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Phantom Restless Legs Syndrome

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Abstract
Background: Amputees often experience a phantom limb consisting in the vivid impression that the limb is not only still present, but in many cases, painful. These patients may also become restless legs syndrome (RLS) sufferers; conversely, a preexisting RLS may persist after limb amputation. ***Summary:*** In this brief essay, papers on phantom RLS (pRLS) are reviewed in order to provide clinical elements for the diagnosis and treatment of this peculiar condition. It is relevant that dopamine receptor agonists yielded a marked reduction of the RLS symptoms in all cases reported. ***Key Messages:*** pRLS indirectly confirms the innate capacity of the central nervous system to retain a primordial internal body image responsible of phantom sensations. Moreover, it has been hypothesized that pRLS may provide clues for a better comprehension of some mechanisms underlying phantom pain and for the development of new treatment strategies.

Introduction

Limb amputation is needed with some vascular diseases, trauma, infection, cancer, and the risk of this dramatic circumstance increase with age [1, 2]. After a limb amputation, most of the patients experience a phantom limb, which consists in the vivid impression that the limb is not only still present but, in many cases, painful [3–5]. Moreover, 60–80% of all amputees sometimes feel as if they are gesturing, feel twitch, or even try to pick things up. The missing limb often feels shorter and may feel as if it is in a distorted and painful position. Phantom limb pain can get worse because of anxiety, stress, and weather changes and is usually intermittent [6]. The frequency and intensity of attacks usually decline with time [6], but 70% of phantoms continue to be painful even 25 years after the loss of the limb [7].

The pathophysiology of phantom limbs and related disturbances is complex including peripheral, spinal, and likely most of all brain mechanisms [3]. In fact, functional magnetic resonance imaging studies have demonstrated that patients have experienced phenomena of cortical remapping [8]. The majority of plastic reorganization occurs as a downward shift of the limb area of the cortex into the area of face representation on the Penfield *homunculus* [9] as can be inferred from the reports of disappearance of the phantom limb experience as a consequence of the occurrence of focal brain lesions in the contralateral parietal cortex [10]. At a cellular level neuroplasticity that underlies the remodeling processes may involve both the gray matter through glycogenesis, vascularization, and synaptogenesis and the white matter that undergoes axonal sprouting and myelination [11, 12]. However, remapping cannot explain all aspects of the phantom limb experience because, for example,

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phantom limbs are occasionally found in patients with congenital absence of limbs, which implies that some aspects of the body image are specified genetically and survive as a phantom limb [5, 13]. Taking these and many other notions into account, Ramachandran and Hirstein [5] have proposed a multifactorial model of the origin of phantom limbs suggesting that this experience depends on integrating involvements from at least 5 different sources: (1) from the stump neuromas, (2) from remapping, (3) the monitoring of corollary discharge from motor commands to the limb, (4) a primordial and genetically determined internal body image, and (5) vivid somatic memory of painful sensations or posture of the original limb carried over into the phantom.

The fourth point partly leads back to the concept of the existence of a neuromatrix, which subserves body sensation and has a genetically determined substrate that is modified by sensory experience [14, 15]. The somatosensory, limbic, and thalamocortical systems are the main contributors to this neurosignature. The persistence of the neurosignature, even after a limb amputation (or of the breast, the penis, or any other innervated body parts [5]) could be the cause of phantom sensations and pain. Phantom pain may also arise from an abnormal reorganization in the neuromatrix to a preexisting pain state [16].

