The nature and course of sensory changes following spinal cord injury: predictive properties and implications on the mechanism of central pain

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Central pain below the injury level after spinal cord injury is excruciating, chronic and resistive to treatment. Animal studies suggest that pretreatment may prevent central pain, but to date there are no measures to predict its development. Our aim was to monitor changes in the sensory profile below the lesion prior to the development of below-level central pain in order to search for a parameter that could predict its risk and to further explore its pathophysiology. Thirty patients with spinal cord injury and 27 healthy controls underwent measurement of warm, cold, heat-pain and touch thresholds as well as graphaesthesia, allodynia, hyperpathia and wind-up pain in intact region and in the shin and feet (below level). Patients were tested at 2–4 weeks, 1–2.5 months and 2.5–6 months after the injury or until central pain had developed. At the end of the follow-up, 46% of patients developed below-level central pain. During the testing periods, individuals who eventually developed central pain had higher thermal thresholds than those who did not and displayed high rates of abnormal sensations (allodynia and hyperpathia), which gradually increased with time until central pain developed. Logistic regressions revealed that the best predictor for the risk of below-level central pain was allodynia in the foot in the second testing session with a 77% probability (90.9% confidence). The results suggest that neuronal hyperexcitability, which may develop consequent to damage to spinothalamic tracts, precedes central pain. Furthermore, it appears that below-level central pain develops after a substantial build-up of hyperexcitability. To the best of our knowledge, this is the first systematic report establishing that neuronal hyperexcitability precedes central pain. Predicting the risk for central pain can be utilized to initiate early treatment in order to prevent its development.

Keywords: central pain; spinal cord injury; sensory; prediction; mechanism

Introduction

Injury to the spinal cord generates severe complications in various body systems. One of the worst consequences of a spinal cord injury is the development of chronic pain in body regions below the level of lesion. This chronic pain, termed ‘below-level central pain’ (Siddall et al., 2000; Widerström-Noga et al., 2008) has an estimated prevalence of 34–67% (Fenollosa et al., 1993; Störmer et al., 1997, Siddall et al., 1999, 2003; Finnerup et al., 2001). Below-level central pain is considered severe and excruciating and has such considerable impact on the quality of life of individuals with spinal cord injury (Davidoff et al., 1987; Westgren and Levi, 1998; Finnerup et al., 2001).
2001; Siddall et al., 2003), that they are willing to trade their remaining motor performances for pain relief.

Below-level central pain is refractory to most treatments despite a variety of pharmacological, surgical and behavioural therapeutic strategies (Finnerup et al., 2005a; Attal et al., 2009; Siddall, 2009; Teasell et al., 2010) for reasons that include the limited knowledge on its pathophysiology and the scarcity of randomized controlled trials. Another reason may be that patients are being treated after below-level central pain has developed i.e. after considerable and perhaps irreversible changes have occurred in the CNS. The fact remains that patients suffer from below-level central pain for years after its development (Siddall et al., 2003; Widerström-Noga et al., 2008).

Data from animal models of central pain suggest that it may be preventable by pre-administration of various substances, such as interleukin-10 and agmatine, at the time of spinal cord injury (Plunkett et al., 2001) or by transplantation of adrenal chromaffin cells (Brewer et al., 1998; Yu et al., 1998); means that have not yet been tested in humans. In addition, it is unreasonable to administer pre-emptive treatments to all individuals in the acute phase of spinal cord injury due to costs and possible side effects. However, preventive treatment to individuals who are at risk of below-level central pain might prove to be an effective solution. The first step in this direction is to predict the risk for below-level central pain prior to its development.

An important observation in this respect is that below-level central pain develops within weeks to months after the spinal cord injury (Siddall et al., 1999; 2003; Widerström-Noga et al., 1999). We intended to employ this delayed onset in order to characterize and follow-up the changes occurring in the nervous system leading to below-level central pain by conducting a series of quantitative sensory tests. The purpose was to construct a battery of predictive tests for below-level central pain and to further explore its pathophysiology.

We chose the sensory tests based on data showing that individuals with spinal cord injury who already suffer from below-level central pain exhibit the following typical sensory profile in the painful regions: (i) deceased/abolished temperature and pain sensitivity indicative of spinothalamic tract damage (Eide et al., 1996; Bouhassira et al., 2000; Defrin et al., 2001; Gracia-Larrea et al., 2002; Finnerup et al., 2003; Ducoux et al., 2006; Siddall and Middleton, 2006; Wydenkeller et al., 2009); (ii) neuronal hyper-excitability indicative by allodynia and hyperpathia (Eide et al., 1996; Defrin et al., 2001; Finnerup et al., 2003; 2007); and (iii) relative preservation of tactile sensation i.e. of dorsal column function (Beric et al., 1988; Bowsher, 1996; Defrin et al., 2001; although see Finnerup et al., 2003).

Based on the above, and on the yet untested hypothesis that central pain may result from hyperexcitability of the nervous system (Defrin et al., 2001; Finnerup and Jensen, 2004), our working hypothesis was that patients who exhibit, soon after the injury, a significant damage to the spinothalamic tract along with signs of hyperexcitability are those who are at risk to develop below-level central pain.

The aim, therefore, was to follow-up changes in the sensory profile of patients with spinal cord injury from the injury to the onset of central pain and then compare the sensory profile between individuals who eventually developed below-level central pain and those who did not in order to search for a biomarker predicting the risk for below-level central pain. Since it is uncertain whether neuronal hyperexcitability precedes, or emerges together with below-level central pain, the finding may add information on its pathophysiology. To the best of our knowledge, this is the first such study on individuals with spinal cord injury.

