

## CLINICAL SCIENCE

# Restless legs syndrome in subjects with a knee prosthesis: evidence that symptoms are generated in the periphery

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**OBJECTIVE:** There are no data addressing the prevalence of restless legs syndrome in subjects who have knee prosthesis. Therefore, we conducted a cross-sectional survey of subjects who underwent knee prosthesis surgery.

**METHOD:** A total of 107 subjects (30 male, 77 female) were interviewed over the telephone regarding restless legs syndrome symptoms. If the patients exhibited symptoms of the syndrome, we conducted face-to-face interviews. Lastly, a therapeutic test with pramipexole was proposed for each subject.

**RESULTS:** In our cohort, 7 males (23%) and 30 females (39%) had restless legs syndrome. Of these, 6 males and 23 females were submitted to face-to-face-interview. Of the males, 5 (83%) had restless legs after the knee surgery-exclusively in the operated leg- and reported no family restless legs history. One man had a prior case of bilateral restless legs syndrome, a positive family history and claimed exacerbation of symptoms in the operated leg. Among the females, 16 (69%) had restless legs prior to surgery. A total of 10 female patients reported bilateral symptoms, with fewer symptoms in the operated leg, while 6 displayed a worse outcome in the operated leg. The 7 females (31%) without restless legs prior to surgery and without a family history experienced symptoms only in the operated leg. All subjects responded favorably to the pramipexole therapeutic test.

**CONCLUSION:** Our results suggest that secondary unilateral restless legs syndrome may ensue from knee prosthesis surgery and that the symptoms are generated in the peripheral nervous system.

**KEYWORDS:** Restless Legs Syndrome; RLS pathophysiology; Knee prosthesis.

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## INTRODUCTION

Restless legs syndrome (RLS) was described as an independent clinical condition by Karl-Axel Ekbom, a Swedish neurologist who also described its main features, in 1945.<sup>1</sup> RLS, or Ekbom's syndrome, is a common neurological disturbance with sensory and motor components.<sup>2</sup> The pathophysiology of RLS is considered unknown; however, a recent theory has suggested that the pathophysiology of RLS is secondary to an imbalance between thyroid hormones system and the dopaminergic system.<sup>3</sup> It has also been debated whether RLS symptoms are generated in the central or peripheral nervous system.<sup>2</sup> In addition, RLS may also occur in patients that have had their leg amputated. In this case, patients report the symptoms as coming from the

amputated limb, which is also known as "phantom RLS".<sup>4,5</sup> Ekbom, who described one of the first phantom RLS cases, suggested that RLS symptoms could be generated in the periphery.<sup>4</sup> Furthermore, RLS may be primary or secondary to various other diseases.

The currently accepted definition of adult RLS from the "International Restless Legs Syndrome Study Group (IRLSSG)"<sup>6</sup> is as follows: 1) an urge to move the legs is usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; 2) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity; 3) the urge to move or unpleasant sensations are partially or totally relieved by movements such as walking or stretching, as long as the activity continues; and 4) the urge to move or unpleasant sensations are worse in the evening or at night than during the day, or only occur in the evening or night. Some supportive clinical features of RLS include a positive family history, periodic limb movements during sleep, and periodic limb movements during wakefulness. An additional supportive clinical feature is the "improvement of RLS symptoms with dopaminergic agonist" therapy.<sup>6</sup>

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To the best of our knowledge, there are no data indicating the prevalence of RLS among patients with knee prosthesis surgery (KPS). Therefore we conducted a cross-sectional survey of this patient group. We also sought determine if the KPS was capable of causing RLS in patients who previously did not suffer from this condition.

## PATIENTS/METHODS

A total of 107 patients underwent KPS, which was performed by one of the members of our surgical team (JLPSN). These patients (n1=107), 30 males (28%) and 77 females (72%) were interviewed over the telephone regarding RLS symptoms. Their age varied from 41 years to 81 years (mean 63 years). Subsequently, the patients that were positive for RLS symptoms were invited to a face-to-face interview (FFI). A total of 6 men attended the FFI, which were considered group n2 (n2=6). A total of 23 women attended the FFI, which made up group n3 (n3=23).

