NCS signs of severe CTS were present only in one patient with PPS who underwent surgical decompression of the median nerve at the wrist with partial resolution but not complete disappearance of pain. The neurological examination was otherwise unremarkable in all patients. There were not any significant differences among the groups for age, and between patients with PPS and healthy controls for gender distribution. Women were more frequent in the CTS group than in the other groups ($P<0.01$).

Neurophysiological assessment

The results of median motor and sensory NCS are summarized in Table 1. The NCS of both the ulnar and radial nerve were normal in all groups and did not differ among them. NCS of the median nerve showed abnormalities suggestive of CTS in 4 hands with painful-PPS and 3 with non painful-PPS (P=NS). These abnormalities involved only limbs with PPS, and were bilateral in 2 patients. The severity of NCS abnormalities suggestive of CTS was graded as minimal in one hand (14.2), mild in 2 (28.5%), moderate in 3 (42.8%), and extreme in 1 (14.2%). In the control group of hands with CTS, median NCS abnormalities were graded as minimal in 4 (9 %), mild in 5 (11.4 %), moderate in 27 (61.3 %), severe in 5 (11.4 %), and extreme in 3 (6.8 %). The amplitude of the sensory nerve action potential was lower in hands with both painful and non painful-PPS than in healthy controls.

Examples of CSP obtained in hands with painful-PPS, CTS and healthy controls are provided in Figure 2. Results of CSP data evaluation are summarized in Table 2. There were no interside differences for the CSP parameters considered in the analysis in healthy controls. The most salient findings of the CSP evaluation were: 1) significantly shorter duration in hands with painful-PPS than the other groups; 2) significantly longer duration and latency to offset in hands with CTS than healthy controls and painful-PPS. The analysis made by patients confirmed the significant reduction of CSP duration in patients with painful-PPS than in other groups (Table 2). In patients with painful-PPS, the duration of CSP in the painful hands was significantly shorter than in the non-painful-hands (32.6 $\pm$ 11.8 ms vs 51.3 $\pm$ 8.2 ms, P=0.001). No effect of age or gender was evident in the comparison of median NCS and CSP parameters among the groups of hands. Taking a duration of CSP lower than 32.4 ms as the minimal cut-off, the CSP was abnormally shortened in 7 of 17 hands with painful-PPS, but in none in the other groups (P<0.01, in all comparisons)

Quantitative sensory testing.

Analysis of parameter distribution showed a non-normal distribution of QST results, and therefore they were log-transformed before ANOVA. Results of QST evaluation are summarized in Tables 3 and 4. In healthy controls there was no significant difference between right and left hands for all QST parameters. The CDT on the dorsum was lower in hands with painful-PPS than in both healthy controls and non-painful PPS. The CDT in the index finger was lower in hands with painful-PPS than in healthy controls and CTS. The HPT was not different among groups. The analysis made by patients confirmed the significant reduction of CDT at both sites identified in the analysis by hands (Table 3). Hypesthesia to cold, to heat-pain and thermal allodynia was more frequent in painful-PPS than in healthy controls at both sites. Reduced cold sensation was also more frequent in painful-PPS than both in non-painful-PPS and CTS groups at all sites evaluated. Warm and heat-pain anesthesia to 50°C was detected in only 4 of 17 hands with painful-PPS, but not in the other groups ($P<0.05$ in all comparisons). In summary, at least one abnormal QST finding in at least one site was detected in all hands with painful-PPS, 12 of 22 with non painful-PPS, and 22 of 104 of healthy controls ($p<0.0001$) No effect of age or gender was evident in the comparison of QST parameters among the groups.

