CASE REPORT

Dopaminergic treatment of restless legs syndrome in spinal cord injury patients with neuropathic pain

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Recent studies report high incidence of restless legs syndrome (RLS) in patients with spinal cord injury (SCI), who may also present pain and sensory disturbances. In the present manuscript, we examine and discuss diagnostic and treatment challenges of comorbid RLS and neuropathic pain (NP) in SCI. We evaluated seven men with a mean age of 55.6 (s.d. = 14.0) years, with chronic complete or incomplete SCI at the thoracic or lumbar level, for complaints of sensory disturbances in the legs, which initially were attributed to drug-resistant NP. Because overlapped RLS was suspected, clinical evaluation of NP and RLS, serum ferritin and iron level assessment, and video polysomnographic (VPSG) studies were conducted. Pramipexole (0.18 mg q.d.⁻¹) was added to treat RLS, and a follow-up was performed at 2 months. We found that in six subjects the RLS was comorbid with NP and in one subject the symptoms of RLS were misdiagnosed as NP. VPSG revealed periodic limb movements (PLMs) in all patients, including PLMs of the legs, arms or both. Serum ferritin was $< 50 \text{ ng ml}^{-1}$ in two patients. RLS improved significantly after 2 months with pramipexole. On the basis of current findings, we recommend physicians to be aware of the comorbidity between RLS and NP secondary to SCI to include suitable diagnostic procedures and effective treatments.

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INTRODUCTION

Restless leg syndrome (RLS) is a sensorimotor disorder that affects 5–10% of the general population and has a substantial negative impact on sleep and quality of life.¹

The diagnosis is based on five essential criteria: (1) an urge to move the legs usually but not always accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs; (2) the unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting; (3) the urge to move the legs or the sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; (4) the urge to move the legs or the unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day; (5) the occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioral condition (for example, myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort and habitual foot tapping). When there is uncertainty regarding the diagnosis, clinical features supporting RLS include family history of RLS among first-degree relatives, periodic limb movements (PLMs), lack of profound daytime sleepiness and reduction in symptoms at least initially with dopaminergic treatment.¹

Isolated cases of RLS have been also reported in patients with spinal cord injury (SCI),^{2–7} but its diagnosis can be particularly challenging in individuals with a complete SCI with absent or reduced volitional motor activity in the affected limbs. In addition, excessive PLMs occurring in sleep¹ have been documented in patients with complete SCI using polysomnographic recordings.^{4,8}

Finally, concomitant pain or sensory symptoms related to SCI can make the diagnosis of RLS a challenge. Nilsson *et al.*³ reported four patients with SCI and RLS, who had been previously misdiagnosed with treatment-resistant neuropathic pain (NP) or spasticity, which responded satisfactorily to dopaminergic medication.

Here, we present seven patients with SCI with comorbid NP and RLS with a positive response to dopaminergic medication and discuss pathophysiological mechanisms of RLS in SCI with NP.

METHODS AND CLINICAL CASES

We retrospectively collected clinical information of seven male patients, aged 55.6 (s.d. = 14.0) years, evaluated at our hospital during the last year for chronic SCI at the thoracic or lumbar level with sensory symptoms in the legs consistent with RLS, although initially attributed to drug-resistant NP. NP was defined as pain in an area of sensory abnormality corresponding to the spinal cord lesion. Pain did not have any primary relation to spasms or any other movement and had to have started after the SCI, be present for at least 6 months and be unresponsive to adequate medication trials. Patients with severe pain of other origin, such as musculoskeletal pain, were excluded.⁹

RLS was diagnosed based on the criteria proposed by the International RLS Study Group.¹ If the patients were wheelchair-bound, we asked whether RLS symptoms appeared in situations in which they moved their arms/body less while sitting in a chair or when lying in bed. Patients were asked to describe (1) the location and characteristics of the sensory disturbances, specifically if the

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urge to move originated or spread from the legs to other parts of the body, and (2) maneuvers or tactics that they applied to achieve symptom relief.

The severity of the symptoms was assessed with the RLS severity scale (10 items, each item ranges from 0 to 4, and 40 as maximum score).¹⁰ Patients were offered the possibility to receive treatment with dopaminergic agonist (pramipexole), and a follow-up was set at 2 months. Numerical rating scale (NRS; 0 = no pain; 10 = the worse pain) was used to evaluate the severity of NP during the past 7 days, except for the worsening in the afternoon or at night, which was measured by the RLS severity scale.