All patients from group n1 were interviewed by one of us (JCPJr.) over the telephone regarding RLS symptoms. During this interview, the patient was questioned if they were, or not, sufferers from RLS symptoms. A positive history of RLS was only considered when the 4 defining criteria of the syndrome were reported.<sup>6</sup>

The n2 and n3 groups, comprised of individuals who suffer from RLS, were submitted to the FFI. At this point of the study, we asked the patient the following questions: 1) if the patient was aware of his/her RLS; 2) if the RLS was present prior to or after the KPS; 3) whether the RLS symptomatology was unilateral or bilateral, and if the symptoms were bilateral, were they more intense in the limb that underwent the KPS, or in the limb without the surgery; 4) if there was a positive family history of RLS; and 5) which was the medical condition that warranted the KPS. All patients from the n2 and n3 groups, except 2 women, underwent a pramipexole therapeutic test (PTT) for at least 3 days with a 0,125 mg dose 2 or 3 hours before bedtime. Women from the n3 group, who did not receive the PTT, were already taking clonazepam, which had been prescribed by their doctors as a therapy for insomnia. It has been established that an alleviation of more than 50% in the severity of RLS symptoms, with PTT or clonazepam, was necessary to consider the patient as an RLS sufferer. If not present a normal cognition to attend coherently the FFI would be a motive to exclude the patient of the study. Other comorbidities, or other sleep disturbances, that the patients might had were not studied in this survey as its main objective was to examine the association between RLS and KPS. Therefore, we also did not consider whether the RLS previously to KPS was primary or secondary to other diseases, iron deficiency, or medications.

## RESULTS

General aspects: Of our initial group (n1=107), 7 males among 30 (23%), and 30 females among 77 (39%) reported RLS during the telephone interview. All of these patients exhibited the 4 criteria that define RLS in accordance with the IRLSSG.<sup>6</sup> A total of 6 men in this study, that attended the FFI (n2=6), were submitted to KPS due to sport or vehicles accidents that damaged the knee articulation. Notably, none of these patients complained of osteoarthritis. Among the 23 women that attended the FFI (n3=23), 16 of them, indicated that the main reason they underwent KPS

was severe osteoarthritis; in 7 women from the 23 that attended the FFI, KPS has been recommended mainly due to injuries that severely damaged the knee. Only 3 women from the entire group knew that they suffered from RLS, even though their problems had not been addressed. Several women reported that their RLS symptoms were present since they were children. The majority of the patients from the n2 and n3 groups sometimes complained of their unpleasant sensations to their orthopedists or clinicians; however, the possibility that they had RLS has never been considered. The majority of our patients also complained of pain, of varying intensity, concomitant with the more typical RLS symptoms. Dysesthesias, mainly a burning pain around the knee, in the limb with the prosthesis was also a common complaint. A total of 5 men among 6 (83%) and 7 women among 23 (30%) developed RLS postoperatively to the KPS. More specific results from this survey are presented in summaries 1 and 2.

### Summary 1: Males (n2 = 6)

A total of 5 patients with unilateral KPS reported symptoms only in the limb with the prosthesis, presented RLS only after the KPS, and did not have relatives with RLS. One of these 5 patients also had RLS symptomatology beyond the legs, which presented in the contralateral wrist and hand. Complaints in the wrist and hand started at the same time as that of the leg, which was weeks after the KPS. One man had RLS prior to the KPS, but after the surgery the symptoms worsened in the KPS limb compared with the limb without prosthesis.

The median IRLSSG severity score rating<sup>6</sup> from group n2 patients was 23. All did well in the PTT; however, a single male subject had insomnia. In 5 patients the elapsed time between KPS and the first RLS unilateral symptoms was of "2 or 3 weeks to 2 or 3 months". A 71-years-old gentleman began to feel RLS symptoms in the operated leg only 9 years after the surgery, when to him was prescribed escitalopram due to a mild depression.

### Summary 2: Females (n3 = 23)

A total of 16 patients from the n3 group were sufferers of RLS prior to KPS and 14 of them knew relatives with similar symptoms; from these 16 patients, 10 (62%) reported that the symptomatology was bilateral, however, the KPS had ameliorated the symptoms in the limb with the prosthesis in relation to the limb without it. Among the 16 patients, 6 (38%) reported bilateral symptomatology that became worse in the limb with the prosthesis compared with the limb without KPS.