Correlation analysis

The VAS score did not correlate with any neurophysiological or QST parameter in patients with painful-PPS. In hands with painful-PPS, the CSP duration correlated significantly only with CDT on the dorsum of the hand (r: 0.53, $P<0.05$). On the contrary, in the other groups, the CSP duration correlated significantly with latency to offset (non painful-PPS, r: 0.59,$p<0.05$; healthy controls, r: 0.79, $p<0.0001$; CTS, r: 0.92, $p<0.0001$). Latency to offset correlated with sensory conduction velocity in painful-PPS (r: -0.57, $p<0.05$), non-painful-PPS (r: -0.77, $p<0.0001$) and healthy controls (r: -0.60, $p<0.05$), but not in CTS. In painful-PPS, the CDT on the dorsum correlated significantly with CDT on the index finger (r: 0.67, $P<0.05$), and it was lower when CSP duration was reduced than when it was normal (25.4 ± 3.5 ° C vs 29.5 ± 2.8 ° C, $P= 0.02$).

DISCUSSION

Pain is a frequent and often severe accompanying symptom of PPS. Previous reports put forward the hypothesis that it may be of neuropathic origin.[2] However no previous studies have systematically investigated the occurrence of possible neuropathic pain in patients with PPS using standardized screening tools, such as the DN4 questionnaire. Moreover, no previous studies have attempted to correlate the occurrence of possible neuropathic pain with the presence of large as well small sensory fiber damage in PPS.

The most striking findings in our series were: 1) all patients complaining of pain at the PPS site had a DN4 questionnaire score ≥ 4, suggesting a possible neuropathic origin of pain itself; 2) in hands/patients with painful-PPS, both QST and CSP findings differed significantly from those obtained in the other groups. In fact, in the presence of painful-PPS, there were lower CDT, shorter CSP duration, more frequent hypesthesia to cold than in healthy controls and in non-painful-PPS, and more frequent thermal allodynia and hypesthesia to heat pain than in healthy controls. The absence of a significant difference for HPT among the groups may be due to the significant presence of both abnormally lower and higher HPT in the hands with painful-PPS, reflecting thermal allodynia and hypesthesia to heat pain, respectively. Therefore, it is reasonable to presume that, in this setting, the mean HPT is less informative than is the number of hands with abnormally reduced or increased HPT values. Even if warm perception was not evaluated, it is noteworthy that about 25% of hands with painful-PPS, but none in the other groups lacked warm or heat pain perception at 50°C. Assessment of CDT is considered a suitable method to evaluate the function of Aδ fibers,[13,24,29] and CSP duration is influenced primarily by Aδ afferents.[13-15] In patients with painful-PPS, our study showed a correlation between the duration of CSP and CDT; moreover, an abnormally reduced CSP duration seems to be associated with a more severe degree of CDT reduction in these patents. Similar results have been described in Fabry disease[13] and suggest that CSP duration is reduced only when damage to Aδ fibers is moderate-to-severe.

Taken together, these observations suggest that there may be a substantial impairment of Aδ and C fibers at the PPS sites.[13,24,29] Previous series reported a similar pattern of sensory impairment in chronic burn lesions.[30,31] Nedelec et al[31] reported significantly reduced CDT, anesthesia to both warm and heat-pain in 27% of cases, but no significant abnormality of mean HPT in grafted skin after burns. The pattern of QST abnormalities in their study was very similar to that observed in our series. Histological evaluations disclosed a severe reduction of both dermal and epidermal nerve fibers in skin grafts after burns.[31] Similar histological findings have been reported in other evaluations of patients with PPS.[6] Therefore, skin lesions after burns seem to be characterized by a moderate-to severe loss of small fibers. However, none of the previous studies of burn lesions correlated with the presence and extent of small fiber damage to the occurrence of possible neuropathic pain.

The prominent role of small fiber damage in the genesis of neuropathic pain has been increasingly recognized.[9,10,32,33] In our patients, pain at the PPS site seems to be associated with moderate-to severe abnormalities of QST and CSP; this observation is in line with the hypothesis that the degree of small sensory fiber loss is related to the probability of development of neuropathic pain as well as to its severity.[33]

We are aware of some possible criticisms of our results. The first point is the role of median mononeuropathy at the wrist in the development of neuropathic pain, and, secondarily, in the genesis of QST as well as CSP abnormalities, in patients with PPS. Some observations suggest that this role seems to be irrelevant: 1) previous studies emphasized the lack of association between Aß fiber damage and the development of neuropathic pain at least in CTS and peripheral neuropathies;[9,32] 2) the frequency of NCS abnormalities suggestive of CTS did not differ between hands with painful and non painful-PPS; 3) only one patient with painful-PPS had clear signs and symptoms suggestive of CTS; 4) the CSP duration is significantly prolonged in hands with CTS than in hands with painful-PPS or in healthy controls, which is in line with other reports.[18] Taken

as a whole, these observations suggest that the occurrence of possible neuropathic pain does not seem to be correlated with the presence of a median mononeuropathy at wrist.

