CASE REPORT

Sensory function after cavernous haemangioma: a case report of thermal hypersensitivity at and below an incomplete spinal cord injury

J Gómez-Soriano^{1,2}, E Goiriena¹, J Florensa-Vila³, JM Gómez-Arguelles⁴, A Mauderli⁵, CJ Vierck Jr⁵, S Albu¹, C Simón-Martínez¹ and J Taylor¹

Study design: Case report of a 42-year-old woman with non-evoked pain diagnosed with a cavernous C7–Th6 spinal haemangioma. **Objectives:** To assess the effect of intramedullary haemorrhage (IH) on nociception and neuropathic pain (NP) at and below an incomplete spinal cord injury (SCI).

Setting: Sensorimotor Function Group, Hospital Nacional de Paraplégicos de Toledo (HNPT).

Methods: T2*-susceptibility weighted image (SWI) magnetic resonance imaging (MRI) of spinal haemosiderin and a complete pain history were performed 8 months following initial dysaesthesia complaint. Thermal pain thresholds were assessed with short 1 s stimuli, while evidence for central sensitization was obtained with psychophysical electronic Visual Analogue Scale rating of tonic 10 s 3 °C and 48 °C stimuli, applied at and below the IH. Control data were obtained from 10 healthy volunteers recruited from the HNPT.

Results: Non-evoked pain was present within the Th6 dermatome and lower legs. T2*-SWI MRI imaging detected extensive haemosiderin-rich IH (C7–Th5/6 spinal level). Cold allodynia was detected below the IH (left L5 dermatome) with short thermal stimuli. Tonic thermal stimuli applied to the Th6, Th10 and C7 dermatomes revealed widespread heat and cold allodynia.

Conclusion: NP was diagnosed following IH, corroborated by an increase in below-level cold pain threshold with at- and below-level cold and heat allodynia. Psychophysical evidence for at- and below-level SCI central sensitization was obtained with tonic thermal stimuli. Early detection of IH could lead to better management of specific NP symptoms, an appreciation of the role of haemorrhage as an aggravating SCI physical factor, and the identification of specific spinal pathophysiological pain mechanisms.

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Keywords: haemosiderin; quantitative sensory testing; tonic thermal stimulation; central sensitization to thermal stimuli; thermal pain threshold; heat and cold allodynia

INTRODUCTION

Although an experimental and a clinical study suggest that intramedullary haemorrhage (IH) associated with spinal cord injury (SCI) maybe related to change in nociception and pain perception,^{1,2} definitive diagnostic evidence for its role in the development of neuropathic pain (NP) has not been forthcoming. Insertion of autologous blood into an experimental anterolateral spinal hemisection initiates a rapid increase in learned escape responses to noxious stimuli when applied below the SCI.¹ Furthermore, a recent clinical case of IH documented the presence of itch and dysaesthesia, although the presence of specific pain types following haemorrhage of a midcervical cavernoma was not fully explored.² As such a definitive diagnosis of NP with a comprehensive graded sensory testing regime³ is required to clearly demonstrate the role of IH in sensory dysfunction, including description of the dermatomal distribution of pain symptoms and signs, corroborated with specific magnetic resonance imaging (MRI) imaging for haemosiderin.

Although SCI NP subtypes are classified as at- or below-level pain, measurement of evoked NP below an incomplete SCI is technically challenging when short test stimuli are adopted, due to different

degrees of sensory deafferentation.⁴ Recently, improvement of pinprick sensitivity below both complete and incomplete SCI⁵ and the description of evoked pain in response to topical application of capsaicin also applied below clinically complete SCI⁶ have demonstrated the potential of further developing sensory tests for NP clinical research. We hypothesized that the role of IH on residual ascending pain pathway function and NP perception could be better investigated with the application of tonic thermal test stimuli. This technique is known to induce temporal summation of psychophysically rated sensory responses⁷ and has been interpreted as evidence for central noxious sensitization, as demonstrated recently in two different pain pathologies.⁸ Here, we show that thermal quantitative sensory testing, using both short (1 s) and tonic (10 s) stimuli, demonstrates that IH leads to an increase in below-level cold pain threshold combined with widespread thermal allodynia.