A total of 7 patients (30%) from the n3 group declared RLS only postoperatively to the KPS and did not have relatives with similar symptoms; their symptoms were felt only in the KPS limb.

A total of 3 patients from group n3 with RLS prior to the KPS also had symptoms in both thighs, and 2 patients also had symptoms in the arms.

One patient from those without RLS prior to KPS had to remove the prosthesis device due to serious infection in the articulation. She was submitted to various surgeries, and the operated limb, although without the prosthesis, manifests now severe RLS symptoms.

The 2 patients that were taking clonazepam reported that they had RLS prior to KPS, and clonazepam had ameliorated their RLS symptoms.

The median IRLSSG severity rating score<sup>6</sup> from the n3 group patients was 24. All did well with PTT; however, 1 patient had severe nausea, 1 patient had a significant headache, and 1 patient had insomnia. To patients that already had primary RLS prior to KPS the elapsed time between the KPS and the worsening or ameliorating the symptoms in the operated leg was of "3 to 6 months"; and to patients that initiated their RLS symptoms after the KPS was of "3 or 4 weeks to 3 or 4 months".

## DISCUSSION

In this study, the overall prevalence of RLS among KPS patients was elevated (male 23%, female 39%) when compared with the normal population (10%).<sup>6</sup> These numbers are explained partly by our cohort being formed mainly of older subjects. However, as many of our patients developed RLS only after the KPS (37%, overall), we can state that KPS may initiate RLS in subjects who never had the syndrome, which may underlie the elevated prevalence of RLS among KPS patients. From our study, secondary RLS (i.e., postoperatively to KPS) should be considered as a relatively common complication of total knee arthroplasty.

In our patients, unilateral RLS in the limb with the prosthesis was common. Similarly, RLS symptoms worsened in the knee with prosthesis for some of these patients that had RLS prior to the KPS. However, also among the many patients that had RLS prior to the KPS, in some of them (n3 group), RLS symptomatology in the limb with the prosthesis was ameliorated compared with the one without prosthesis. During KPS, it is unavoidable that various nerve bundles are injured. Subsequently, the scarring of neural and non-neural tissues occurs differently among different subjects. The various ways with which tissues heal, and recover their new histological stability, are what likely differentiate the outcomes in relation to RLS symptoms after the KPS.

One of our patients had to remove the prosthesis device, yet still suffers from RLS (acquired only after the KPS). This implies that it is not the prosthesis itself that causes the syndrome. However, the unilateral nature of this patient's RLS implies that her symptomatology was secondary to the KPS-induced damage of the peripheral nerves within the affected leg. To gain a better understanding of this, somatosensory system physiology and its "principle of labeled lines" need to be discussed. Nevertheless, our findings might suggest that RLS symptoms are generated in the periphery of the nervous system, which is what Ekblom in 1961 had already assumed.<sup>4</sup>

In the somatosensory system, various sensory receptors capture different stimuli and convey them to the sensory cortex. Each type of receptor is specialized, whereby it receives the stimulus to which it is predetermined to receive. Immediately after it is stimulated, the receptor sends a signal to the somatosensory cortex via nerve fibers. Accordingly, the area of the cortex that receives this signal determines the mode of the subsequent perception.<sup>7,8</sup> This mechanism is called the principle of "labeled" lines. In other words, somatic receptors are the structures designated to receive stimuli, however, if their afferent fibers are stimulated at any point while approaching the cortex, the mode of perception by the cortex is identical to when the somatic receptor is stimulated directly.<sup>8</sup>

The typical dysesthesias associated with RLS secondary to KPS are generated in the peripheral of sensorial system as

this study demonstrates, and may be better explained by discussing the basic mechanisms underlying the generation of peripheral perceptions. The dorsal sensory ganglia axons contain a number of receptors. These include proprioceptors, thermoreceptors, nociceptors, mechanoreceptors, and combinations of these receptors families.<sup>7</sup> We assume that the hyper-stimulation of various types of tegument receptors can cause a variety of different sensations experienced by RLS patients. This assumption is made considering that sensations felt as coming from the periphery (be they normal or abnormal) have to follow their appropriate physiological mechanisms inherent to the sensation phenomena.