Restless legs syndrome (RLS) is characterized by uncomfortable sensations, usually affecting the legs, associated with an urge to move, with worsening at rest, in the evening and at night [7]. The symptoms of RLS cause significant distress or impairment in social, occupational, educational, or other important areas of functioning by its impact on sleep, vitality, daily activities, behavior, cognition, or mood [17]. When there is uncertainty regarding the diagnosis, clinical features supporting RLS include family history of RLS among first-degree relatives, presence of periodic limb movements during sleep (PLMS), lack of profound daytime sleepiness and reduction in symptoms, at least initially, with dopaminergic treatment [17]. The pathophysiology of RLS is still unclear. There are 2 major putative causes for RLS that postulate the involvement of the central nervous system (CNS) dopamine or iron [18, 19]. RLS may manifest in its primary form when other causes are excluded by means of laboratory examinations and has a positive familial history. On the contrary, when RLS may be explained by the presence of other conditions – such as pregnancy, renal failure, neuropathy – it can considered to be secondary [20–23]. The motor cortex may be hyperactive in RLS because of a decreased inhibitory tone of subcortical inputs at the level of the basal ganglia [24], resulting in intentional movements such as urge to move the limbs. This motor output may activate descending the dopaminergic system in the striatum [24], with a consequent occurrence of periodic limb movements, and conceptually equivalent virtual movements in the phantom limbs [25].

Since an early description in 1964 [26], it is known that some amputees may experience a phantom RLS (pRLS) in the context of a phantom limb syndrome.

The aim of this essay is to review papers published on pRLS and then integrate the notions about phantom limb sensations and RLS in order to establish a possible link. This review also aims to provide practical clinical elements for the diagnosis and treatment of this peculiar condition.

Methods

This review includes articles published in peer-reviewed journals, which were identified using the National Institutes of Health National Library of Medicine PubMed literature search system. Search terms were *phantom restless legs syndrome, atypical restless legs syndrome, amputated limb*, and *phantom restless legs*. Inclusion criteria required that the original research articles included the clinical combination of restless and phantom limbs. The titles and abstracts of retrieved studies were independently reviewed by the 2 authors against the inclusion and exclusion criteria. The full-text article was consulted if there were any aspects of the abstracts that were unclear and for the final selection of articles. Of one article written in Swedish in 1964 [26] a satisfactory summary in a later paper by the same author was found and it was then included in the review, but with reservations about comments due to the incompleteness of the available data. Studies that did not explicitly report adherence data were excluded.

Results

The search produced a final group of 7 studies investigating pRLS that are listed in Table 1 including 5 case reports [27–31] and 2 case series presenting, respectively, 33 out of 283 cases of possible pRLS [32] and 18 out of 86 cases of phantom pain worsening at night, interpretable at least as pRLS mimics [26]. This gives a total of 66 cases in the international literature to date that can be taken into account. There are obvious issues about the diagnoses of the 2 case series as already explained for the study by Brenning [26] and for the use of a questionnaire not specifically built for the identification of RLS in the study by Giummarra and Bradshaw [32]. This section will follow some paragraphs: (1) methodological issues concerning