MATERIALS AND METHODS

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this case report. All procedures were approved by the Toledo Hospital

¹Sensorimotor Function Group, Hospital Nacional de Paraplégicos, SESCAM, Toledo, Spain; ²Departamento de Enfermería y Fisioterapia, EU Enfermería y Fisioterapia de Toledo, Universidad de Castilla La Mancha, Toledo, Spain; ³Unidad de Resonancia Magnética, Hospital Nacional de Paraplégicos, SESCAM, Toledo, Spain; ⁴Unidad de Neurología, Hospital Virgen de la Luz, SESCAM, Cuenca, Spain and ⁵College of Dentistry, University of Florida College of Medicine, Gainesville, FL, USA
Correspondence: Dr J Taylor, Sensorimotor Function Group, Hospital Nacional de Paraplégicos, SESCAM, Finca 'La Peraleda' s/n, 45072 Toledo, Spain.
E-mail: jscott@secam.org or juliantaylorgreen@yahoo.es

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Ethics Committee, in compliance with the Helsinki Declaration. A 42-year-old woman suddenly complained of dysaesthesia that developed while house cleaning, which was initially perceived as a small uncomfortable back sensation. Within 5–6 days dysaesthesia had developed into a general ‘sharp’ pain localized at the Th6 dermatome, accompanied by general weakness and fatigue of the left leg. At 2 weeks an uncomfortable chest sensation with evoked pain upon palpation was present, in addition to urinary incontinence. At this time she was diagnosed with IH by MRI at the local hospital. At 2 months ‘burning’ pain was present. The local hospital then extirpated the Th5 haemangioma.

At 8 months following initial dysaesthesia, the individual with SCI was admitted into the Hospital Nacional de Paraplégicos de Toledo (HNPT). This person was recruited for the study following written informed consent. A T2* susceptibility weighted image (SWI Siemens Trio 3T) MRI sequence revealed a hypointense haemosiderin-rich area extending from C7/Th1–Th8 (Figure 1a), while a Th6 ventrally projected central hypointense area was also detected with T2 turbo spin echo axial imaging (Figure 1b). No radiological evidence of spinal compression or ischaemia was obtained. SCI due to IH, as measured with the American Spinal Injury Association Impairment Scale (AIS), was diagnosed neurologically at this time as sensory incomplete (AIS-C) with a Th2 neurological level,⁹ that included loss of sensitivity to light touch and pinprick over the right leg (Figure 2a), and mechanical hypoaesthesia over most of the left leg (Figure 2a). Normal median nerve sensory evoked potentials were recorded from Cz’ when referenced to Fz in response to stimulation at 5 Hz with 0.2 ms pulses.¹⁰ Lower limb sensory evoked potentials evoked from the posterior tibial nerve were absent. In addition left lower limb muscle hypertonia was diagnosed at the left ankle joint (2/5 Ashworth score)¹¹ accompanied by an increase in lower limb tendon reflexes (3/4). Mild left leg painful spasms (1/4 Penn score)¹² were also identified.

Thermal detection and pain thresholds were tested following initial neurological examination in a dedicated 1 h psychophysical testing session using a computer controlled thermode,⁷ with the application of short 1 s stimuli every 5 s at the C7, Th6 and L5 dermatomal levels. Thresholds were detected with the method of levels¹³ and defined when >5 of 6 sensory responses were detected by the patient. Normal thermal threshold data was generated specifically for this case report following signed informed consent from 10 healthy subjects recruited from the HNPT. The thermal detection and pain threshold method used with the peltier device⁷ is known to generate high heat and low cold pain thresholds (Figure 2e, personal communication CV).

Figure 1 Haemosiderin-rich magnetic resonance images. (a) T2* susceptibility weighted image (SWI Siemens Trio 3T) MRI sequence imaging revealed a hypointense haemosiderin-rich area extending from C7/Th1 to Th8, predominantly on the left side, and a loss of tissue at the Th5 spinal level corresponding to the original cavernoma and surgical site. (b) T2 turbo spin echo axial imaging revealed a Th6 ventrally projected central hypointense area probably adjacent to the original extirpated cavernoma site, and a posterior isointense image, possibly corresponding to gliotic intramedullary tissue. No radiological evidence was identified for compression or ischaemia.

In a separate 1 h psychophysical testing session also performed at 8 months following initial dysaesthesia, sensory ratings in response to tonic 10 s 48 and 3 °C stimuli were recorded with an electronic Visual Analogue Scale (eVAS) potentiometer, before and up to a minimum of 120 s after the application to the C7, Th6 and L5 dermatomes. eVAS data were subsequently integrated for quantification (Spike 2, CED, Cambridge, UK, Figure 3). The eVAS was anchored by the descriptors ‘no sensation’ (0) up to ‘maximum pain imaginable’ (10), with pain threshold set as (2/10),⁷ which facilitated innocuous and painful sensation ratings.