There are receptors that adapt slowly (e.g., free nervous endings, Merkel receptors, and hair receptors), and rapidly (e.g., Meissner, Ruffini, and Pacinian corpuscles). Proprioceptors all adapt rapidly.<sup>7,8</sup> The rapidly adapting receptors may be more involved than the others in RLS symptoms, in what the symptomatology has of "intriguing". After rapid receptors have detected a specific tissue alteration, they become quiescent and do not signal for a short time. Then, they promptly recover their detection ability.<sup>8</sup> That is, they "glitter" continuously, which may result in a perception of vibrations deep within the legs. All the leg's sensory receptors combined in an enhanced signaling network may generate the unpleasant limb sensations that RLS patients report. We postulate that an overstimulation of peripheral receptors in the legs and/or an insufficient modulation of the inputs on the synapses they have to pass through, as they travel to cortex, lead to (after KPS) RLS symptoms, and we suggest that this might be the case of primary RLS as well. Thus, it could be postulated that RLS should be considered as a functional neuropathy. There are other types of neurons interspersed among the somatosensory neurons along their pathway to the cortex,<sup>7</sup> which include many dopaminergic neurons.<sup>9</sup> The majority of these interspersed neurons have neuromodulatory functions.<sup>7</sup> Because dopamine agonists are effective in ameliorating RLS symptoms, a diminished modulation of these sensory inputs to the sensory cortex by the dopaminergic system might be central to RLS pathophysiology.<sup>3</sup> We also postulate that RLS may, more informatively, be considered as a "functional peripheral neuropathy".

Peripheral receptors transform different stimuli into neural activity and then send these signals to the somatosensory cortex. These inputs are interpreted by the cortex as sensations, which are in accordance with the area of the neural map that receives the input signal. If these peripheral receptors are inadequately stimulated, then transmissions inputs may be "read" as abnormal sensations.<sup>10</sup> These sensory receptors may undergo one, or more than one, of the following "dysfunctions": 1) diminishing of their threshold for the stimuli received from the environment (hyperesthesia), or elevation of the threshold (hypoesthesia) or, 2) to become susceptible to stimuli that are not specific for that kind of receptor (dysesthesia).<sup>10</sup> Our study indicates that the RLS symptoms secondary to KPS are generated in the periphery of the somatosensory system. Therefore, not being logical that RLS symptoms to be felt can prescind the somatosensory physiological apparatus, we postulate that in primary RLS, as the same, the symptoms are generated through an "adulteration" of the receptive ability of peripheral receptors. It also might be possible that normal

stimuli received by normal receptors are not sufficiently modulated when the inputs travel to sensory cortex. In a previous article we hypothesized that primary RLS may be secondary to an insufficient modulation of thyroid hormone by the dopaminergic system.<sup>3</sup>

Considering the findings of the current study, we believe that injuries to sensitive nerves adjoining the knee articulation during KPS result in secondary RLS. During the KPS, infrapatellar branches of the saphenous nerve are cut. In addition, the superficial fibular nerve that passes by the lateral side of the knee commonly suffers variable damage secondary to severe stretching and circulatory stress due to tourniquet application to the limb.<sup>11,12</sup> Inflammatory involvement of the fibular nerve and compression of the nerve due to severe edema also frequently occur.<sup>12</sup> Due to its proximity to the knee articulation, it is possible that the saphenous nerve that passes by the medial side of the knee<sup>13</sup> also suffers similar damage from the KPS, however, this has not been reported in the literature. These three mentioned nerves are sensitive, so damage to any of them may induce disturbance of sensory stimuli but not necessarily motor activity.<sup>13</sup>

Injuries to peripheral nerves may evoke variable histopathological responses, such as Wallerian degeneration. Damage to the myelin sheath may induce variable degrees of segmental degeneration, and axon compression may damage the axon's inner canaliculi.<sup>10,11</sup> This neural damage may induce variable degrees of hypoesthesia or even anesthesia, or this damage may induce opposite effects such as hyperesthesias, and paresthesias/dysesthesias. Nerves that have been damaged become more exposed to tissue environment and may be stimulated by nonspecific stimuli (tissue pressure on the damaged nerve) that are converted to action potentials<sup>10,11</sup> that are, then, turned into specific sensations by the sensory cortex. In addition, the axon may be damaged and become unable to isolate neural potentials so that they "jump" to another axon, which is known as ephaptic neurotransmission.<sup>10</sup> Furthermore, if the nerve is cut, neuromas may ensue, which can be a source of pain. Sometimes these are so small that they cannot be detected even by RMI.<sup>11</sup> Whatever the cause of action potential firing, or whether the signal is receptor mediated or not, the somatosensory cortex will always perceive the input as coming from the sensory receptor located at the distal end of the sensory neuron's axon (i.e., principle of labeled lines).<sup>8</sup> We postulate that abnormal neural transmissions initiated at the region of the nerve around the knee (mainly from the sensitive fibular nerve and perhaps also the saphenous nerve) are the cause of the newly diagnosed RLS cases after KPS in the cohort presently studied.