Table 1. Studies investigating phantom RLS

Reference	Article type	Cause of limb amputation	Clinical annotations, response to therapy, neurophysiological findings
Brenning [26], 1964	Case series of 86 patients (unspecified mean age) with referred various sensations occurring after operation. About 40% of the patients experienced *molimina crurum nocturna*, which is a disturbance referring particularly to nocturnal leg cramps and restless legs. Among these patients, 52% had feelings of cramps and pain in the phantom leg	Unspecified	Symptoms referred to *molimina crurum nocturna* showed up fairly soon after amputation Enantaldehyde-furaldehyde (unspecified dosage) alleviated the pain and nocturnal cramps in 4 of the patients vPSG or PSG not performed
Dempewolf et al. [30], 2011	Case report of a 54-year-old man who had an above knee amputation of his left lower leg 15 years before the appearance of RLS	Cancer: leiomyosarcoma	RLS symptoms showed up initially at the amputee side then passed to the other side and the clinical condition worsened progressively Pramipexole 0.18 mg/day, levodopa, tilidine, gabapentin, amitriptyline were discontinued because of side effects; pramipexole, until used, yielded a persistent benefit on RLS symptoms PSG was found to be useful by detecting PLMS more proximally to the stump or in the other limb; there was an improvement on the PLMS index with pramipexole
Giummarra and Bradshaw [32], 2010	Case series of 283 amputees (205 males; mean age of the 5 patients with possible RLS 70 years) Lower limb amputees (241): partial foot/ankle (8), below knee (128), through knee (6), above knee (83), hindquarter (9); upper limb amputees (42): fingers (6), partial hand/wrist (7), below elbow (11), above elbow (14), forequarter (6); brachial plexus avulsion (11). Side of amputation (right): 52%	Trauma (131); vascular disease (49); cancer (25); infection (19); diabetes and vascular disease (13); diabetes only (14); congenital limb deficiency (7); correction of congenital limb deficiency (8); toxic shock syndrome (3); Charcot-Marie-Tooth (2); anti-rejection drugs following organ transplant (1); rheumatoid arthritis (1); poliomyelitis (1); Dupuytren's contracture (1)	Many amputees (33 cases = 13% of the sample) experienced phantom pain that was significantly worse at night, together with symptoms strikingly similar to those of RLS, especially in five subjects with a below knee unilateral amputation Therapy not administered vPSG or PSG not performed
Hanna et al. [27], 2004	Case report of a 78-year-old man who had bilateral above-knee amputation with RLS appearing shortly after	Vascular disease	In addition to RLS symptoms, the patient later developed a parkinsonism that was exacerbated by metoclopramide Both RLS and extrapyramidal signs were prominent on the left side Pramipexole up to 1.5 mg, 3 times a day yielded a persistent benefit on RLS symptoms vPSG or PSG not performed
Nishida et al. [31], 2013	Case report of a 64-year-old woman with RLS secondary to end-stage renal disease. RLS persisted in the phantom limb after an above knee amputation of the left lower leg	Vascular disease: severe obliterative arteriosclerotic arteriopathy leading to gangrene in chronic renal failure due to diabetic nephropathy	Restless sensations were almost identical to those experienced before amputation with symptoms appearing mainly in the left phantom limb, starting at around 4 p.m. and continuing until midnight every day; laboratory findings indicating kidney failure; nerve conduction study: polyneuropathy due to diabetes Talipexole 0.8 mg/day yielded a persistent benefit Hemodialysis was also useful PSG with increased PLMS index recorded in the right lower limb
Skidmore et al. [28], 2009	Case report of a 54-year-old man who had an above knee amputation of his left lower leg 22 years before the appearance of RLS	Trauma	When the patient was asked to image movements of both the phantom and the normal limb, he had no benefit on restless sensation Ropinirole (unspecified dosage) yielded a persistent benefit vPSG or PSG not performed
Vetrugno et al. [29], 2010	Case report of a 56-year-old man who had a bilateral above-knee and right below-elbow amputations, 5 years before the appearance of RLS	Vascular disease: severe obliterative arteriosclerotic arteriopathy leading to gangrene in the course of chronic renal failure due to glomerular nephropathy	Correction of dialysis-related hyperphosphoremia and iron deficiency were noted to transiently ameliorate RLS symptoms Ropinirole 1 mg yielded a persistent benefit vPSG found to be useful as supporting evidence by detecting PLMS more proximally to the stumps

PLMS, periodic limb movements in sleep; PSG, polysomnography; RLS, restless legs syndrome; vPSG, video polysomnography.

diagnosis and questionnaires; (2) the utility of neurophysiology; (3) discrimination between primary and secondary forms of RLS and between cases in whom the syndrome was present before limb amputation or those in whom it appeared later; and (4) response to drugs.

