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CLINICAL REVIEW

Restless legs syndrome in multiple sclerosis

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SUMMARY

Restless legs syndrome (RLS) is a sleep-related sensory-motor disorder characterized by an irresistible urge to move the legs accompanied by unpleasant sensations in the lower extremities. According to many recent studies patients with multiple sclerosis (MS) suffer frequently from symptoms of RLS. The prevalence of RLS in MS patients varies 13.3%–65.1%, which is higher than the prevalence of RLS in people of the same age in the general population. MS patients with RLS have higher scores in the Expanded Disability Status Scale compared to MS patients without RLS. Presence of RLS has a negative impact on sleep quality and fatigue of MS patients. Iron deficiency and chronic inflammation may be factors contributing to development of RLS in MS. The relationship between the course and treatment of MS and RLS requires further prospective studies.

Introduction

Restless legs syndrome (RLS) is a sleep-related sensory-motor disorder characterized by an irresistible urge to move the legs during rest. This is usually accompanied by unpleasant sensations and discomfort of the lower extremities. The symptoms appear or increase in the evening or night and during periods of rest. Moving the legs brings total or partial relieve [1]. The essential, supportive and additional clinical features of RLS, published in 2003 by the International Restless Legs Syndrome Study Group (IRLSSG) are presented in Table 1. RLS is frequently accompanied by periodic limb movements (PLMs) which are sleep-related rhythmic, repetitive movements of the legs that may resemble the Babinski sign. PLMs are present in most RLS patients but can also be found in many other sleep and wake disorders [2].

In adults, the prevalence of symptoms of RLS vary between five and 15% and the prevalence of clinically significant RLS is between one and five percent [3]. The prevalence is higher in women and it increases with age [4,5].

There are two forms of RLS, idiopathic and secondary RLS. In idiopathic RLS the first symptoms of RLS appear usually before the age of 50 y, while secondary RLS starts often later in life. In idiopathic RLS 40–90% of patients report a positive family history indicating a strong genetic influence [6]. Four genes have been associated with RLS in genome-wide association studies: *BTBD9*, *MEIS1*, *PTPRD* and *MAP2KP/SCOR1*. However, the possible role of these genes in determining the clinical course of RLS is unknown [7–9]. There is a strong line of evidence linking RLS to decreased iron stores in the brain. This central iron deficiency may cause disturbances in the metabolism of dopamine [10]. Disordered dopaminergic transmission is probably one of the most important components in pathophysiology of RLS, as concluded from the efficiency of dopaminergic drugs and from studies of animal models of RLS [11]. It has been postulated recently that the dopaminergic neurons located in the A11 region, which are probably the only source of dopaminergic pathways for the spinal cord, are involved in the pathology of RLS [12]. Deregulation of spinal dopaminergic transmission may lead to hyperexcitability of spinal motor and sensory pathways and cause the symptoms of RLS and PLMs [13,14].

The conditions that cause secondary RLS include iron deficiency [15], pregnancy [16], and end-stage kidney disease [17]. The prevalence of RLS is increased in many diseases, such as neuropathies

Abbreviations: RLS, restless legs syndrome; PLMS, periodic limb movements in sleep; MS, multiple sclerosis; EDSS, expanded disability status scale; NAWM, normally appearing white matter; sTfR, soluble transferrine receptor; NO, nitric oxide; NOS, nitric oxide synthase; TNF-α, tumor necrosis factor alpha; REMS, The Restless Legs Syndrome in Multiple Sclerosis Study; Il-6, interleukine - 6; CNS, central nervous system; REM, rapid eye movement; MRI, magnetic resonanse imaging; MBP, myelin basic protein; PLP, proteolipid protein; CNPase, cyclic nucleotide phosphohydrolase; MOG, myelin oligodendrocyte glycoprotein; nNOS, neuronal nitric oxide synthase; IRLSS, International Restless Legs Syndrome Severity Scale; IRLSSG, International Restless Legs Syndrome Study Group; FSS, Fatigue Severity Scale.

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Table 1
Clinical features of restless legs syndrome (RLS) (Allen et al., 2003).[1].