Patients and methods

Subjects

A total of 57 individuals, both males and females, participated in this study. Thirty participants suffered from spinal cord injuries (average age 33.6 ± 14 years). Twenty-seven subjects were sex- and age-matched healthy volunteers (average age 32.7 ± 4 years). Patients with spinal cord injury were recruited from the Department of Neurological Rehabilitation at the Chaim Sheba Medical Centre (Tel-Hashomer, Israel) on a voluntary basis. The patients were admitted consecutively to the department. Inclusion criteria for subjects with spinal cord injury were as follows: (i) neurological level of spinal lesion above T10 (in order to avoid lesions to the conus medullaris and cauda equina); (ii) incomplete spinal lesion classified according to the American Spinal Injury Association standards for classification of spinal cord injury (ASIA, 2003); and (iii) spinal injury of no longer than 3 weeks. Exclusion criteria for patients and controls were as follows: (i) acute or chronic pain (either evoked or spontaneous) at or below the injury level for patients with spinal cord injury and acute or chronic pain for controls; (ii) known or clinical signs of concomitant cerebral damage; (iii) history of severe neurological disorders other than spinal cord injury (e.g. multiple sclerosis, cerebral palsy, traumatic brain injury); (iv) concurrent severe medical problems; (v) diseases causing potential neural damage (e.g. diabetes mellitus); (vi) skin lesions in the testing sites; and (vii) any psychiatric or cognitive status that might interfere with the trial.

The study was approved by both the Tel-Aviv University and the Sheba Medical Centre institutional ethical committees. Informed consent was obtained from all the participants according to the Declaration of Helsinki, after receiving a full explanation of the goals and protocols of the study.

Protocol

Testing took place in a quiet room. Participants either sat in their wheelchairs or on a comfortable armchair or were lying in their bed. For healthy controls, sensory testing was performed in one session. For patients with spinal cord injury, sensory testing was performed in 1–3 sessions at the following time periods: first testing session at 2–4 weeks after the spinal cord injury (around the time of admission to the ward); the second testing session at 1–2.5 months after the spinal cord injury (during admission); and third testing session at 2.5–6 months after the spinal cord injury (after discharge from the ward) (Fig. 1A). These testing periods were chosen based on a few considerations including the changes occurring after spinal cord injury, the rehabilitation process in the ward, previous findings regarding the onset of central pain after spinal cord injury and the compliance of the patients in the different rehabilitation stages. Our aim was to conduct at least two testing sessions for each patient prior to the development of central pain within a reasonable time frame, and with an inter-session interval of ~3–4 weeks considering that onset
can vary between a few weeks to months after the spinal cord injury and is averaged at 6 months (Siddall et al., 1999; 2000; Widerström-Noga et al., 1999; Defrin et al., 2001). Testing was discontinued if the patient developed central pain (below and/or at the injury level).

Due to the above-mentioned factors, the first testing session was performed in all the participants with spinal cord injury; however, the second and third testing sessions were performed in a smaller number of patients. After the testing sessions were completed, we continued to follow-up the participants by way of telephone calls and clinical evaluations until 18 month after the injury, in order to identify the participants who eventually developed central pain. This was followed by the division of patients into two groups; those who developed (below-level central pain group) and those who did not develop central pain (no central pain group).

The presence of central pain was determined by clinical neurological examination as well as imaging studies, x-ray and electromyography and according to the definition and characteristics of central pain (Widerström-Noga et al., 2008): (i) below level pain—spontaneous and/or evoked burning, stabbing, shooting pain diffusely located in body regions at least 2–3 dermatomes below the level of the spinal lesion; and (ii) at level pain—spontaneous and/or evoked burning, stabbing, sharp pain located in dermatomes corresponding to the level of spinal injury. As this definition is of exclusion, care was taken to exclude local or pathologies that may underlie the pain (e.g. pressure sores, urinary lithiasis and radicular pain).

Each testing session lasted ~1.5 h. Sensory testing was conducted at two locations within each leg, which were below the injury level for all patients with spinal cord injury; the mid-dorsal surface of the foot and the lateral upper part of the shin (Fig. 1B). These sites were chosen because they were found to be frequently affected by below-level central pain in previous studies regardless of the level of spinal injury (Defrin et al., 2001; Widerström-Noga et al., 2001; Finnerup et al., 2003; 2007) and therefore were considered susceptible. In addition, sensory testing was conducted on the region above the upper trapezius muscle, which was intact for all participants (Fig. 1B). In healthy volunteers, sensory testing was conducted at the same locations as those chosen for subjects with spinal cord injury. In total, there were five testing regions for each subject. The results of the sensory testing were thus compared between the below-level central pain and the no central pain group, and between these groups and healthy controls.

### Sensory testing

#### Thermal testing

Warm, cold and heat-pain sensations were tested to evaluate the function of the spinothalamic tract (Nathan et al., 1986; Willis and Westlund, 1997). The threshold of each sensation was measured with a Peltier-based computerized thermal stimulator (TSA II; Medoc Inc.) and a 3 × 3 cm contact probe. The principles of the Peltier stimulator have been described elsewhere (Wilcox and Giesler, 1984; Verdugo and Ochoa, 1992). Briefly, passage of current through the Peltier element produced temperature changes at rates determined by an active feedback system. As soon as the target temperature was attained, probe temperature actively reverted to a preset adaptation temperature by passage of an inverse current.