Diagnostic Criteria and Severity Questionnaires

RLS diagnostic accuracy is an important issue considering that each individual aspect of this disease may apply to a number of other conditions [33]. Therefore, the International RLS Study Group diagnostic criteria must be met and this was the case of the 5 case reports [27–31], but all of these studies are earlier than 2014 and therefore to the current updated diagnostic criteria [17]. Moreover, an easy-to-use instrument is available, which can be applied to all patients with RLS to measure disease severity for clinical assessment, research, or therapeutic trials – the International RLS study group rating scale (IRLS) [34] – which was found to have high levels of internal consistency, inter-examiner reliability, test – retest reliability over a 2–4 weeks period, and convergent validity. In 3 [29–31] of the 5 case reports under consideration, the IRLS was administered with an indisputable *ex adiuvantibus* utility in assessing the benefit on RLS symptoms by dopamine receptor agonists intake. No RLS rating scale was administered in 2 studies [27, 28], and this methodological limit was acknowledged by the authors of one [28] of the articles. In the case series by Brenning [26], diagnosis is entrusted to the clinical acumen of the author and the description is that of "*nocturnal sensations of leg cramp without simultaneous muscular cramp*"; this significantly reduces the possibility of an in-depth evaluation of diagnostic accuracy and clinical severity. In the study by Giummarra and Bradshaw [32], a questionnaire to qualify pain was used leading to highlight the presence of 33 cases (13% of the sample) with unpleasant sensations of the limbs at night inducing to assume that some could have been real pRLS patients and some others pRLS mimics. With a more thorough investigation, 5 of the 33 cases clearly met the diagnostic criteria of RLS and, possibly, might not be mimics. These are all cases of lower limb amputation; the subjects reported not only worse nocturnal pain but also sensation of spontaneous phantom limb movements characterized by jerking, spasm, tremor worsening when lying down with an urge to move.

Neurophysiological Findings

Polysomnographic (PSG) and even more video-PSG (vPSG) data are useful in this context in order to consider prolonged sleep latency and reduced sleep efficiency [35]. Moreover, in the *pre-dormitum*, vPSG may show that patients present motor restlessness in bed with stretching, fidgeting, tossing, and turning of stumps [36]. PSG also allows to detect PLMS, which are frequently observed in RLS sufferers and are associated with arousal from sleep [37]. They have very specific characteristics consisting on repetitive episodes of leg movement activity (at least 4 in a row) with a duration of up to 10 s and an inter-movement interval of 10–90 s [38]. The number of PLMS, quantified by the PLMS index, drops after adequate therapy and is a good objective marker of the effectiveness of dopamine receptor agonists on RLS symptoms [39]. In amputees, PLMS can be recorded from the unharmed limb [31] or from the stumps [36]. Three of the 5 case reports include a neurophysiological evaluation [30, 31, 36] allowing a more in-depth assessment of their pathophysiological features.

Primary and Secondary pRLS

Both Nishida et al. [31] and Vetrugno et al. [29] described patients with pRLS secondary to chronic renal failure. The other 3 case reports relate to primary forms of the disease [27, 28, 30]. The patient described by Nishida et al. [31] was the only one who had a RLS diagnosis prior to amputation with a post-operation persistence of the symptoms.

The patient described by Hanna et al. [27] was first placed on metoclopramide because of diabetes-related gastroparesis and gastroesophageal reflux and then developed classic signs of Parkinson's disease (PD), predominantly on the left side, including rigidity, bradykinesia, and severe left arm tremor at rest.

Response to Therapy with Dopamine Receptor Agonists

Therapy with dopamine receptor agonists yielded a marked reduction of pRLS symptoms [27–31] with lower scores at IRLS [29–31] and decreased PLMS index [29–31]. The patient described by Dempewolf et al. [30] was treated with pramipexole 0.18 mg/day, levodopa, tilidine, gabapentin, amitriptyline, and all these drugs were soon suspended for their side effects on the *sensorium*; however, pramipexole, until it was used, yielded a benefit on pRLS symptoms.

Discussion

The number of pRLS cases in the international literature is still limited. More reports and clinical trials are needed to improve our knowledge on this particular phenomenon. In

Table 2. Research agenda for pRLS

– Better define the prevalence and characteristics of RLS in amputees
– Develop follow-up studies on pRLS with patients reporting which are the most common triggers for pain and uncomfortable or unpleasant sensations
– Test the hypothesis that RLS may be, at least in part, a pain pattern in the chronic pain population
– Ponder whether the pRLS can be instrumental in supporting the hypothesis of a central dopaminergic dysfunction in the development of RLS
– Consider that central somatosensory circuitries might be impaired in RLS

RLS, restless legs syndrome; pRLS, phantom RLS.

future reports, it will be very important to diagnose pRLS by strictly applying the standard international criteria [17] as well as with the use of the validated RLS severity questionnaire (IRLS) [34] and with vPSG recording at baseline and during the follow-up (long-lasting follow-up studies are still missing). Three of the studies reported here did use both questionnaires and neurophysiology [29–31].