A second possible criticism is the possibility that abnormalities of CDT and the CSP may be due to modulation of spinal circuitry induced by the pain itself. Furthermore, previous studies have put into question the role of both QST and CSP for the definition of the neuropathic ethiology of pain.[7,34] Previous reports have suggested that both nociceptive and neuropathic pain may modulate spinal cord circuitry through the activation of diffuse noxious inhibitory control, which acts through inhibition of wide dynamic range neurons in the dorsal horn.[16,35] This mechanism of spinal cord modulation by pain was investigated by the use of painful heterotopic stimulation which, when applied unilaterally, reduces the duration of the CSP[16] and CDT[35] bilaterally. However, our study showed no correlation with this mechanism, because in patients with painful-PPS, the QST and CSP abnormalities were confined only to the painful hands, even if there was a non painful-PPS in the other hand. We agree with previous reports that the best neurophysiological tool to confirm the neuropathic nature of pain is laser evoked potentials.[7,34] However, no safety studies are available for the use of these potentials in patients with burn lesions. Therefore our choice fell to non-invasive and previously tested evaluations such as QST in this particular setting.[30,31]

When all these observations are taken into consideration, some thought should be given to the level of certainty of neuropathic pain in PPS. Our study documents that in PPS, a condition characterized by a moderate-to-severe loss of epidermal and dermal nerve fibers,[5,6,31] possible neuropathic pain is associated with laboratory evidence of small fiber damage. Moreover, pain is confined only to areas involved by PPS. Therefore, pain in PPS seems to be associated with a definite lesion of the somatosensory system (*i.e*. the small sensory fiber loss that occurs in PPS) and has a neuroanatomically plausible distribution (*i.e*. is confined to areas involved by the PPS with laboratory evidence of more severe small fiber damage). Therefore, in a very conservative way, the grading of certainty for pain in PPS may be, at least, probable neuropathic pain.[3]

Further studies are required to obtain a more precise definition of the nature and degree of small fiber damage necessary to induce neuropathic pain in patients with PPS. This may be of great importance for the therapy of this pain for which treatment has not been satisfactory.[2]

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LIST OF ABBREVATIONS

cMAP: compound muscle action potential; CDT: cold detection threshold; CSP: cutaneous silent period; CTS: carpal tunnel syndrome; DML: distal motor latency; DN-4: douleur Neuropathique en 4 questions; HPT: heat-induced pain threshold; mA: milliAmpere; MCV: motor conduction velocity; ms: milliseconds; mV: milliVolts; μV: microVolts; NCS: nerve conduction studies; ND: not done; PPS: post burn pathologic scars; QST: quantitative sensory testing; SAP: sensory action potential; SCV: sensory conduction velocity. SD: standard deviation; VAS: visual analog scale

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Table 1. Summary of median nerve conduction studies data in post-burn scars and controls

	Painful-PPS	Non-painful PPS	CTS	Healthy controls
Median NCS				
MCV (m/s)	50.2 ± 8.9	55.9 ± 2.9	48 ± 15.4	56.9 ± 4.5
	(52.7 ± 8.3)	(56.1 ± 3)	(48 ± 15.1)	(56.9 ± 4.5)
CMAP amplitude	6.5 ± 3.3	6.1 ± 1.6	5 3 ± 3.1*	9.2 ±2.5
(mV)	(6.6 ± 3.2)	(6.1 ± 1.7)	(5.4 ± 3.1)	(9.2 ± 2.5)
CMAP latency (ms)	3.7 ± 1.6	3.6 ± 0.5	5.5 ± 1.7†	3.3 ±0.4
	(3.7 ± 1.3)	(3.5 ± 0.4)	(5.5 ± 1.8)	(3.3 ± 0.4)
SCV (m/s)	47.5 ± 13.2	55.4 ± 7.4	29.9 ± 15.6‡	56.7 ± 4.2
	(48.9 ± 12.3)	(56.4 ± 7.4)	(30.1 ± 15.4) ‡	(56.7 ± 4.2)
SAP amplitude (μV)	19.2 ± 14.9§	26.8 ± 7.4§	12.9 ± 10.5§	41.6 ±19.3
	(18.7 ± 13.2) §	(26.7 ± 7.4) §	(13.2 ± 10.3)	(41.6 ± 19.3)