Warm, cold, heat-pain thresholds were measured using the method of limits. For warm and cold sensation thresholds determination, subjects received four successive ramps of gradually increasing or decreasing temperature, in random order, starting from a baseline temperature of 32°C (rate of 2°C/s). Thermal stimuli were applied every 15s. The subjects were asked to press a switch when a thermal sensation (either warm or cold) was first perceived, thus defining the thermal threshold and resetting the probe temperature to baseline values. Warm and cold thresholds were the averaged reading of four successive stimuli in each session. Heat-pain threshold was measured with the same protocol. Four successive stimuli were applied at 30s intervals to minimize tissue damage during which the subject was asked to press a switch when the first pain sensation was perceived,
thus defining heat-pain threshold. If subjects failed to press the switch, the stimulation stopped automatically at 51°C (Yarnitsky and Ochoa, 1990; Defrin et al., 2006).

Light touch and graphaesthesia testing
Sensations of light touch and graphaesthesia were tested to evaluate the function of the dorsal column-medial lemniscal system (Noordenbos and Wall, 1976; Nathan et al., 1986; Nathan, 1990; Hagen and Pardo, 2002). The threshold of light touch was evaluated with Semmes-Weinstein Monofilaments (Touch-Test™ Sensory Evaluator 20 piece Kit, North Coast Medical Inc.). The 20 calibrated monofilaments ranged between 1.65 and 6.65 U. Each filament was attached to a plastic holder. Vertical pressure applied with the handle induces a calibrated force ranging between 0.008 and 300 g (Johansson et al., 1980; Bell-Krotski and Tomancik, 1987). While subjects were blindfolded, the examiner applied the monofilaments in an increasing order, starting with the smallest filament. The subject was asked to report as soon as they perceived touch. At that point, they were asked to localize the stimulus perceived. The threshold for light touch was the calibrated force of the monofilament first perceived.

Graphaesthesia testing consisted of identification of a number or a geometric shape, which was traced on the skin with a monofilament no. 4.74. A four-point rank order scale was constructed for graphaesthesia (Lahuerta et al., 1990; Defrin et al., 2001), as follows: 0 = complete loss of identification of the shape drawn on the skin, 1 = vague sensation of the moving trace on the skin with no identification of the above (both rank 0 and 1 were considered as loss of graphaesthesia), 2 = decreased sensation (hypoesthesia) of the trace with identification of the above, 3 = normal sensation of graphaesthesia.

Evaluation of neuronal hyperexcitability
Hyperexcitability and hyper-reactivity of the nervous system have been suggested to be manifested by dynamic allodynia (Kolzenburg et al., 1992; Ochoa and Yarnitsky, 1993; Jensen et al., 2001), exaggerated wind-up (Price et al., 1989; Bennett, 1994) and hyperpathia (Bennett, 1994; Merskey and Bogduk, 1994). Patients with central pain express high rates of allodynia (Defrin et al., 2001; Ducrux et al., 2006; Finnerup et al., 2007), exaggerated wind-up (Eide et al., 1996; Defrin et al., 2001) and hyperpathia (Defrin et al., 2001, 2002) and therefore these traits were evaluated herein.

Dynamic mechanical allodynia, defined as pain evoked by a non-noxious mechanical stimulus (Merskey and Bogduk, 1994), was examined by gently dragging a Semmes-Weinstein monofilament no. 4.74 along the patient’s skin for 3 cm or 1 s. The patient was asked to report the quality of sensation evoked by the stimulus (Defrin et al., 2001). Mechanical wind-up, which is a gradually increasing pain due to a repeatedly administered mechanical stimulus of identical intensity, was measured with a Semmes-Weinstein Monofilament no. 6.65. The examiner applied the filament four consecutive times at two different rates; every 3 and every 10s (0.3 and 0.1 Hz, respectively), the latter of which was a control. The subject was asked to rate the intensity of pain following the first and fourth stimulus on a visual analogue scale. The first stimulus of the series produced no pain or minimal pain sensation. If the fourth stimulus administered at a rate of 0.3 Hz evoked a considerable pain whereas that of 0.1 Hz did not, then an exaggerated wind-up was determined (Price et al., 1992; Defrin et al., 2001). Hyperpathia was tested by heating the skin, from an adaptation temperature of 32°C at a rate of 2°C/s. Emergence of a sudden, strong painful sensation, which persisted after stimulation was turned off at body regions with high heat-pain threshold, was defined as hyperpathia (Merskey and Bogduk, 1994).

Characteristics of central pain
Patients with spinal cord injury who eventually developed central pain were interviewed about their pain (location, intensity, quality, etc.) and completed the McGill pain questionnaire, which provides a quantitative evaluation of the patient’s pain experience (for a full description, see Melzack and Torgerson, 1971; Melzack, 1975). The quantitative parameters were as follows: (i) number of words chosen from a list of descriptors; (ii) pain rating index, which is the sum value of these descriptors; (iii) perceived pain intensity at its worse; and (iv) perceived pain intensity at its least.

Data analysis
Data were processed with PASW statistics software (version 17). In body regions with complete sensory loss, a cut-off value was assigned to allow for average calculations. The values were: mean + 2 standard deviations (SDs) of normal warm and heat-pain thresholds and mean – 2 SD of normal cold threshold (Defrin et al., 2002; Ofek and Defrin, 2007) adjusted for each testing region separately (foot, shin). There was no need to assign cut-off values for touch and graphaesthesia as these were never absent. Parametric and non-parametric models were used to compare between: (i) patients who eventually developed central pain (below-level central pain group), patients who did not develop central pain (no central pain group) and healthy controls; (ii) first and second testing sessions; and (iii) body regions tested (shin, foot). The independent variables were as follows: threshold for warm, cold, heat-pain and touch (continuous variables, described as mean ± SD), graphaesthesia (median), allodynia, wind-up pain, hyperpathia (categorical variables, described as counts and per cent). The models included main effects, interactions and pair-wise comparisons (t-tests for the continuous variables, Wilcoxon test for graphaesthesia and McNemar test for the dichotomy variables). Correlation coefficients were calculated between the intensity of central pain (as measured with the McGill pain questionnaire) and the thresholds of sensations tested in the first and second testing session. Multiple testing problems were addressed by using the Bonferroni correction.

