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Case Scenario: Anesthetic Implications of Restless Legs Syndrome

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RESTLESS legs syndrome (RLS) is characterized by sensory (urge to move, usually associated with legs paresthesia and dysesthesia) and motor (voluntary and involuntary leg movements) symptoms occurring selectively when the individual is at rest, during the evening and night. This neurologic, dopa-responsive condition is common, especially in middle-aged women, yet poorly recognized. Acute exacerbation of RLS may occur in perioperative settings because it is worsened by immobilization, perioperative use of neuroleptics and antihistamines, withdrawal of dopaminergic agents, sleep deprivation, and blood loss. The patients become agitated, with limb jerks, generalized akathisia and major pain, possibly leading to surgical consequences. The purpose of this Case Scenario is to highlight the anesthetic implications of RLS.

Case Report

A 74-yr-old woman experienced an acute exacerbation of RLS during surgery for breast cancer. She suffered for 12 yr from familial, idiopathic RLS and was treated for 3 yr with small doses of pramipexole (0.09 mg at 6 PM and 0.18 mg at 10 PM), a dopamine agonist. She initially described the leg sensations as “a kind of bone tingling,” irradiating from the

ankles to the lumbar area, accompanied by an irresistible need to move. She spent 2 h per night on an exercise bike in her room to alleviate the leg restlessness. During the nighttime video and sleep monitoring, she had a long sleep onset latency (150 min) with frequent voluntary movements before sleeping, and involuntary, periodic movements (foot and leg flexion) repeated every 20 s when asleep (fig. 1). She used to sleep 4 h per night. Once she had been treated with pramipexole, she achieved complete relief of symptoms and slept all night long. During a systematic mammography, an abnormal nodule was discovered in the left breast. A nodulectomy with breast conservation and axillary dissection under general anesthesia was scheduled. She mentioned her RLS during the preoperative anesthetic evaluation. The patient came to the hospital the day before surgery and received oral hydroxyzine (100 mg) as a premedication at 8 PM. Although she had taken her usual dose of pramipexole at 6 PM and 10 PM, she experienced unbearable discomfort in the legs for the remainder of the night, which is associated with deep sensations of electrical shock in the legs, which radiated to the thighs and forearms. She stood up, walked in the corridor all night long, and continuously scraped together her legs and forearms. As soon as she stopped walking, the paresthesia returned. She spent the night battling total and distressing insomnia. The next morning, she received intravenous general anesthesia including propofol (100 mg), midazolam (5 mg), sufentanyl (20 μ g), and droperidol (0.5 mg). The patient was then intubated and mechanically ventilated. The surgeon removed the breast nodule (an epithelial, infiltrating cancer classified as T3N0M0) and axillary lymph nodes. After surgery, the patient was transferred to the postanesthesia care unit. As she woke up, she experienced intense and diffuse pain in all the four limbs. The pain radiated to the back and was associated with feelings of electrical shocks and involuntary, symmetrical limb jerks. She could not refrain from moving. She developed tachycardia and systolic hypertension at 240 mmHg. One hour after she arrived in the postanesthesia care unit, a large, subcutaneous hematoma appeared during motor restlessness; the scar was breached. She was taken back to the operating room for evacuation of

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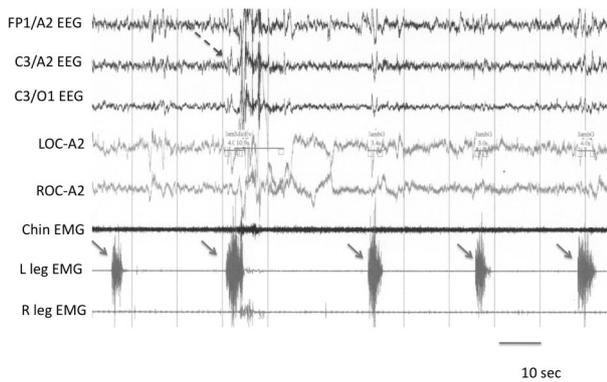