The severity and level of SCI were assessed according to the American Spinal Cord Injury Association Impairment Scale (AIS) and the International Standards for Neurological Classification of Spinal Cord Injury: AIS-A, sensory and motor complete SCI; AIS-B, motor complete and sensory incomplete SCI; AIS-C, D, sensory and motor incomplete SCI; AIS-E, normal neurologic function.¹¹

All patients underwent blood testing for serum ferritin. A ferritin level $< 50 \text{ mcg l}^{-1}$ was considered clinically relevant for RLS.¹²

Video polysomnographic (VPSG) recordings and analyses of 8-h bedtime periods (usually from 23:00 to 07:00 hours) were conducted by a physician with expertise in sleep medicine (J.S.). Sleep stages were scored according to standard criteria¹³ and included superficial electromyography (EMG) of both anterior tibial muscles synchronized with audiovisual recording. PLMs were defined as a sequence of ≥ 4 consecutive movements during sleep associated with EMG activity in the tibial anterior muscle lasting 0.5–5 s, at an interval between 5 and 90 s. The PLM index was calculated as the number of PLMs per hour of sleep. On the other side, periodic movements in other parts of the body (upper limbs, trunk or pelvis) were evaluated using the synchronized audiovisual recording without calculating the PLM index.

After the diagnosis of RLS associated with symptoms of NP was suspected, pramipexole was administered (0.18 mg once daily) in all patients, and a follow-up was performed at 2 months.

RESULTS

Clinical and demographic characteristics of SCI patients with RLS are shown in the Table 1. The characteristics of the RLS are reported in Table 2.

CASE 1

A 66-year-old man with an incomplete thoracic SCI was complaining of daily electrical discharge and burning-like sensations in the legs, more severe in the right knee, which began a few months following injury. The symptoms were worse in the evening and at night when he was sitting or lying in bed and were relieved by moving the legs, walking or touching the floor with naked feet. The conventional treatment of NP provided an insignificant relief. After the RLS was diagnosed, the patient underwent treatment with pramipexole (0.18 mg daily) that led to 29% improvement in RLS according to the RLS severity scale (Table 2).

CASE 2

A 53-year-old man with a complete lumbar SCI developed tingling, electrical discharge and burning-like sensations in the sole of both feet, gastrocnemius and anus a few weeks following the injury, and the symptoms were present during the past 11 months. The symptoms usually began in the evening when he was sitting or lying in bed and worsened at night, causing difficulties falling asleep and an urge to move the legs or to touch the floor with naked feet to achieve partial relief. He was first diagnosed with NP and received different medications with mild improvement. After the RLS was suspected, the patients received pramipexole

Table 1. Demographic and clinical characteristics of SCI patients with RLS

Subject	Age (year)	Sex	Etiology	Duration of SCI (year)	Neurological level of lesion	AIS	AIS motor score: right/left L2, L3, L4, L5, S1	Serum ferritin (mcg l^{-1})	NP treatment
1	66	M	Trauma	19	Th12	D	5/5, 5/5, 4/5, 2/5, 3/5	97	Gabapentin; clonazepam; amitriptyline; pregabalin; carbamazepine; and epidural infiltration with corticosteroids.
2	53	M	Trauma	1	L3	A	5/5, 5/5, 5/5, 5/5, 4/4	168	Gabapentin, clonazepam and pregabalin.
3	60	M	Trauma	4	L2	D	4/4, 4/4, 0/4, 0/4, 4/4	68	Gabapentin, clonazepam, amitriptyline, pregabalin, tramadol, topiramate and paroxetine.
4	50	M	Trauma	2	Th12	A	0/0, 0/0, 0/0, 0/0, 0/0	530	Gabapentin and clonazepam.
5	41	M	Non-trauma	3	L2	D	5/5, 5/5, 5/4, 4/4, 4/4	485	Gabapentin, pregabalin, clonazepam, amitriptyline, oxycodone and tramadol.
6	40	M	Non-trauma	7	L3	C	5/5, 5/5, 0/4, 0/2 0/3	39	Gabapentin and clonazepam.
7	79	M	Non-trauma	7	Th5	D	5/5, 5/5, 5/5, 5/5 5/5	40	Gabapentin.