In order to assess the ability of the independent variables to predict the risk for below-level central pain logistic regressions were applied for each testing session separately with the dependent variable below-level central pain (yes/no). Based on the results of the logistic regression, we calculated the probability of each of these variables to predict central pain using the reliability equation. $P < 0.05$ were considered as being statistically significant.

Results
General information and characteristics of central pain
Out of the cohort of 30 subjects, one patient died several weeks after the first test session and contact was lost with another patient after the second test session. Since it was impossible to determine whether these patients developed central pain or not, their results were excluded from the final analysis. Out of 28
Table 1 Patients who eventually developed central pain

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Spinal cord injury level</th>
<th>Spinal cord injury mechanism</th>
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<th>Test 1</th>
<th>Test 2</th>
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<td>+</td>
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<tr>
<td>2</td>
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<td>C</td>
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<td>+</td>
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<td>MVA</td>
<td>C</td>
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<td>C</td>
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<td>+</td>
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<tr>
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<td>FOH</td>
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<td>MVA</td>
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<td>+</td>
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<td>T8</td>
<td>MVA</td>
<td>C</td>
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ASIA = American Spinal Injury Association; C = cervical; FOH = fall of height; MVA = motor vehicle accident; T = thoracic.

Table 2 Patients who did not develop central pain

<table>
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<th>Spinal cord injury mechanism</th>
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patients, 13 (46.4%) eventually developed central pain below the lesion level (below-level central pain) and four of them also had at-level central pain. Tables 1 and 2 present the two spinal cord injury subgroups; patients who developed below-level central pain (Table 1) and those who did not (no central pain) (Table 2). The groups did not differ in age, sex distribution, and in any of the features of the spinal cord injury.

Onset of below-level central pain averaged at 3.8 ± 2 months after injury (range 1–8 months). According to the McGill questionnaire, present pain intensity worst ranged from 2 to 5 (median = 4) and present pain intensity least ranged between 0 and 5 (median = 2) on a 0–5 scale. Number of words chosen was 12.5 and pain rating index was 21.3. Pain was reported mostly as burning, lancinating, pressing, electric-like and cold. The factors reported to exacerbate the pain were as follows: cold temperature (either by contact or weather), illness, long duration physical activity and stress. Reported alleviating factors were medications, heating, resting and relaxation.

Pain in the feet was reported by 11 patients (84.6%) and pain in the shin by nine patients (69.2%). Additional locations included upper leg (46.2%), distal parts of the forearm and hands (38.5%), lower back (23%) and abdomen (23%).

Sensory testing above the injury level

Table 3 presents the results of the tests conducted above the injury level in the two spinal cord injury groups and normal controls. There were no significant differences between the spinal cord injury groups in any of the testing sessions and not between healthy controls and between the spinal cord injury groups except for warm sensation threshold in the first testing session, which was lower (34.7 ± 2°C) compared with patients with below-level central pain (36.6 ± 2°C, P < 0.05) and patients with no central pain (35.9 ± 1°C, P < 0.05). None of the participants had hyperpathia above the lesion. One patient with spinal cord injury exhibited
mechanical allodynia and paradoxical sensations during thermal testing. In the second testing session, there were no significant differences between the spinal cord injury groups.

### Sensory testing below the injury level

Since only the minority of patients underwent three testing sessions (mainly due to the development of central pain prior to the third session), we could not use the data from the third session for comparisons and therefore we present the results from the first two testing sessions. During initial analysis, we compared the values of the eight variables tested (thresholds of warm, cold, heat-pain and touch, graphesthesia, wind-up, allodynia and hyperpathia) between the shin and the foot within each group in order to examine possible differences between the two body regions. Out of 16 comparisons (eight variables \times two sessions), significant differences between these body regions were found only in four instances: threshold of heat-pain and touch in the shin and foot within each patient. Due to the small number of differences between the body regions, we decided to average the data obtained from the shin and foot within each patient.

#### First testing session

Both groups with spinal cord injury had significantly higher thresholds than healthy controls in all the sensation tested (below-level central pain group: \( P < 0.0001 \) for warm, heat-pain and touch thresholds and for graphesthesia, \( P < 0.001 \) for cold threshold; no central pain group: \( P < 0.0001 \) for warm, heat-pain and touch thresholds, \( P < 0.01 \) for graphesthesia, \( P < 0.05 \) for cold threshold). In addition, the group with below-level central pain exhibited significantly higher rates of allodynia and hyperpathia compared with healthy controls (\( P < 0.05 \) for allodynia, \( P < 0.01 \) for hyperpathia). In essence, healthy controls did not exhibit allodynia or hyperalgesia and only two subjects had wind-up pain; however, this is not apparent for all the between-group comparisons due to the Bonferroni corrections (data not shown).