CMAP: compound muscle action potential; CTS: carpal tunnel syndrome; MCV: motor conduction velocity; ms: milliseconds; μV: microVolts; mV: milliVolts; NCS: nerve conduction studies; PPS: post-burn pathologic scars; SAP: sensory action potential; SCV: sensory conduction velocity.

Data are presented as mean ± standard deviation.

Data obtained in the analysis by patients are indicated in parentheses

* *lower than healthy controls (p: 0.001)*

† *higher than all the other groups (p<0.0001)*

‡ *lower than all the other groups (p<0.01)*

§ *lower than healthy controls (p< 0.01).*

Table 2. Summary of cutaneous silent period evaluation in post-burn scars and controls

	Painful-PPS	Non-painful PPS	CTS	Healthy controls
CSP parameter				
Latency to onset (ms)	84.6 ± 15.1*	63.4 ± 11.5	76.6 ±16.7†	71.1 ± 6.2
	(81.7 ± 14.7) *	(63.5 ± 11.5)	(75.5 ± 18.5)	(71.1 ± 6.2)
Duration (ms)	31.9 ± 11.9‡	62.9 ± 13.6	70.3 ± 35.9§	52.6 ± 10.1
	(35.6 ± 13.5) ‡	(61.4 ± 14)	(71 ± 35)	(52.6 ± 10.1)
Latency to offset (ms)	118.7 ± 14.4	126.4 ± 11.6	147.2 ± 43.2§	123.9 ± 10.7
	(119.3 ± 13.2)	(128.1 ± 13.2)	(145 ± 48.1)	(123.9 ± 10.7)
Threshold for electric	6.4 ± 1.8	6.3 ± 1.9	7.5 ± 2.7	6 ± 1.8
shock perception (mA)	(6.3 ± 1.9)	(6.3 ± 2)	(7.2 ± 3.1)	(6 ± 1.8)

CSP: cutaneous silent period; CTS: carpal tunnel syndrome; mA: milliAmpere; ms: milliseconds; PPS: post-burn pathologic scars.

Data are presented as mean ± standard deviation.

Data obtained in the analysis by patients are indicated in parentheses

* *higher than healthy controls and non-painful-PPS (p<0.01)*

† *higher than non-painful-PPS (p: 0.01)*

‡ *lower than all the other groups (p<0.01)*

§ *higher than healthy controls and painful-PPS (p< 0.05)*

Table 3. Summary of sensory thresholds evaluated by quantitative sensory testing

	Painful PPS	Non-painful PPS	CTS	Healthy controls
Thresholds (°C)				
Heat pain perception				
Dorsum	44.4 ± 1.1	44.4 ± 1.1	ND	43.4 ± 1.1
	(44.3 ± 5.83)	(44.6 ± 4.57)		(43.4 ±1.1)
Index	43.5 ± 1.1	42.9 ± 1	46.7 ± 1	44.6 ± 1
	(44.5 ±4.54)	(43 ±3.6)	(46.8 ± 3.4)	(44.6 ± 1)
Cold perception				
Dorsum	27.9 ± 3.7*	30 ± 2 .5†	ND	31.6 ± 0.3
	(28.7 ± 5.3)*	(30 ± 2.6)		(31.6 ± 0.3)
Index	28.7 ± 3.4‡	30 ± 1.2	30.4 ± 1.3	31.2 ± 0.5
	(29.8 ± 3.9) †	(30.1 ± 1.3)	(30.6 ± 1.4)	(31.2 ± 0.5)