Fig. 1. Repeated ($n = 5$, plain arrows), involuntary periodic leg movements during non-rapid eye movement sleep stage N2 in the patient with restless legs syndrome, causing in 1/5 movements a brief cortical arousal (broken arrow). The sleep and movement recordings last 2 min and show, from the top to the bottom: 3 frontal (FP1/A2), central (C3/A2), and posterior (C3-O1) electroencephalography (EEG) bipolar channels, with a mastoid (A2) reference; 2 channels monitoring the eye movements (LOC/A2 and ROC/A2); and 3 channels monitoring the surface electromyography (EMG) of the chin and the right and left EMG of the tibialis anterior muscles. L leg = left leg; LOC = left oculogram; R leg = right leg; ROC = right oculogram.

the hematoma. Hemostasis was secured, and the superficial sutures were reset. The distressing sensations lasted until the middle of the next night. The RLS remained poorly controlled for 1 month after surgery, despite a transient increase in the pramipexole dose, with restlessness occurring earlier (at 7 PM) and chronic insomnia. The patient's physician controlled the serum ferritin level, which was low (22 mg/ml). After combining oral iron with pramipexole, the patient resumed her basal, painless condition 6 weeks after surgery. She reported the experience as "suicidal-like" and asked the neurologist to provide a letter about the risk of exacerbating RLS for the next anesthesia perioperative procedure.

Discussion

Important issues to consider in this case include the following:

What is RLS?

RLS is a sensory-motor disorder characterized by an urge to move the limbs (classically the legs), typically associated with unpleasant sensations. The symptoms develop electively during inactivity, worsen during the evening or the night, and are alleviated by movement (walking or stretching the legs).¹§ The international criteria used to define RLS, as well as supportive criteria, are indicated in table 1. The leg sensations are usually deep and bilateral, mostly located between the knees and the ankles, and described as creepy, crawly, itchy, or even painful. Although it is not mandatory for the diagnosis of RLS, 80% of patients also experience some involuntary leg or foot jerks, typ-

ically repeated every 5–90 s during sleep (called periodic leg movements during sleep) and sometimes occurring while the patient is awake during evening rest. There is a family history of RLS in most idiopathic cases, and neurologic examination of the limbs is normal. In addition to the discomfort and pain, the syndrome impacts sleep, causing organic insomnia, abnormal movements during sleep, daytime tiredness, irritability, depressed mood, and altered quality of life. The disease affects children and adults of both sexes but is twice as frequent in women and increases with age. Vulnerable groups include pregnant women,² mothers of several children,³ patients with renal failure,⁴ and patients with hereditary neuropathy.⁵

How Can an Exacerbation of RLS Be Diagnosed during a Perioperative Procedure?

Acute exacerbation may occur during perioperative procedures in patients with previously diagnosed, severe RLS or in patients who have a previously undiagnosed or mild form of RLS as a consequence of various factors (including drug changes). The sensitive and motor symptoms of RLS exacerbation are described as painful with sudden-onset changes in the quality and increased intensity of the sensations (in this case, a shift from paresthesia to "suicidal-like" dysesthesia and pain), extension in their topography to the upper limbs (in this case, to the whole body), a shift in timing from evening/night-time to night and day, and newly apparent limb jerks (table 2).

What Are the Factors of Perioperative Procedures that Can Exacerbate RLS?

The perioperative conditions expose patients with RLS to acute exacerbation because they combine procedure-related (immobilization, insomnia, and blood loss) and drug-related factors. The drug changes are the most important exacerbating factors. Immobilization, a potent trigger of RLS, is frequent during perioperative procedures. Accordingly, RLS exacerbation has been reported in patients under locoregional anesthesia,⁶ in patients who undergo minor surgical procedures under local anesthesia and who are instructed not to move, and when the legs are maintained in a plaster cast. Notably, one patient reported: "I had a strong desire to move my legs but could not because of the motor block."⁶ Whether spinal anesthesia may induce RLS beyond the immediate postoperative day remains a matter of debate^{7,8} and may depend on the systematic use of parenteral opioids, which unmask RLS symptoms.⁹ Perioperative movements may dramatically alter the results of the surgical procedure, especially during microsurgery.

Insomnia is generally caused by RLS sensations, but the poor sleep caused by perioperative stress and pain may also exacerbate RLS. RLS symptoms can be triggered or worsened in the presence of iron deficiency, especially if there is acute blood loss during surgery. The severity of the syndrome parallels ferritin levels in the serum and, even more closely, levels in the cerebrospinal fluid.¹⁰ This deleterious consequence can last several weeks until the iron deficiency is compensated.