Abbreviations: A, complete SCI, no sensory or motor function is preserved in the sacral segments; AIS, American Spinal Cord Injury Association Impairment Scale; spinal cord injury (SCI); C, incomplete SCI, motor function is preserved below the neurological level, and more than half of the key muscles below the neurological level have a muscle grade ≥ 3 ; D, incomplete SCI, motor function is preserved below the neurological level, and at least half of the key muscles below the neurological level have a muscle grade ≥ 3 ; L, lumbar; M, male; NP, neuropathic pain; Th, thoracic.

Table 2. Characteristics of the RLS

Subject	Sensory symptoms	Localization	RLS duration (years)	Time of symptom worsening	Relief maneuvers	Video polysomnography PLMs	NRS for NP with pramipexole treatment		RLS rating scale (0–40) with pramipexole treatment		
							Before	After	Before	After	
Location							Index (mov h ^{−1})				
1	Electrical discharge and burning	Lower extremities, more severe in the right knee	2	Evening	Walking, moving the legs, putting naked feet on the ground	Legs	107.8	10	6	35	25
2	Tingling, electrical discharge and burning	Lower extremities	1	Evening	Moving the legs or putting the feet on the ground	Legs	63	8	3	32	16
3	Burning, electrical discharge and tingling	Right foot	1	Evening	Moving around, putting the feet on the ground	Arms and legs	9	10	1	30	9
4	Electrical discharge and cramps	Lower extremities, predominantly on the right calf muscle	2	Afternoon	Rubbing the thighs and knees and pressing the thighs	Arms and legs	15	10	3	27	8
5	Tightness, electrical discharge and burning	Lower extremities	3	Evening	Walking, moving around the legs, stretching and rubbing the knees	Legs	125	8	2	32	7
6	Tingling, crawling and electrical discharge	Soleus, tibial anterior muscle and feet	5	Evening	Moving around, stretching the feet, abduction and adduction of both hips and massaging the thighs	Legs	5	8	3	29	12
7	Burning and tingling	Lower extremities, predominantly in the right knee and ankle	2	Afternoon	Walking, moving the legs, massaging and rubbing the knee	NA	NA	8	5	29	10
Abbreviations: NA, not available; NP, neuropathic pain; NRS, numerical rating scale; PLMs, periodic limb movements; RLS, restless leg syndrome; TA, tibial anterior muscle. PLM index of lower limbs was calculated based on EMG, which was recorded only from TA. PLM index was calculated for lower limbs, but we also reported PLMs in the other part of the body, which were based on video PSG recordings.											

Abbreviations: NA, not available; NP, neuropathic pain; NRS, numerical rating scale; PLMs, periodic limb movements; RLS, restless leg syndrome; TA, tibial anterior muscle. PLM index of lower limbs was calculated based on EMG, which was recorded only from TA. PLM index was calculated for lower limbs, but we also reported PLMs in the other part of the body, which were based on video PSG recordings.

(0.18 mg daily), with 50% improvement according to the RLS rating scale (Table 2).

CASE 3

A 60-year-old man with an incomplete lumbar SCI complained of burning-like and paroxysmic pain sensations in the right foot, which started 3 years after injury. Usually the symptoms began in the evening when he was sitting or lying down and worsened around midnight. The sensation determined him to move around and touch the ground with naked feet. He was diagnosed with NP and different medications were administered, with mild improvement. After the RLS was suspected, pramipexole (0.18 mg daily) was administered, with 70% improvement in symptoms' severity, as measured by the RLS rating scale (Table 2).

CASE 4

A 50-year-old man with a complete thoracic SCI began to experience electrical discharge-like symptoms on his calf muscles 5 months following the spinal injury, predominantly on the right side, which usually started in the afternoon and worsened at night when he was resting. Rubbing the thighs and knees and pressing the thighs induced mild alleviation of symptoms. He was diagnosed with NP and was administered conventional treatment, with mild improvement. When RLS was suspected pramipexole was added to treatment, which determined a 70.4% improvement in the severity of symptoms according to the RLS rating scale (Table 2).

CASE 5

A 41-year-old man with an incomplete SCI was complaining of apparently continuous tightness and electrical discharge-like symptoms in the knees and burning-like sensation in the ankles, which began a few weeks after injury. The patient was diagnosed with NP and received treatment, with some improvement. A more detailed evaluation revealed that although the symptoms were continuous the patient experienced worsening in the evening at rest and that walking around, moving the legs, stretching muscle and rubbing the knees induced partial alleviation of pain. The administration of pramipexole led to a 78% reduction in RLS severity (Table 2).