RESULTS

Standard neurological examination at the HNPT identified the presence of intense non-evoked NP within the Th6 dermatomal level and lower legs (Figure 2b) 8 months after initial dysaesthesia complaint. Non-evoked NP was described by the individual in her own words as ‘presión-pressure’ and ‘quemazón-burning’ pain, accompanied with the sensation of infrequent itch sensations above the IH. In addition neurological testing identified evoked at-level (Th5) and below-level pain (left S1 dermatomal area) to pinprick (Figure 2c). Quantitative sensory testing with five coarse brush strokes (3 × 3 cm wide, medium stiffness) applied within the corresponding AIS sensory testing points failed to evoke mechanical allodynia either at- (Th5) or below-level (left L5), although a paradoxical cold sensation was noted with brush applied below the IH. Furthermore, quantitative sensory testing failed to evoke pain in response to five applications of a 512-mN von Frey filament during 1 s within the left L5 AIS sensory testing point, although a slow temporal summation of sensory perception of evoked pain, as rated with a 0–10 numerical rating scale (see protocol for eVAS descriptors) during 50 stimuli applied every second (0–0/10, 10–1/10, 20–2/10, 30–2/10, 40–2.5/10 and 50–2.5/10).

The 7-day numerical rating score for non-evoked at-level pain intensity was high (8–10/10) and was accompanied by maximum pain unpleasantness (10/10). The SF-McGill questionnaire¹⁴ identified severe scores for the descriptors of ‘hot-burning’, ‘aching’, ‘tender’, ‘tiring-exhausting’, ‘fearful’, ‘punishing-cruel’ during the previous week, while pain adjectives such as ‘sharp’, ‘gnawing’, ‘heavy’, ‘sickening’ were also present and rated as moderate. Application of the Spanish version of the DN4 questionnaire¹⁵ indicated the presence of below-level NP (7/10), which was described as ‘burning’, ‘cold pain’, ‘tingling’, ‘pins and needles’ with ‘numbness’, and which was accompanied by hypoaesthesia to touch and pinprick (left L5 AIS sensory testing point). Interestingly, the DN4 questionnaire failed to detect NP at the level of SCI based on descriptors, although touch hypoaesthesia was detected for this pain subtype. No cognitive impairment was detected with the Spanish version of the Mini-Mental State Examination (Mini-Examen Cognoscitivo, 33/35),¹⁶ which has previously been identified in NP patients.¹⁷ As such, thermal psychophysical sensory rating and pain questionnaire data generated by this individual were unlikely to be unduly affected by cognitive impairment. However, measurement of anxiety as a NP comorbidity, performed with the Spanish version of the State-Trait Anxiety Inventory¹⁸ (as recommended by the IMMPACT group),¹⁹ detected a moderate level for this case report (State: 50, Trait: 21). Associated pain aggravating factors identified by the individual included fever, anger/anxiety, smoking, full bladder, extended sitting and spasms. Lastly, trunk and leg movement was noted to produce a sharp pressure-like pain intensity of 5/10 measured on the NRS. Standard pharmacological treatment with Pregabalin at this time provided some relief of at-level pain.

In the first psychophysical thermal sensory testing session, cold detection and heat pain thresholds were measured within the normal

Figure 2 NP distribution and quantitative sensory examination following IH. (a) Dermatome mapping of sensory abnormalities identified an area of hypoaesthesia to light touch and pinprick (black, left leg) and loss of touch and pinprick sensitivity (grey, right leg). (b) Non-evoked and (c) evoked pain to a high intensity mechanical punctate filament 512 mN (Optihair von Frey filament, Marstock Nervtest, Marburg, Germany) were present at and below the IH. (d, e) Patient thermal detection and pain thresholds (black line) were compared with the 25 and 75th percentile range of the median normal ratings (shaded areas) following application of a 1 s pre-heated or cooled thermode applied to the C7, Th6 and L5 dermatomal levels. Thermal quantitative sensory testing revealed below the IH an increase in heat detection threshold (d) and an elevated cold pain threshold (e).

range (Figures 2d and e). At-level cold and heat detection and pain thresholds in the patient were normal (C7 and Th6, Figures 2d and e). Below-level (L5) cold detection and heat pain thresholds were also normal (Figures 2d and e). However, an increase in left L5 heat detection threshold (Figure 2d, 47 compared with 38 °C) and cold pain threshold were identified (16 compared with <3 °C, Figure 2e).