The drug-related causes of RLS exacerbation include the sudden discontinuation of oral RLS treatment and the use of

§ http://www.ninds.nih.gov/disorders/restless_legs/detail_restless_legs.htm. Accessed March 30, 2010.

Table 1. Clinical Features of Restless Legs Syndrome

Diagnostic features (mandatory for a definite clinical diagnosis)

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs
2. The urge to move or unpleasant sensations begins or worsens during periods of rest or inactivity, such as lying or sitting
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching
4. The urge to move or unpleasant sensations are worse in the evening or night compared with during the day, or they only occur in the evening or at night

Supportive clinical features (may increase the probability of a diagnosis in doubtful cases)

1. Positive family history
2. Positive response to dopaminergic therapy
3. Presence of periodic limb movements (during wakefulness or sleep)

Associated features (typical but do not contribute to diagnosis)

1. Variable clinical course, but it is typically chronic and often progressive
2. Physical examination normal in idiopathic or familial forms
3. Sleep disturbance is a common complaint in more affected patients

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drugs that trigger RLS. When the oral dopamine agonist or opiate is withdrawn, a rebound, acute RLS can be observed, especially in patients with severe RLS. The half-life of these treatments is usually short and does not exceed 8 h. These treatments are usually taken once during the evening/night in freely moving patients but may be needed three times daily. When patients are bedridden, the drugs that trigger RLS are mainly the neuroleptics, the antihistamines and the antidepressants (tricyclics, quadricyclics, and selective serotonin reuptake inhibitors). In perioperative conditions, there is little chance for antidepressants to be newly introduced, but the parenteral use of neuroleptics (metoclopramide,¹¹ droperidol,⁶ and prochlorperazine¹²) is common, especially to avoid nausea and vomiting. Furthermore, phenothiazine antihistamines, such as hydroxyzine, alimemazine, and promethazine, which are

used as premedications because they are sedative, antiallergic, and block central dopamine receptors, possibly exacerbate the RLS. The perioperative use of neuroleptics and phenothiazines should be contraindicated (table 3). The use of these drugs can be replaced by other antiemetic drugs, such as domperidone, which does not cross the blood-brain barrier, or ondansetron, which is not a neuroleptic, or sedative drugs such as benzodiazepine (clonazepam).

How Can an Exacerbation of RLS Be Alleviated?

As long as the oral route is not feasible, oral dopamine agonists cannot be used. Subcutaneous apomorphin (1 mg), a dopamine agonist, can be administered, but the effect of the drug does not exceed 1 h; this drug should be taken together with an antiemetic drug such as ondansetron. A transdermal patch of rotigotine, a dopamine agonist, is now available for

Table 2. Symptoms and Signs of Acute Exacerbation of RLS during Perioperative Procedures and Factors of Exacerbation

Symptoms of Acute Exacerbation of RLS

Motor restlessness: urgent need to move, especially the legs; suicidal-like restlessness and discomfort
Electrical discharges in the legs or pain in the legs, extending to the arms and sometimes the whole body
Symptoms, which were initially restricted in the evening and the night, occur during the day

Signs of Acute Exacerbation of RLS (sometimes labeled “acute akathisia”)

Inability to remain seated or lying down or to keep the legs still
Repeated, semipurposeful or purposeless movements of feet and legs
Sudden, involuntary periodic legs or limb jerks

Factors Triggering Acute Exacerbation of RLS

Forced immobilization (on the operating table, during epidural anesthesia)
Major sleep deprivation
Acute iron deficiency (blood loss, major inflammation, dialysis)
Acute withdrawal of a dopaminergic agent (levodopa, dopamine agonist such as ropinirole, pramipexole, peribedil, and bromocriptine)
Use of neuroleptics (droperidol, prochlorperazine), especially if injected, and other drugs (mainly sedative, antiemetic and antihistaminic) that block central dopamine receptors (metoclopramide, metopimazine, hydroxyzine, alimemazine, and promethazine)
Use of antidepressants in patients with previous RLS

RLS = restless legs syndrome.