CTS: carpal tunnel syndrome; ND: not done; PPS: post-burn pathologic scars

Data are presented as means ± SD

Data obtained in the analysis by patients are indicated in parentheses

** P<0.05 vs all the other groups*

† P<0.05 vs healthy controls

‡ P<0.05 vs both healthy controls and CTS

Table 4. Frequency of cold hypesthesia, heat-pain hypesthesia and thermal allodynia evaluated by QST in hands with post-burn scars and controls

	Painful PPS (17)	Non-painful PPS (22)	CTS (44)	Healthy controls (104)
Sensory abnormalities				
Hypesthesia to cold	12 [70.7]*	7 [31.8]†		0 [0]
Dorsum	12 [70.7]*	5 [22.7]†	ND	0 [0]
Index	11 [64.7]*	6 [27.3]†	5 [11.4]†	0 [0]
Hypesthesia to heat pain	9 [52.9] †	8 [36.4] †		14 [13.4]
Dorsum	9 [52.9] †	8 [36.4] †	ND	9 [8.6]
Index	5 [29.4] †	4 [18.2]	10 [22.7] †	6 [5.7]
Thermal allodynia	7 [41.1] †	5 [22.7]		9 [8.6]
Dorsum	6 [35.3] †	3 [13.7]	ND	8 [7.7]
Index	6 [35.3] ‡	3 [13.7]	2 [4.5]	4 [3.8]

CTS: carpal tunnel syndrome; ND: not done; PPS: post-burn pathologic scars; QST: quantitative sensory testing

Data are presented as means ± SD

Numbers of hands in each group are indicated in parentheses

Percentages of hands with sensory abnormalities in each group are indicated in brackets

Cold hypesthesia defined for thresholds lower than 30.9° C on the dorsum and 30.2° C on the index finger. Heat-induced pain hypesthesia defined for thresholds higher than 45.6° C on the dorsum and 46.6° C on the index finger.

Thermal allodynia defined for thresholds lower than 41.5° C on the dorsum and 42.5°C on the index finger.