Figure 2 presents the measurements obtained from the two groups with spinal cord injury in the first testing session (13 individuals in the below-level central pain group and 15 individuals in the group with no central pain). The group with below-level central pain exhibited significantly higher warm (43.1 ± 4 versus 40.6 ± 3°C, respectively, \( P < 0.01 \)) and cold (23.1 ± 7 versus 26.4 ± 3°C, respectively, \( P < 0.01 \)) thresholds (Fig. 2A) and also slightly higher touch threshold (3.3 ± 1 versus 2.8 ± 1 U, respectively, \( P = 0.052 \)) and graphesthesia score (3 versus 1 score, respectively, \( P = 0.051 \)) (Fig. 2B) compared with the group with no central pain. In addition, the below-level central pain group exhibited higher rates of allodynia (31.7% versus 7.7%, respectively, \( P < 0.05 \)) and hyperpathia (50% versus 17.3%, respectively \( P < 0.01 \)) than the group with no central pain (Fig. 2C). Note that the rates of these abnormal sensations in the group with below-level central pain were 2–4-fold that of the rates in the group with no central pain.

Thermal thresholds significantly correlated with the intensity of central pain as assessed by the McGill questionnaire: warm sensation threshold positively correlated with number of words chosen (\( r = 0.57, P < 0.01 \)), pain rating index (\( r = 0.46, P < 0.05 \)), worst-pain (\( r = 0.52, P < 0.01 \)) and least-pain rating (\( r = 0.41, P < 0.05 \)); cold sensation threshold negatively correlated with pain index (\( r = -0.46, P < 0.05 \)), and heat-pain threshold positively correlated with number of words chosen (\( r = 0.79, P < 0.0001 \)) and pain rating index (\( r = 0.75, P < 0.0001 \)). Namely, the more extreme the threshold values

---

### Table 3 Measurements above the lesion level (intact body regions)

<table>
<thead>
<tr>
<th>Testing session</th>
<th>Sensations</th>
<th>Central pain</th>
<th>No central pain</th>
<th>Central pain versus no central pain</th>
<th>Healthy controls</th>
<th>Spinal cord injury groups versus controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Warm(^a)</td>
<td>36.6 (2)</td>
<td>35.9 (1)</td>
<td>NS</td>
<td>34.7 (1)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Cold(^a)</td>
<td>29.83 (1)</td>
<td>29.52 (1)</td>
<td>NS</td>
<td>30.7 (1)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Heat-pain(^a)</td>
<td>42.59 (3)</td>
<td>41.72 (3)</td>
<td>NS</td>
<td>40.81 (4)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Touch(^a)</td>
<td>2.29 (1)</td>
<td>2.24 (0.3)</td>
<td>NS</td>
<td>2.20 (0.2)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Graphesthesia(^b)</td>
<td>3</td>
<td>3</td>
<td>NS</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Wind-up(^a)</td>
<td>2 (15.4)</td>
<td>2 (13.3)</td>
<td>NS</td>
<td>2 (7.4)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Allodynia(^c)</td>
<td>0</td>
<td>1 (6.6)</td>
<td>NS</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Hyperpathia(^c)</td>
<td>0</td>
<td>0</td>
<td>NS</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Second</td>
<td>Warm(^a)</td>
<td>36.0 (1)</td>
<td>34.9 (1)</td>
<td>NS</td>
<td>34.7 (1)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Cold(^a)</td>
<td>29.3 (1)</td>
<td>29.42 (1)</td>
<td>NS</td>
<td>30.7 (1)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Heat-pain(^a)</td>
<td>42.2 (2)</td>
<td>43.1 (3)</td>
<td>NS</td>
<td>40.81 (4)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Touch(^a)</td>
<td>2.29 (0.3)</td>
<td>1.65 (0.3)</td>
<td>0.058</td>
<td>2.20 (0.2)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Graphesthesia(^b)</td>
<td>3</td>
<td>3</td>
<td>NS</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Wind-up(^a)</td>
<td>2 (25)</td>
<td>1 (10)</td>
<td>NS</td>
<td>2 (7.4)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Allodynia(^c)</td>
<td>0</td>
<td>0</td>
<td>NS</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Hyperpathia(^c)</td>
<td>0</td>
<td>0</td>
<td>NS</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = non-significant.
\( a \) Mean (SD).
\( b \) Median.
\( c \) Number (%).
(higher temperatures for warm and heat-pain sensations and lower temperatures for cold sensation), the more severe the central pain intensity. There were no significant correlations between touch and graphaesthesia and between central pain intensity.

**Second testing session**

Figure 3 presents the measurements obtained from the two spinal cord injury groups in the second testing session (eight individuals in the below-level central pain group and 10 individuals in the no
central pain group). In this testing session, the below-level central pain group exhibited higher cold (25.9 ± 2°C versus 27.3 ± 2°C, respectively, \( P < 0.05 \)) and heat-pain (50.1 ± 1°C versus 47.7 ± 2°C, respectively, \( P < 0.0001 \)) thresholds compared with the group with no central pain (Fig. 3A). Note that mean heat-pain threshold in the below-level central pain group (50.1 ± 1°C) was 2 SD higher than that of the group with no central pain (47.7 ± 2°C). In addition, patients with spinal cord injury with below-level central pain exhibited significantly higher rates of all abnormal sensation tested; wind-up pain (58.3% versus 7.5%, \( P < 0.0001 \)), allodynia (76.9% versus 2.5%, \( P < 0.0001 \)) and hyperpathia (69.2% versus 20%, \( P < 0.0001 \)). The rates of these sensations in patients with below-level central pain were 3–30-fold of those found in the subjects with no central pain (Fig. 3C). The groups did not differ in touch (2.9 ± 1 versus 3.0 ± 1 U) and graphaesthesia (3 versus 2.5 score) (Fig. 3B).