Table 3. Anesthetic Implications of RLS**Preventing the RLS Exacerbation**

Contraindicate the use of neuroleptics and phenothiazine antihistamines

To prevent nausea and vomiting, domperidone and ondansetron can be used in RLS patients

To achieve sedation, benzodiazepines such as clonazepam can be used in RLS patients

Avoid the discontinuation of RLS treatment, and reintroduce the oral dopamine agonist as soon as possible

When the oral route is forbidden, use subcutaneous injections of apomorphine (1 mg every hour) or transdermal (24 h) rotigotine patches

Alleviating Postoperative RLS Exacerbation

Use largely parenteral opiates and morphine

If available, use subcutaneous injection of apomorphine (1 mg every hour)

Authorize the patients to move and walk as early as possible under supervision or to move their legs passively if bedridden

Alleviating Long-term Exacerbation of RLS after Surgery

Closely monitor serum levels of ferritin, especially if there has been acute blood loss during surgery

If the serum ferritin level is lesser than 50 mg/mL, provide oral iron (100 mg/d) or intravenous iron (iron low-molecular-weight dextran [300 mg over several hours] or ferric carboxymaltose) if treatment through the oral route is not possible

Transiently increase the daily dose of dopamine agonist and administer 3 to 4 doses per day if the patient is bedridden

RLS = restless legs syndrome.

continuously alleviating RLS symptoms during a period of 24 h. It can be difficult to switch the patient to the transdermal dosage that corresponds to the equivalent oral treatment with another dopamine agonist, but the shift can be anticipated in coordination with the treating neurologist. However, rotigotine is not currently available in all countries. More frequently, parenteral opiates can adequately replace oral dopamine agonists, allowing physicians to immediately evaluate the dose–response effect with the patient. In bedridden patients, RLS improves more when patients are allowed to walk sooner (under supervision). If possible, one can also passively move the legs of the patient to obtain transient relief. After surgery, serum ferritin levels should be monitored. If the levels are lesser than 50 µg/ml, iron supplementation should be started, either orally or intravenously (if oral route is not possible). This intravenous route is preferred to the intramuscular route because intramuscular iron precipitates under the skin and can permanently stain it. Because there is a risk of allergy to intravenous iron, a small dose is initially infused over a period of 20 min while pulse rate, blood pressure, respiration, and potential adverse reactions are evaluated. The infusion of low-molecular-weight iron dextran (300 mg over several hours) or ferric carboxymaltose iron takes several hours, but the benefit is usually much more rapid than with oral iron.

Basic Science Note

RLS is a newly recognized syndrome, although one can find some early descriptions of “*anxietas tiliarum*” by well-known physicians in the 18th and 19th centuries.¹³ The father of the syndrome is Karl-Axel Ekbom, a Swedish neurologist studying pain in the context of neurology, who described the nosography of RLS in a series of patients in 1945; hence, RLS is also known as Ekbom syndrome. Ekbom was the first to

evaluate the prevalence of the syndrome and to find an association with iron deficiency.¹⁴

The pathophysiology of the syndrome is not entirely known, but major advances have recently been achieved (fig. 2). A genetic contribution to RLS has been well documented: 42–92% of patients with idiopathic RLS (mostly those with