As we observed, some patients in this study that had already suffered from RLS prior to KPS had an amelioration of their RLS symptoms after the KPS, when comparing the limb with the prosthesis to the one without it. In these cases we believe that the damage to nerves in their region around the knee led to neural hypoesthesia, thereby minimizing the RLS symptoms that the patients previously felt from their primary RLS.

It is interesting to note that the superficial fibular nerve is highly predisposed to sensorial neuropathies.<sup>11</sup> Asbury described (1972) that this nerve is occasionally subjected to inflammation restricted to the perineurium, which causes compression of the nerve bundles. The clinical condition that ensues is one of a patchy, burning, painful, partially

remitting distal cutaneous sensory neuropathy.<sup>14</sup> Considering that spontaneous inflammatory processes in the superficial fibular nerve may occur, we believe that an identical process occurs secondary to KPS.

One of our patients, a 43-year-old man, presented not only with RLS in the operated leg but also in the contralateral wrist and hand, which both initiated 2-3 weeks after the KPS. We hypothesize that his wrist and hand symptoms are a form of referred paresthesia, whereby the plethora of inputs coming from the superficial fibular nerve "contaminate" the sensory nerves that come from the contralateral wrist and hand. In the PTT, this patient experienced notable amelioration of RLS symptoms in both regions.

We believe that this study contributes to the understanding of the neural basis of RLS pathophysiology. Examining the role of the superficial fibular nerve (and perhaps saphenous nerve) in RLS secondary to KPS may improve our understanding of not only of RLS secondary to peripheral neuropathies but also of primary RLS. Our study suggested a peripheral etiopathogenesis of RLS secondary to KPS, and possibly also primary RLS, whereby the sensory receptors of the leg may have a diminished threshold for the initiation of inputs that will be perceived by the cortex as RLS symptoms. The spinal cord and thalamus, the pathways transmitting sensory stimuli to the cortex, have a number of interspersed neurons that serve to modulate the synapses connecting the sensory receptors with the cortex. It is possible that a decrease in this modulation function also may be part of the RLS pathophysiology. The notable effects of dopamine agonists to relieve RLS symptoms are an indication that these medications may act through the modulatory functions of the dopaminergic system in the spinal cord. The reader is encouraged to read the review (1983) by Lindvall and colleagues.<sup>9</sup> One of the effects of dopamine release is a down regulation of the thyroid axis.<sup>15,16</sup> This pharmacological fact cannot be considered as a simple side effect of this neurotransmitter's release. It is plausible that an undermodulation of the thyroid axis by the dopaminergic system may result in RLS symptoms.<sup>3</sup> The principle of the labeled-lines that we have remembered in this article may be the reasoning that allows us to consider that there is resemblance between both conditions RLS secondary to KPS and phantom limb RLS.<sup>17</sup>

Orthopedists should be aware that KPS may cause secondary RLS, so that they can better address this potential condition in their patients. Refinement of the KPS procedure may reduce the risk of injury to the superficial fibular nerve, thereby diminishing the incidence of RLS secondary to KPS.

This study has been approved by the "Committee of Ethics of Research on Humans" of our institution - Faculdade de Medicina de Jundiaí, São Paulo, Brasil.

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## AUTHOR CONTRIBUTIONS

Pereira Jr JC conceived and designed the study, was also responsible for the telephone and face-to-face interviews, the writing of the manuscript, and researches for the pertinent literature. Silva Neto JLP has operated all the patients (total knee arthroplasty), and introduced concepts regarding surgery techniques. Pradella-Hallinan M was responsible for the revision of the manuscript and provided important notes to it.

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