** $P<0.05$ vs all the other groups*

† $P<0.05$ vs healthy controls

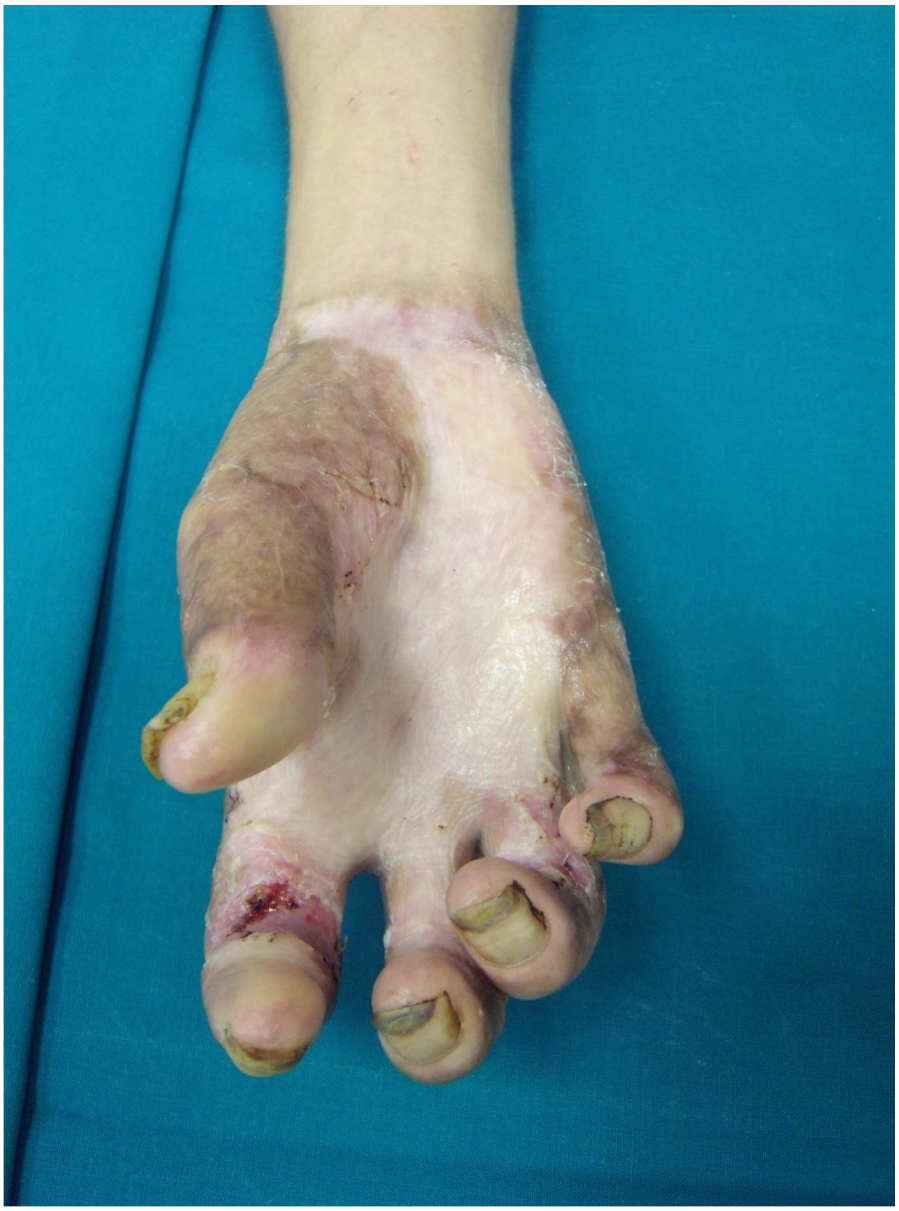
‡ $P<0.05$ vs both healthy controls and CTS

LEGEND TO FIGURES

Figure 1. An example of hyperthrophic post-burn pathologic scar, involving the hand.

Figure 2. Examples of cutaneous silent period in painful post-burn pathologic scars (a), healthy control (b) and carpal tunnel syndrome (c). Cutaneous silent period was recorded from the abductor pollicis brevis during an isometric contraction at maximum force against resistance. Electrical stimulation was delivered to the second digit at an intensity 8 times the sensory threshold for an electric shock. Latency to onset and latency to offset are indicated by arrows.

The duration of the CSP is reduced in post-burn pathologic scar (28 ms, a) and increased in carpal tunnel syndrome (254 ms, c) compared to a healthy control (43 ms, b). The latency to onset is increased in carpal tunnel syndrome (98 ms), compared to post-burn pathologic scars (70 ms) and in the healthy control (72 ms)



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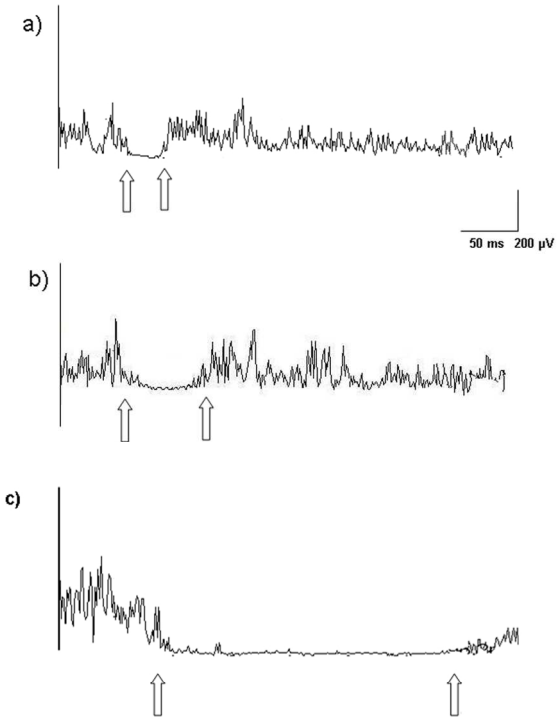

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