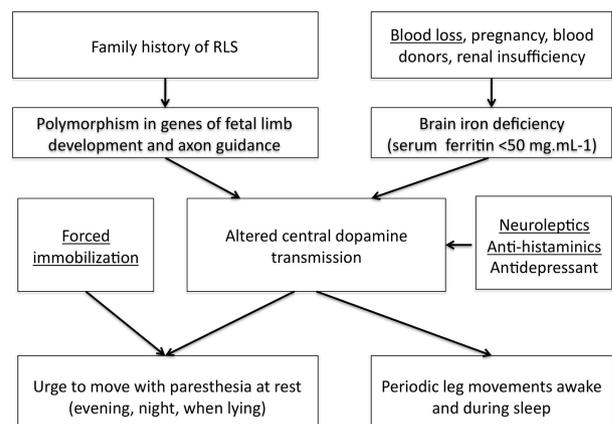


Fig. 2. Suspected mechanisms of restless legs syndrome (RLS). The main factors promoting RLS during anesthesia are highlighted. (Left, upper part) The idiopathic RLS cases, which are mostly familial, have genetic polymorphisms of high frequency, possibly leading to altered central dopamine transmission. (Right, upper part) In this background, or in subjects without family history, several acquired conditions can promote or exacerbate the RLS. The central iron store deficiency (caused by blood loss, pregnancy, gastrectomy, blood donors, inflammation) may alter the central dopamine transmission, the use of neuroleptic and antihistamine drugs blocks the dopamine transmission, and forced immobilization exacerbates the urge to move. As a consequence, the RLS symptoms (urge to move, mostly with paresthesia/dysesthesia) and involuntary legs movements (during sleep and sometimes awake), appear or worsen.

a young age at onset) report a positive family history, and 83% of monozygotic twins are concordant.¹⁵ The transmission seems to be autosomal dominant, with variable expressivity. Nine loci of susceptibility on different chromosomes have been identified in multiplex RLS families. Genome-wide association studies reveal associations with variants in four genes playing a role in fetal limb development and axonal guidance.^{16–18} In addition, the allelic variant of one of these genes (BTBD9) correlates with serum ferritin levels and periodic limb movements during sleep.¹⁹ The potential central role of iron insufficiency in RLS is indicated primarily by the RLS caused by deficient iron stores and alleviated by iron supplementation.^{10,20} In primary RLS, serum ferritin levels correlate with RLS severity.^{21,22} Most patients with primary RLS have lower ferritin levels in their cerebrospinal fluid than controls.¹⁰ Neuropathologic analysis shows that the immunostaining for iron management proteins is altered in the substantia nigra of RLS brains. The profile of proteins responsible for iron management in neuromelanin cells indicates iron deficiency.²³

The dramatic treatment response to dopamine agonists and levodopa²⁴ as well as the adverse reactions of patients to dopamine blockers²⁵ provide the main basis for the hypothesis of dopamine pathology as a cause of RLS. However, the attempts to document any dopamine pathology using brain imaging studies in RLS to date are unconvincing.²⁶ Nonetheless, the levels of dopamine D2 receptors are decreased in the putamen of RLS brains. The magnitude of this degree is significantly greater for more severe RLS.²⁷ RLS brains also show significant increases, and not decreases, in tyrosine hydroxylase, an enzyme of dopamine synthesis, in the substantia nigra. Because iron is a cofactor of tyrosine hydroxylase and stabilizes D2 receptors, these data suggest that a primary iron insufficiency produces a dopaminergic abnormality characterized as an overly activated dopaminergic system, as a part of the RLS pathology.

Epidemiology

RLS is a common disease. Population-based studies report a prevalence of 5 to 10% in western industrial countries but a lower prevalence in Asian populations.¹⁹ When systematically investigating the presence of the four RLS criteria in 359 patients before spinal or general anesthesia, 8.9% have preexisting RLS.⁸ The syndrome affects women twice as frequently as men (10.8% *vs.* 5.8% in France).^{28,29} The frequency increases progressively with age up to around 64 yr old and decreases thereafter.²⁹ As many as 1.9% of subjects are affected almost all nights,²⁹ and 2.7% have weekly symptoms that affect their sleep (“sufferers”).²⁸ Children may be affected too.

Anesthetic Implications of RLS

Any surgery and diagnostic procedure requiring anesthesia may exacerbate the condition in patients with RLS. This risk can be prevented if the neurologists inform their patients and the anesthesiologists about it and if the anesthesiologists are

aware of the RLS diagnosis and its anesthetic implications. However, RLS is poorly recognized by physicians and frequently confused with venous, arterial, or joint disease.^{28,29} Furthermore, only one of the five subjects requires chronic treatment, but the other four of the five may experience an acute exacerbation or unmasking of the RLS during a perioperative procedure. In these latter cases, the anesthesiologist will be the first physician in a position to diagnose RLS. In the perioperative context, the urge to move can be differentiated from confusion and delirium because patients with RLS are not confused, are not demented, and have no hallucinations. Similarly, anxiety is rather a psychologic feeling, whereas RLS is uniquely physical. RLS should be easily differentiated from arterial, venous, and joint leg diseases because symptoms are exacerbated by resting and lying down and alleviated by walking, whereas these other conditions, in contrast, are alleviated by resting and worsened by walking. Sensory and painful polyneuropathies are also characterized by paresthesia and pain, but the sensations are more distal (toes and soles instead of calves), occur continuously (including during the morning and early afternoon, which is rare in RLS), and are not alleviated by walking.