In the second psychophysical sensory testing session the individual rated the application of tonic 10 s 48 °C stimuli as painful (heat allodynia) when applied at all dermatomal levels, compared with non-painful ratings made by healthy subjects (Figure 3, eVAS integral and duration were 9–13-fold and 3–4-fold greater than normal eVAS ratings, respectively). Cold allodynia was identified at all dermatomal levels following application of 10 s 3 °C stimuli (Figure 3, eVAS integral and duration were 3–64-fold and 1.5–3-fold greater than normal eVAS ratings, respectively).

DISCUSSION

Collectively the general pain history, dermatome mapping of specific SCI pain types, thermal quantitative sensory testing of allodynia and

identification of spinal haemosiderin, led to a definite diagnosis of NP³ following extensive C7–Th5/6 IH. In contrast, to at-level SCI pruritis reported by Dey *et al.*,² itch sensation was only observed infrequently above the IH in our case study. The increase in below-level cold pain threshold, accompanied by slow temporal summation to repeated mechanical punctate stimulation, also suggests that IH potentiates a change in nociception and pain perception, as originally suggested in the experimental animal model of haemotoxic SCI.¹ Indeed, the increase in cold pain and heat detection thresholds below the SCI are consistent with peripheral neuropathy and central injury sensory dysfunction, specifically when pathophysiological mechanisms of deafferentation and abnormal activity are known to be present at the injury site. Finally, the observation of widespread allodynia to tonic thermal stimuli at and below the IH also suggests that spinal haemorrhage leads to local and remote central sensitization.

Although haemorrhage within the CNS induces ectopic activity²⁰ and lipid peroxidation,²¹ specific pathophysiological mechanisms related to activation of glia²² and generation of free radicals²³ are also known to contribute to change in nociception after SCI.^{24,25}

Figure 3 Real-time eVAS intensity ratings (>2 = painful) to tonic (10s) thermal stimuli applied at and below the IH. Heat (48°C, left column) and cold (3°C, right column) tonic stimuli evoked allodynia (coarse grey broken line) applied at (C7–Th6) or below (Th10) the IH, when compared with the innocuous sensory ratings recorded from 10 healthy subjects (median: unbroken black line, 25–75th percentile range: grey shaded area). The delayed eVAS rating was particularly high when tonic cold stimulation were applied to the Th6 dermatomal level, which suggested hyperpathia (see inset for complete time course, patient cold-pain rating 322 VAS.s vs normal median rating of 5 VAS.s, 2–16). The patient's pain response to tonic cold was almost double her pain rating for tonic heat (patient heat-pain rating 188 VAS.s vs normal median rating 15 VAS.s, 12–18).

Analysis of specific pain symptoms and signs related to IH in this case study also indirectly suggests a role for neuroinflammation in the development of local and remote cold allodynia. Acute cerebrospinal fluid levels of the inflammatory cytokine tumour necrosis factor- α has been correlated with NP shortly after SCI,²⁶ specifically with perception of 'sharp' pain, which is similar to the sensation described by our patient during the first month. Cold sensitivity in naïve rats is increased after spinal injection of the C5a complement component,²⁷ while it is reduced in tumour necrosis factor- α receptor-deficient mice following peripheral nerve injury.²⁸ Interestingly, spinal dorsal horn neuronal hyperexcitability to cold stimuli has been recorded in rats following experimental ischaemic SCI,²⁹ which most probably involves a component of IH. At the clinical level spinal IH amplification of sensory input would be expected to potentiate the impact of SCI pain evoked by cold ambient temperature and other aggravating factors,³⁰ similar to that described by this individual.

This case study is also novel in that both at- and below-level thermal allodynia were better detected with psychophysical sensory rating of tonic thermal stimuli, when compared with the presentation of short 1 s stimuli used for pain threshold testing. Furthermore, tonic thermal stimulation evoked an exquisite at-level Th6 cold pain rating after IH, when compared with sensory ratings evoked from the adjacent C7 and Th10 dermatomal levels. Future clinical research studies should examine the utility of tonic thermal stimuli for dermatomal mapping of change in nociception and pain relative to the neurological level of SCI. Such a study would be useful to determine the role of spinal pathophysiological mechanisms of NP following different types of SCI, such as compression, ischaemia and haemorrhage.

To summarize, although dysaesthesia, itch and pain have been previously described following IH,² here we confirm the diagnosis of NP symptoms and signs at and below spinal haemorrhage using a graded sensory testing regime.³ The development of dysaesthesia and

non-evoked NP may reflect rapid sensitization of local and supraspinal pain-processing centres, as observed previously with the experimental haemotoxic SCI animal model.¹ Given the high impact of IH on NP development, we believe that better radiological identification of spinal haemosiderin could markedly improve the management of NP following SCI.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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