Central Neuropathic Pain in Multiple Sclerosis Results from Distinct Thoracic Spinal Cord Lesions

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BACKGROUND

•Approximately 30-40% of patients with multiple sclerosis (MS) suffer from central neuropathic pain (CNP), usually focused symmetrically in both feet and legs and often accompanied by cold allodynia and deep hyperesthesia.

•Sympathetic interneurons in the mid-thoracic intermediomedial and intermediolateral (IMM/IML) neurons project to brainstem but not the thalamus, implying they could be involved in homeostatic sensory integration at both brainstem and spinal levels.

•We hypothesized that ascending projections from lumbosacral lamina I neurons to bilateral mid-thoracic autonomic nuclei are mirrored by descending projections; thus, a mid-thoracic lesion that damaged bilateral autonomic descending projections to lumbosacral lamina I neurons might underlie bilateral central pain in MS.

•The lesion in the mid-upper thoracic cord could interrupt the homeostatic integration pathway between the parabrachial nucleus in the brainstem, the IMM/IML region of T2-6 segments of the spinal cord, and lumbar lamina 1.

Table 1. Demographic data of MS patients with and without Central Neuropathic Pain (CNP)

	(+) CNP	(-) CNP
Cohort	N=32	N=30
Median Age*, years (interquartile range)		
MS diagnosis	34.6 (27.4-45.5)	36.6 (31.6-47.1)
First clinical Symptom	33.2 (23.1-44.3)	35.9 (27.81-44.05)
Gender, female (%)	23 (73)	22 (73)
Race/ethnicity, No. (%)	White, 26 (81.3) African American, 2 (6.3) Hispanic, 4 (12.5)	White, 22 (73.3) African American, 1 (3.3) Hispanic, 5 (16.7) Native American, 1 (3.3) Middle Eastern, 1 (3.3)

Table 2. Clinical and radiological characteristics of MS patients with and without CNP

	(+) CNP	(-) CNP
Multiple sclerosis subtype		
Relapsing- remitting, No. (%)	22(68.8)	27 (90)
Secondary-progressive, No. (%)	8 (25)	1 (3.3)
Primary progressive, No. (%)	2 (6.2)	2 (6.7)
Disease duration, years (interquartile range)	4.7 (2.5-12.8)	2.0 (0.7-7.2)
Clinical follow-up time, years (interquartile range)	2.2 (0.5-4.8)	0.9 (0.5-5.3)
MRI thoracic spinal cord		
Presence of thoracic spinal cord lesion, No. (%)*	31 (97)	15 (50)
Central thoracic spinal cord focus, No. (%)*	31 (97)	6 (20)
MRI thoracic lesion (T1-T6), No. (%)*	31 (97)	6 (20)
Contrast enhancement present on MRI:		
Brain, No. (%)	4 (13)	3 (10)
Cervical spine, No. (%)	1 (3)	2 (7)
Thoracic spine, No. (%)	2 (6)	0 (0)
Abnormal cerebrospinal fluid profile, No. (%)	18 (90)	14 (78)
Exposure to DMT, No. (%)	29 (91)	23 (77)

DMT = disease modifying therapy
*p < 0.001

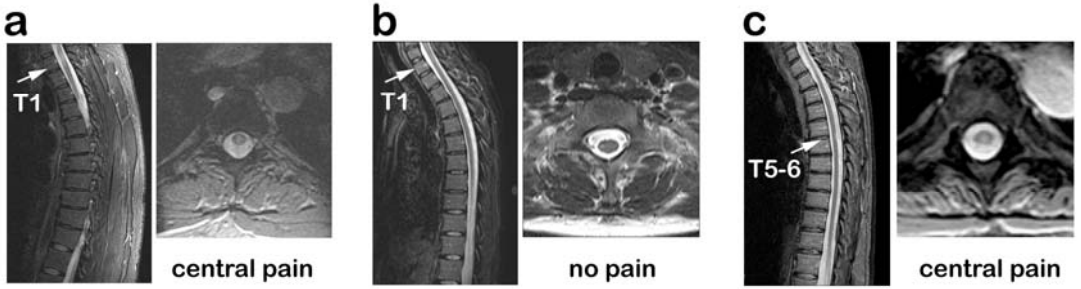

Figure 1: **Clinical Evidence.**

(a) Sagital short inversion time inversion recovery (STIR) MRI sequence of the thoracic spinal cord demonstrating a focus of hyperintensity at T1 in a 38-year-old man diagnosed with MS (1999) and central neuropathic pain, and axial T2-weighted gradient-echo (GRE) MRI of the T1 lesion demonstrating a central hyperintense focus within the upper thoracic spinal cord.

(b) Sagital STIR MRI of the thoracic spine demonstrating a focus of hyperintensity at T1 in a 40-year-old woman with demyelinating disease without central neuropathic pain, and axial T2-weighted turbo spin-echo MRI of the T1 lesion demonstrating a small hyperintense focus positioned at the right lateral aspect of the spinal cord.

(c) Sagital STIR MRI of the thoracic spine demonstrating a focus of hyperintensity at T5-6 in a man with demyelinating disease with central neuropathic pain, and axial T2-weighted turbo spin-echo MRI of the T5-6 lesion demonstrating a central hyperintense focus within the mid-thoracic spinal cord.