There are at least 3 indirect types of evidence of a CNS impairment during pRLS.

(1) Preexisting restless symptoms persisted even after amputation of the affected limb suggesting that the area responsible for this end-stage renal disease-related RLS case may be at the spinal level or in the higher CNS [31].

(2) As introduced above, a case was reported of pRLS with a later onset of PD triggered by metoclopramide [27]. The asymmetry of parkinsonian symptoms suggests that metoclopramide may have favored the emergence of an underlying/subclinical PD. Therefore, it can be supposed that this subject had a central dopamine-deficient state predisposing him to both RLS and PD. The authors of this interesting report then propose to expand the spectrum of phantom limb phenomena to include pRLS.

(3) The dopaminergic system seems to play a central role in the pathophysiology of RLS, based on the demonstration of the efficacy of the therapy with *L*-Dopa and dopamine receptor agonists for RLS symptoms [40]. Dopamine receptor agonists yielded a marked reduction of the pRLS symptoms [27–31]. In RLS, anatomopathological [41], cerebrospinal fluid [42], and imaging studies [43] have shown reduction of brain iron content at the level of the *substantia nigra* and in the thalamus, which includes different sensorimotor and limbic/nociceptive networks. This might trigger a consequent metabolic dysfunction of the mesolimbic and nigrostriatal dopaminergic pathways, and in turn, a dysregulation of limbic and sensorimotor networks within the dopaminergic system in the brain [43]. These are also structures contributing to the neurosignature of the phantom phenomena [5, 14–16]. In detail, with an analysis of high-resolution 3-dimensional MRI, the comparison of RLS patients and normal controls disclosed a significant regional decrease in gray matter volume in the bihemispheric primary somatosensory cortex, which additionally extended into the left-side primary motor areas, and all clusters correlated with both severity of RLS symptoms and disease duration [44]. Furthermore, the delineation of potential cerebral white matter tract disruption in RLS was investigated by quantitative whole brain-based diffusion tensor imaging in patients with the idiopathic form. The computation of regional fractional anisotropy was included, as a quantitative marker of white matter integrity. Reduced fractional anisotropy was observed in RLS patients bihemispherically, in close proximity of the primary and associate motor and somatosensory cortices [45], which are brain areas whose reorganization plays a pivotal role in mechanisms underlying the phantom limb pain [3, 5, 14–16, 46]. This finding allows to assume that the brain areas responsible for RLS and phantom limb pain might overlap. Giummarra and Bradshaw [32] reported clear similarities in sensory symptoms of phantom limb pain and RLS and suggested that a model of RLS may provide new insights into the mechanisms underlying phantom pain with central changes associated with an abnormal reorganization in the neuromatrix to a preexisting pain state [16]. Defining the mechanisms underlying phantom pain may finally suggest advancements in its treatment [32].

Finally, taking into consideration the whole knowledge about pRLS, it is possible to speculate that it can be included in the wide area of neuropsychiatric pathology where the preexisting self-perception remains stably in an abnormal state, such as in the case of anorexic persons that continue to perceive themselves fat despite their cachectic state [47].

Conclusions

Overall, the reports reviewed in this brief essay point out that RLS may be part of the spectrum of phantom limb phenomena, indirectly confirming that the brain retains a neurosignature, even after limb amputation, responsible for the unpleasant experience. The methodology and results of the interesting study by Giummarra and Bradshaw [32] inevitably indicate the need of a proper differentiation between RLS and RLS mimics [48] by means of the proper use of updated diagnostic criteria [17] and vPSG for the measurement of PLMS before and after the introduction of an adequate drug therapy. Studies are now warranted to test the hypothesis that RLS may be, at least in part, a pain pattern in the chronic pain population. Table 2 summarizes this and some other research objectives arising from this brief review.

Disclosure Statement

The authors declare no conflicts of interest.

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