Thermal thresholds significantly correlated with the intensity of central pain as assessed by the McGill questionnaire: warm sensation threshold correlated positively with the number of words chosen \( (r = 0.56, \ P < 0.05) \), pain rating index \( (r = 0.76, \ P < 0.01) \), worst-pain rating \( (r = 0.52, \ P < 0.05) \) and least-pain rating \( (r = 0.53, \ P < 0.05) \); cold sensation threshold correlated negatively with the number of words chosen \( (r = -0.59, \ P < 0.05) \) and with worst-pain rating \( (r = -0.54, \ P < 0.05) \), and heat-pain threshold correlated positively with pain rating index \( (r = 0.69, \ P < 0.05) \) and with worst-pain rating \( (r = 0.65, \ P < 0.05) \). Here again, as in the first session, the greater the deviation of the thermal thresholds from the norm, the more severe was the central pain intensity. Touch and graphaesthesia did not correlate with central pain intensity.

Changes in the sensory profile with time

Figure 4 presents the changes in the sensory profile with time in the group with below-level central pain from Session 1 to Session 2 (the data include only patients who underwent two testing
sessions, n = 8). A significant main effect was found for time (df = 1, f = 2.89, P < 0.05) with a significant interaction between testing sessions and test variables (df = 4, f = 4.75, P < 0.01), indicating that changes in thresholds between the sessions were not uniform. Whereas warm and heat-pain thresholds significantly increased with time (from 41.0 ± 3°C to 42.4 ± 3°C, P < 0.05 and from 48.6 ± 3°C to 50.1 ± 1°C, P < 0.01, respectively) indicating worsening of spinothalamic tract function (Fig. 4A), the threshold for touch significantly decreased (from 3.4 ± 1 to 2.6 ± 1, P < 0.05) and the degree of graphesthesia increased slightly but not significantly (P = 0.08), possibly indicating small improvement or stability of dorsal column function (Fig. 4B).

An increase in the occurrence of all abnormal sensations occurred with time (Fig. 4C). Wind-up increased from 38.5% to 54.5%, but the increase did not reach a significant level, whereas allodynia significantly increased from 37.5% to 76.9% (P < 0.05) and there was a trend towards an increase in hyperpathia from 46.17% to 73.3% (P = 0.14).

In the group with no central pain, time did not significantly affect the thresholds, although heat-pain thresholds significantly decreased with time (from 48.8 ± 2°C to 47.6 ± 2°C, P < 0.05) (Fig. 4A) and cold threshold decreased slightly but not significantly with time (from 26.3 ± 3°C to 27.3 ± 2°C, P = 0.09) (data not shown). Touch and graphesthesia thresholds did not change significantly with time (Fig. 4B), and its effect on abnormal sensations was non-significant (the rate of wind-up pain decreased from 27.5% to 7.5%, that of allodynia remained at 2.5% and that of hyperpathia from 17.5% to 20%) (Fig. 4C).

**Prediction value of the various tests**

Logistic regressions were conducted for each testing session separately. Table 4 present the models that best predicted below-level central pain (yes/no) in each session and the calculated prediction probability. Note that the variables inserted into the models are the separate values of the shin and feet and not the combined values for these regions. The reason is that predictions should be based on measurements in a specific body region so that they could be of practical use thereafter.

In the first testing session, the combination of variables that had the highest percentage correct (89.1%) was: warmth threshold and allodynia in the shin and touch threshold and hyperpathia in the foot. Each of these variables alone did not produce a high enough percentage correctness, the better of which were hyperpathia in the foot and allodynia in the shin, which produced percentage correct of 72.9 and 67.4%, respectively. Based on the results of the logistic regression, we calculated the probability of each of these variables to predict below-level central pain using the reliability equation. Since the equation requires the positioning of actual values, it was impossible to calculate the probability of prediction of the continuous variables (warmth and touch thresholds). However, calculating the prediction value of hyperpathia and allodynia alone produced rates of 78 and 73%, respectively. That is, there was a 75 and 73% probability that patients who exhibit hyperpathia or allodynia, respectively, will develop below-level central pain (with confidence of 72.9 and 67.4%, respectively) (Table 4).

In the second testing session, allodynia in the foot alone was the best predictor for below-level central pain (model percentage correct of 90.9%). The reliability equation of the logistic regression showed that there was 77% probability that those who exhibit allodynia would develop below-level central pain (with confidence of 90.9%) (Table 4). The sensitivity of allodynia in the foot was 100% and its specificity was 90.1%.

**Discussion**

Our aim was to characterize the changes in the sensory profile of patients with spinal cord injury from the injury to the onset of central pain, in order to search for a clinical biomarker for below-level central pain.

**Changes in the sensory profile with time prior to emergence of below-level central pain**

Significant sensory changes in below-level body regions occurred from the time of spinal cord injury to the onset of below-level central pain, including an increase in warm- and heat-pain thresholds, a decrease in touch threshold and an increase in the graphesthesia score. Since the spinothalamic tract conveys thermal sensations and the dorsal column conveys light touch and