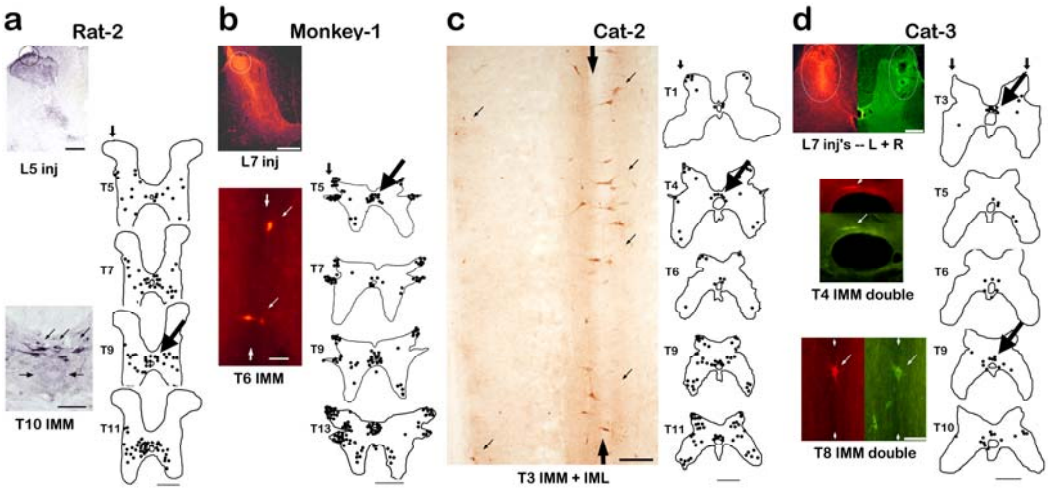

Figure 2: **Neuroanatomical evidence.**

(a) An iontophoretic injection of CTb in lamina I of the left L5 segment in rat-2 produced retrogradely labeled neurons bilaterally in the intermediate zone and VH of thoracic segments. The lower photomicrograph shows labeled IMM cells at T10 in a transverse section. In all drawn figures, dots represent location of labeled cells, diagonal arrows indicate labeled cells in central canal and vertical arrows indicate injection sites.

(b) Pressure injections (5) of 200nL Alexa546-dextran(10K) in the left superficial L7 dorsal horn of monkey-1 produced retrogradely labeled neurons concentrated in lamina I and the autonomic nuclei of thoracic segments. The lower photomicrograph shows labeled cells in the T6 IMM in a horizontal section.

(c) Pressure injections (3) of 100nL CTb in the left superficial L7 dorsal horn produced retrogradely labeled neurons in lamina I, the IMM and the IML of thoracic segments. The photomicrograph shows labeled cells in the T3 IML and the IMM in a horizontal section.

(d) Pressure injections (3) of 500nL Alexa546-dextran(10K) in the left L7 dorsal horn and (5) of 500 nL LuciferYellow-dextran(10K) in the right L7 dorsal horn produced retrogradely double-labeled neurons concentrated in the IMM of thoracic segments. The photomicrographs show double-labeled cells in the T4 IMM (transverse) and the T8 IMM (horizontal).

VH = ventral horn, IMM = intermediomedial, IML = intermediolateral.

DESIGN/METHODS

Parallel clinical and neuro-anatomical studies were performed. A clinical investigation of consecutively acquired MS patients with and without CNP within a single MS center was pursued. A multivariate logistic regression model, incorporating significant covariates, was used to assess the relationship between an upper central thoracic spinal cord focus and CNP.

To identify the hypothesized autonomic interneurons with bilateral descending projections to lumbosacral sensory neurons, anterograde and retrograde labeling experiments with CTb and fluorescent tracers were performed in three animal species.

RESULTS

•MS patients with CNP are distinguished by the presence of a lesion focused in the center of the mid-thoracic spinal cord, and neurons with bilateral descending projections to the lumbosacral superficial dorsal horn are concentrated in the autonomic IMM nucleus surrounding the mid-thoracic central canal. (See figure 1).

•Clinical data were available in MS patients with (n=32; F:23; median age: 34.6y (range:27.4-45.5)) and without (n=30; F22; median age: 36.6y (range:31.6-47.1)) CNP (See table 1). The value of a central focus between T1-T6 in relation to CNP demonstrated a sensitivity of 96.9% (95% CI: 83.8-99.9) and specificity of 83.3% (95% CI: 65.3-94.4). A significant relationship between CNP and the presence of a centrally located focus within the thoracic spine was also observed (OR: 155.0 [95% CI lower limit: 16.0]; p<0.0001, 2-tailed Fisher exact test) (See table 2).

•In all animal models, neurons with bilateral descending projections to the lumbosacral superficial dorsal horn were concentrated in the autonomic intermediomedial nucleus surrounding the mid-thoracic central canal (See figure 2).

CONCLUSIONS

The association of centrally positioned upper-thoracic spinal cord lesions to central pain, coupled with the neuroanatomical data provide extremely strong evidence for the etiology of central neuropathic pain, for which no explanation has been previously available. These data can not only lead to advances in our understanding of the pathogenesis of central pain in MS but can also enable specific development of effective symptomatic approaches toward relieving the disabling pain and suffering experienced by this patient population.

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