In patients who remain partially conscious during surgical or diagnostic procedures such as eye surgery and colonoscopy, the urge to move may be so intense that, in our experience, the patients with RLS can move even though the surgeon is operating on their eyes. Although the term “akathisia,” first used for patients treated chronically with neuroleptics, describes in neurology chronic, slow, continuous, rubbing-like movements of the legs occurring during daytime with no associated body sensations or sleep disturbances,³⁰ the term “acute akathisia” has been used by several authors to describe the acute motor exacerbation of RLS induced by metoclopramide,¹¹ droperidol,⁶ and prochlorperazine¹² during perioperative procedures. The involuntary leg jerks caused by exacerbation of a preexisting RLS are sudden, dorsal flexions of the toes, foot, leg or thigh, resembling the spinal cord flexor reflex³¹ and lasting 0.5 to 5 s, longer than a myoclonus. These movements are repeated every 5 to 90 s during sleep in classic RLS but may occur while patients with severe cases are resting awake. As they may also be observed during spinal³² and epidural anesthesia,³³ the origin of these movements appears to be spinal. When observed by anesthesiologists, they have been labeled as involuntary periodic movements,³⁴ myoclonia,³⁵ localized clonic convulsions,³⁶ or periodic bursts of rhythmic dyskinesia.³³

Immobilization is a potent trigger of RLS, to the point that an objective diagnostic test for RLS is the “Forced Immobilization Test,” administered between 9 PM and 10 PM. Use of this test was later replaced by the “Suggested Immobilization Test,” as blocking the legs in a stretcher was perceived as torture.³⁷ For an unknown reason, if patients with RLS realize that they cannot easily move their legs (*e.g.*, when attending a theater play, as leg movements could disturb the show; in a plane when one should remain seated; or as a

passenger in a car), the urge to move increases. One may therefore understand how painful hospital conditions are for the RLS patient when lying prostrate during a local microsurgery or colonoscopy, during motor block of the legs, when in a cast; when suffering from acute bradykinesia due to parkinsonism,³⁸ or when bedridden by a stroke.³⁹ RLS remains even after leg amputation (phantom RLS),^{40,41} which demonstrates that it is a central nervous system disease, sharing similarities with neuropathic pain syndromes.

The patients treated every night with a dopaminergic agent usually have a severe or very severe form of the disease.⁴² Compared with the doses used to treat Parkinson disease, the doses used to treat RLS are much smaller and typically administered once a day in the evening. However, some cases require several doses per day, sometimes in combination with opiates and benzodiazepines. The treatment of RLS is not satisfactory as there remain some patients who experience incomplete responses, rebound symptoms, tolerance, and augmentations. Rebound RLS is the development of symptoms in the early morning, mostly as a consequence of the short half-life of a drug. Augmentation is mostly defined by the sudden 2–4 h phase in advance of the time of symptom onset.⁴³ The acute exacerbation of RLS, as can be observed in the perioperative context, shares numerous similarities with a severe form of augmentation.

Knowledge Gap

A longitudinal cohort could help to establish the frequency of cases of acute RLS exacerbation during perioperative procedures using patients previously diagnosed as RLS as well as those who were not previously diagnosed. Future investigations will be necessary to determine whether the systematic use of parenteral opioids prevents RLS in patients with locoregional or general anesthesia. Specific attention should be paid to patients who cannot express their feelings (children, patients who cannot speak for various reasons, or patients with dementia) to determine whether some sudden agitation in these patients has unmasked an acute RLS exacerbation. It will also be necessary to evaluate the benefit or risk of choosing a general rather a locoregional anesthetic for use in patients with RLS who are at high risk of moving during the surgical procedure. The timing and topography of leg and arm jerks observed during spinal and epidural anesthesia, and sometimes at the onset of general anesthesia, should be studied with surface electromyography (and distinguished from propriospinal myoclonia) because such movements may represent evidence for a spinal generator of periodic leg movements.

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