**Table 4** Logistic regression models for prediction of central pain in the two testing sessions

<table>
<thead>
<tr>
<th>Testing session</th>
<th>Variables</th>
<th>Sig</th>
<th>Exp (B)</th>
<th>95% CI for Exp (B)</th>
<th>Percentage correct</th>
<th>Prediction value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First session</td>
<td>Warm&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.006</td>
<td>0.642</td>
<td>0.467-0.883</td>
<td>89.1</td>
<td>NC</td>
</tr>
<tr>
<td></td>
<td>Touch&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.027</td>
<td>0.055</td>
<td>0.004-0.723</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperpathia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.023</td>
<td>0.031</td>
<td>0.002-0.626</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Allodynia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.036</td>
<td>0.015</td>
<td>0.000-0.768</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First session</td>
<td>Hyperpathia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.003</td>
<td>0.136</td>
<td>0.037-0.502</td>
<td>72.9</td>
<td>78</td>
</tr>
<tr>
<td>First session</td>
<td>Allodynia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.032</td>
<td>0.155</td>
<td>0.028-0.856</td>
<td>67.4</td>
<td>73</td>
</tr>
<tr>
<td>Second session</td>
<td>Allodynia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.000</td>
<td>0.010</td>
<td>0.001-0.118</td>
<td>90.9</td>
<td>77</td>
</tr>
</tbody>
</table>

CI = confidence interval; Exp = exponent; NC = not calculated; Sig = significance.

<sup>a</sup> Shin.

<sup>b</sup> Foot.
graphaesthesia, the results suggest a worsening of the spinothalamic tract function and small improvement of dorsal column function with time towards the emergence of below-level central pain. Such changes were not observed in the group with no central pain. In contrast, heat-pain and cold sensation threshold tended to decrease, indicating perhaps some improvement of spinothalamic tract function in this group.

Although both spinal cord injury groups had higher thresholds than controls, the group with below-level central pain exhibited higher thermal thresholds than the group with no central pain in the two testing sessions, suggesting that the former exhibited more extensive spinothalamic tract damage. Many studies show that the spinothalamic tract is significantly damaged in patients with spinal cord injury already suffering from central pain (Eide et al., 1996; Bouhassira et al., 2000; Defrin et al., 2001; Finnerup et al., 2003, 2004; Duceux et al., 2006; Siddall and Middleton 2006). Using refined analysis of contact-heat-evoked potentials, Wydenkeller et al. (2009) showed that although patients with spinal cord injury with and without central pain exhibited spinothalamic tract damage (defined by missing or delayed potential), subjects with central pain exhibited a slower peak frequency that correlated with the extent of spinothalamic tract deafferentation. Here, we demonstrate that more extensive spinothalamic tract damage exists prior to the emergence of below-level central pain and that it worsens with time towards its onset.

Changes in hyperexcitability prior to emergence of below-level central pain

Early onset of allodynia, hyperpathia and exaggerated wind-up was recorded in below-level body regions in individuals who eventually developed below-level central pain, at rates 2–4-fold that of the group with no central pain. Within the below-level central pain group, the rates increased with time towards the emergence of below-level central pain. We may therefore conclude that hyperexcitability and hyperactivity of the nervous system precede below-level central pain and do not result from it

Abnormal sensations have been found frequently in individuals with spinal cord injury suffering from central pain (Bowsher, 1996; Eide et al., 1996; Siddall et al., 1999; Defrin et al., 2001; Finnerup et al., 2003; Duceux et al., 2006). In a follow-up study, Siddall et al. (1999) found that allodynia was especially prevailing in individuals with incomplete spinal cord injury who suffered from below-level central pain. In accordance with our findings, the authors also reported that allodynia can develop in the first few weeks after spinal cord injury in these patients.

Pathophysiology of central pain following spinal cord injury

The results of the present study contribute new knowledge on two aspects of the pathophysiology of below-level central pain. Firstly, several authors have suggested that neuronal hyperexcitability develops mainly after spinothalamic tract lesions (Vestergaard et al., 1995; Beric, 1998; Boivie, 1999). Our results confirm this possibility by showing an increased rate of abnormal sensations among the group with below-level central pain concurrent with worsening of spinothalamic tract function. Furthermore, abnormal sensations were significantly more abundant in the below-level central pain group in which the spinothalamic tract function was worst. Secondly, hyperexcitability of the nervous system as inferred by the presence of allodynia and hyperpathia preceding below-level central pain has been observed in this group with a gradual increase in its extent as well as in spinothalamic tract dysfunction towards below-level central pain onset.

Based on the previous reports and on our results, damage to the ascending spinothalamic tract seems to induce a reactive reduction in descending inhibition. As a result, residual spinal neurons are released from descending control and may become hyperexcitable and hyper-responsive. Changes in response properties of residual neurons were recorded in humans (Loeser et al., 1968; Kjerulf and Loeser, 1973; Lenz et al., 1987; Edgar et al., 1993; Wasner et al., 2008). Furthermore, ketamin (Eide et al., 1994), lidocain (Attal et al., 2000; Finnerup et al., 2005b), lamotrigine (Finnerup et al., 2002) and pregabalin (Siddall et al., 2006) reduce central pain in humans by blocking voltage-gated ion channels and NMDA receptors. Although translating data from animal models to humans remains speculative, increased abnormal, spontaneous and evoked activity of spinal neurons in animals with spinal cord injury pain (Yezierski and Park, 1993; Vierck et al., 2000; Hains and Waxman, 2006; Boroujerdi et al., 2011) may further reflect reduced inhibitory control possibly underlying hyperexcitability.

An indicator of a possible causal relationship between below-level central pain and spinothalamic tract involvement leading to hyperexcitability is the gradual worsening of spinothalamic tract function along with a gradual increase in hyperexcitability prior to below-level central pain, present only in patients who eventually developed below-level central pain, a seemingly time-dependent relation. This causal relationship may also be reflected by the significant correlations found between central pain intensity and the thermal sensory thresholds measured in the first and second testing sessions. We found that the higher the deviation from the norm of spinothalamic tract function (higher temperatures for warm and heat-pain sensations and lower temperatures for cold sensation), the more severe the central pain intensity. On the other hand, touch and graphaesthesia did not correlate with central pain intensity.