CASE 6

A 40-year-old man with an incomplete SCI started complaining of tingling, crawling and electrical discharge-like symptoms in the legs a few months following SCI, and these symptoms had persisted for the past 5 years. The symptoms were present during the whole day, with worsening in the evening while sitting or lying down. The severity of symptoms was partially improved by moving around, strengthening the feet, doing abduction and adduction movements of the hips or massaging the thighs. The antiNP treatment led to an insignificant relief. We also suspected RLS therefore pramipexole was added to the treatment, which determined a 58.6% improvement of symptoms according to the RLS rating scale (Table 2).

CASE 7

A 79-year-old man with a thoracic incomplete SCI presented with burning, tingling and pressure-like sensation in his legs, from the pelvis to feet, predominantly in the right knee and ankle that started 5 years after spinal injury. The symptoms were continuous but worsened in the afternoon at rest. He was diagnosed with NP and received conventional treatment. A more detailed assessment of the symptoms revealed that walking around, moving the legs,

massaging or stretching the muscles and rubbing the knee induced partial improvement of symptoms. We suspected RLS and added pramipexole to his treatment, which led to 54% improvement in RLS according to the RLS rating scale (Table 2).

SLEEP STUDY: VIDEO POLYSOMNOGRAPHY

PLMs were recorded in all patients with at least some preserved activity in the tibial anterior muscles (Table 1). Most subjects had PLMs only in the lower limbs (subjects 1, 2, 5 and 6). In subject 4 with complete SCI, VPSG showed rhythmic arm movements on both sides. In subject #3, VPSG showed rhythmic leg movements and EMG activity in the left tibial anterior muscle, which had some preserved function, and also rhythmic arm movements on both sides. PLMs of the tibial anterior muscle were also observed in subject #6 on the left side, which had some preserved function, but not on the right side. In addition, this patient presented rhythmic pelvis movements just before falling asleep.

Only two patients showed ferritin level $< 50 \text{ mcg l}^{-1}$ (Table 1).

DISCUSSION

This article presents a case series of patients with RLS secondary to SCI that was challenging to diagnose because of the motor impairment and comorbid NP. Initially, the patients presenting pain below the level of SCI were diagnosed and treated for NP, with an insignificant relief. However, because the sensory complaints appeared to worsen at rest, during the evening or at night and were alleviated by movements, the RLS was suspected. VPSG revealed that depending on the severity and/or level of SCI, patients presented rhythmic movement of the upper or lower limbs or pelvis just before falling asleep or during sleep. The improvement of sensory symptoms with dopamine agonist was useful as a supportive diagnostic criterion of RLS. In addition, the dopamine agonist has also significantly reduced the comorbid NP.

Common and uncommon symptoms in RLS and NP

NP is a common complication of the SCI, and most patients report more than one pain problem.¹⁴ The diagnosis of NP, according to the International Spinal Cord Injury Pain (ISCI-P) Classification, is based on complaints of pain/sensory symptoms at or below the level of spinal lesion that should be confirmed by neurophysiologic or neuroimaging studies or surgery, the presence of sensory alterations distributed similarly to the symptoms of pain and the exclusion of nociceptive or peripheral NP is also required. The supportive criteria include a delayed onset of pain symptoms, non-related with movements or inflammation, and the presence of positive sensory symptoms.¹⁵ RLS-related sensory symptoms typically are symmetrically located in the lower extremities, but asymmetric distribution was also reported in patients with more severe forms or late-onset RLS.^{16,17} Although the sensory symptoms of RLS in patients with SCI could also meet the basic criteria for NP, the careful evaluation of the supportive criteria could increase the diagnosis accuracy. The predictive utility of verbal descriptors to distinguish between neuropathic and non-NP types is limited,^{15,18} as most individuals with SCI report more than one pain problem.¹⁴ When asked to identify each different chronic pain experienced in a group of 194 SCI patients, the majority (80.9%) reported more than one type of pain, and 'burning,' 'aching' and 'sharp' were the most frequent descriptors used.¹⁹ Interestingly, most patients with RLS report spontaneous 'electrical,' 'prickling,' 'burning,' 'tingling' and 'itching' sensations that can be easily confounded with symptoms of NP²⁰ and the presence of other symptoms, and objective signs in the legs suggest that neurologic deficit may lead to false-negative diagnosis of RLS.²¹ In our study, most frequently patients described their sensory symptoms as 'electrical discharges',