From our results, it appears that the neuronal hyperexcitability develops and expands gradually after spinothalamic tract deafferentation and that once it reaches a certain, critical level, spontaneous activity is generated leading to the emergence of below-level central pain. At this point, both spontaneous and evoked-pain are present, as found in patients already suffering from below-level central pain (Siddall et al., 1999; Defrin et al., 2001; Finnerup et al., 2003, 2007). It is noteworthy that damage to the spinothalamic tract is found also in patients with spinal cord injury without central pain albeit to a lesser extent (Defrin et al., 2001; Finnerup et al., 2007). Therefore, below-level central pain may develop either in cases where substantial damage to the spinothalamic tract and reactive hyperexcitability propagates or, alternatively and not mutually exclusive in individuals who are genetically
predisposed to hyperexcitability after spinothalamic tract damage, as supported by animal studies (Wiesenfeld-Hallin et al., 1993; Gorman et al., 2001; Mills et al., 2001).

Whether the increase in hyperexcitability with time suggests that it has reached supraspinal levels can only be speculated. Wasner et al. (2008) suggested that spinal hyperexcitability of residual spinal neurons may lead to secondary thalamic (Lenz et al., 1994; Pattany et al., 2002; Durec et al., 2006; Hains and Waxman, 2007; Dostrovsky and Craig, 2009; Masii et al., 2009; Gustin et al., 2010; Murai et al., 2010) and cortical changes (Brewer et al., 2003; Wriley et al., 2009). Activation of ascending pathways from the spinal ‘pain generator’ may thus contribute to the maintenance of central pain. That patients with below-level central pain exhibit pathologically evoked pain at the injury site (Finnerup et al., 2007) may further support the critical role of hyperexcitability in central pain. Nevertheless, it remains speculative whether measures of sensory hyperexcitability are precursors or predictors of central pain development or whether they are more sensitive in revealing central pain-related symptoms.

Can central pain be predicted?

Since neuronal changes leading to central pain may be permanent, predicting its risk is clinically beneficial. Logistic regressions revealed that the best biomarker for below-level central pain was foot mechanical allodynia in the second session for the following reasons: (i) the probability of developing below-level central pain if allodynia is present is 77% with 90% confidence level; (ii) measurement of mechanical allodynia is simple, does not necessitate sophisticated or computerized equipment and is therefore clinically practical; and (iii) the test should only determine presence/absence with no need for cut-off values or additional calculations. The only disadvantage is that the highest prediction confidence for allodynia was obtained in the second session, which is closer to the onset of below-level central pain and may coincide with its development. Heat-pain threshold may also serve as a partial biomarker because its value in the second session in the group with below-level central pain (50.1 ± 1.02°C) was >2 SD than in the group with no central pain (47.7 ± 2.2°C). Nevertheless, adding heat-pain threshold to the logistic regression along with allodynia did not produce a higher prediction value than allodynia alone.

In the first testing session, there was no single biomarker with enough percentage correctness. Only the combination of four variables (warmth, touch, allodynia and hyperpathia) produced ~90% correct, probably due to the increase in the between-group differences with time. Thus, prediction of below-level central pain around a month after the injury (first testing session) is possible, but would require several measurements and the use of fairly sophisticated equipment. As there is some degree of confidence in the predictive ability of shin allodynia in the first testing session, we propose that monitoring the presence of allodynia in the feet and shins from the time of injury may increase its predictive value.

Clinical implications

The risk for below-level central pain can be predicted by testing mechanical allodynia in the feet and shins. The test is simple, feasible and enables rapid response. Monitoring mechanical allodynia as soon as possible after the spinal cord injury is highly recommended. If allodynia is found, the aim would be to reduce hyperexcitability by administering agents able to block/delay its progress (e.g. lidocain, lamotrigine or gabapentin) and possibly prevent below-level central pain. Other preventive means that delayed/decreased allodynia and pain behaviour in animals e.g. interleukin-10 (Plunkett et al., 2001), N-Methyl-D-aspartate (Hao et al., 1991) and nerve growth factor (Gwak et al., 2003) antagonists, have as yet not been tested on humans but may serve as such in the future.

Although this study provides novel information on the prediction and mechanism of below-level central pain it has several limitations. Firstly, the results are applicable to below-level central pain, because sensory measurements were conducted below level. Secondly, although the follow-up period of 18 months covers a large onset range, some patients may have developed below-level central pain after the study has ended. Note that earlier onset of below-level central pain was one of the reasons why only 18 patients underwent two testing sessions. Thirdly, the first testing session was conducted >2 weeks after the injury because patients underwent surgical procedures or stayed in the emergency ward. Had testing been conducted earlier, prediction could possibly have been better. Finally, although allodynia is simple and feasible clinically, it is subjective and depends on patients’ collaboration. Biomarkers such as MRI and evoked potentials might provide more objective information about the development of central pain; however, the clinical approach using allodynia as a biomarker is advantageous considering costs and viability.

In summary, the changes of the sensory profile in body regions below the level of injury following spinal cord injury suggest that below-level central pain develops in those instances in which a substantial hyperexcitability builds up. These changes also show that the presence of mechanical allodynia in the shin and feet of patients after spinal cord injury may predict the risk for below-level central pain. Future studies may use this advantage in order to provide pretreatment to patients who may be at risk for below-level central pain.

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References