'burning' or 'tingling' sensations, which were localized either symmetrically or asymmetrically in the lower limbs, and the distribution was similar to that of the NP. Most patients with RLS often have to use analogies or emotive/affective words as descriptors so that differentiating between pain and dysesthesia can improve the characterization of sensory sensations in RLS.²²

The high incidence of RLS in SCI has been recently reported,¹² and the sensory symptoms of RLS are similar to NP.¹² One of the determinant criteria in the differential diagnosis between RLS and NP could be the relationship between the sensory complaints and movement. The 'urge to move the legs' that induces alleviation of the unpleasant sensations is the core symptom in the RLS and was reported by all patients evaluated in the present study. On the contrary, NP does not improve with movements⁹ or can even be exaggerated in response to imagined movements,²³ whereas the musculoskeletal pain is usually worsened by movement and reduced with rest.²⁴

In addition to the characteristics of the sensory disturbances and the alleviation of symptoms with movement, changes in the intensity of symptoms with circadian rhythm made us suspect the presence of RLS. All the patients in the present study experienced pain worsening in the evening or at night. Similar temporal profile of pain intensity was also described in subjects with diabetic neuropathy and postherpetic neuralgia and appears to be unaffected by treatment.^{25,26} Yet, these pathologies were excluded in our patients.

Spinal disinhibition/ hyperexcitability in RLS and NP

A recent functional magnetic resonance imaging study revealed maladaptive neuroplastic changes in the thalamocortical circuits in drug-free RLS patients, which correlated with the severity of RLS symptoms and therefore may account for the sensory alteration in RLS.²⁷ However, similarly to our study, RLS was also reported in individuals with complete lesion of the motor and sensory pathways. An increased spinal motor neuron excitability has been suggested as a potential mechanism for movement generation in PLMS in RLS.^{28,29} Disconnection from higher nervous structures might disinhibit motor spinal generators because PLM can be observed in the absence of volitional activity or changes in autonomic function,^{4,6} which is in accordance with VPSG findings in our study.

Spinal disinhibition could also have a relevant role in the development of sensory disturbances associated with the RLS. Recent research showed that individuals with idiopathic RLS present a generalized pin-prick hyperalgesia, more pronounced in the lower limbs,^{30,31} hyperalgesia to blunt pressure, hyperesthesia to vibration,³⁰ reduced thermal pain thresholds and greater temporal summation of heat pain relative to controls, which suggest that central sensitization mechanisms could be involved in the development of the RLS-related sensory symptoms.³²

Role of the dopaminergic system in RLS and NP

Alterations in the dopaminergic system functioning are considered a relevant pathophysiological mechanism of primary RLS, and the reduction in related motor and sensory symptoms with dopaminergic treatment supports the diagnosis. However, the role of dopamine in pain modulation and sensory perception alteration mechanism is not completely understood. Dopaminergic innervation of the spinal cord is largely derived from the supraspinal structures and mainly acts on postsynaptic substantia gelatinosa neurons.³³ Administration of dopaminergic agonists modulates cold and tactile allodynia,³⁴ and reduces spinal nociceptive responses to thermal and chemical irritants.^{35,36} In the present study, besides the relief of the RLS-related sensory symptoms, which supported the diagnosis, pramipexole administration also led to an improvement in the severity of NP. Although there is no evidence for dopamine deficiency associated with SCI,

the positive response to dopaminergic medication in individuals with comorbid deafferentation pain and RLS^{37,38} suggests that maladaptive neuroplastic changes in the spinal dopaminergic system could be involved in common pathophysiological mechanisms of RLS and NP.

CONCLUSIONS

RLS may develop in SCI patients who also suffer from NP, causing confusion between symptoms. PLM, as documented by video polysomnography, can involve muscles above the SCI level, suggesting widespread hyperexcitability/disinhibition of spinal circuits. Given the comorbidity of RLS and NP and their positive response to dopaminergic medication, future researches should evaluate the role of dopamine-mediated circuits in the maladaptive neuroplasticity and spinal hyperexcitability/disinhibition underlying RLS and NP.

COMPETING INTERESTS

The authors declare no conflict of interest.

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