Essential diagnostic criteria
1) An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs)
2) The urge to move or unpleasant sensations begin or worsen 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, at least as long as the activity continues
4) The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present

Supportive clinical features
1) The prevalence of RLS among first-degree relatives of people with RLS is 3–5 times greater than in people without RLS
2) Nearly all people with RLS show at least an initial positive therapeutic response to either L-dopa or a dopamine-receptor agonist
3) Periodic limb movements in sleep occur in at least 85% of cases

Associated features
1) When the age of onset of RLS symptoms is less than 50 y, the onset is often more insidious; when the age of onset is greater than 50 y, the symptoms often occur more abruptly and more severely
2) Disturbed sleep is a common major morbidity for RLS
3) The physical examination is generally normal and does not contribute to the diagnosis, except for those conditions that may be comorbid or secondary causes of RLS.

[18], primary headaches [19], myasthenia gravis [20], rheumatoid arthritis [21], celiac disease [22] or liver diseases [23].

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system. Its etiology is not completely understood. It is characterized by appearance of relapsing or progressing focal neurological deficits. An association of MS with sleep disorders, such as narcolepsy, REM sleep behavior disorder, sleep disordered breathing or insomnia, has been described [24].

Sensory symptoms, and also symptoms of RLS are common in MS as noted for the first time by Rae-Grant and collaborators in 1999 [25]. Patients with MS describe their painful symptoms as burning, itching, electric or formicatory pain, resembling pain described by patients with RLS. Patients with MS localize their symptoms to legs and feet, trunk, arms and hands. The first epidemiological study on the occurrence of RLS in multiple sclerosis (MS) was reported by Auger et al. in 2005 [26]. Since that time numerous papers focusing on the relation between RLS and MS have been published [27,28–37]. The aim of this review is to analyze the available data on the epidemiology and etiology of RLS in MS patients and to suggest future directions of research.

Epidemiological data

The prevalence of RLS in MS reported by the studies published to date ranges from 13.3% to 65.1% (Table 2). The data available from these studies are presented in Table 2. All published papers (with one exception [38]) showed that RLS is significantly more prevalent in MS patients than in the general population.

RLS in the general population is characterized by the following traits: a higher prevalence among women and in older individuals and a high prevalence of subjects with a positive family history. This pattern was not fully replicated in studies of RLS in MS patients. A significant relationship with the female sex was found in only two studies [28,35] and MS patients with RLS were older than patients without RLS in only five studies [27,28,32,35,37]. Li et al. analyzed the menopausal status of the female patients with MS. The authors found that premenopausal women are at higher risk (OR = 5.08) of developing RLS than postmenopausal women (OR = 2.00). The authors hypothesized that this is a consequence of lower iron levels resulting from menstrual loss of blood [36].

The authors of some of the published papers focused on the prevalence of RLS in the families of MS patients. A positive family history of RLS was found in 2.4%–27.1% of the patients with MS having also RLS [27,28,34,35,37,39], which is significantly less than the occurrence of family history in idiopathic RLS in the general population [6].

The most prominent fact regarding the studies of the occurrence of RLS in MS patients is the wide range of results. There are few reasons for those discrepancies. All groups that performed those studies applied the 2003 diagnostic criteria of RLS proposed by the IRLSSG. Nonetheless the publications differed regarding the mode of application of the criteria. The authors used patient-filled questionnaires, interviews and structured interviews. The highest RLS prevalence rates were found in studies using patient-filled questionnaires. Some symptoms of RLS are difficult to explain in the form of a short question included in a questionnaire. Some symptoms of MS (paraesthesias in the limbs, sensory symptoms as described by Rae-Grant et al. [25] and also spastic symptoms) can resemble the symptoms of RLS. Ideally, the exact nature of the RLS symptoms should be verified in an interview and neurological examination by a physician with experience in RLS. Personal interviews with the patients are preferred to patient filled questionnaires. The patients who participated in the study performed by Deriu et al. filled a questionnaire (which gave a prevalence rate of 45%) and then underwent an interview that reduced the frequency of the diagnosis of RLS to 27% [30]. These results suggest that the application of a self-administered questionnaire may lead to numerous false-positive diagnoses. Also personal

Table 2
Prevalence of RLS in MS patients according to published studies.

Publication: First author (year of publication)	Number of MS patients/controls	Method	Prevalence of RLS in MS (%)	Prevalence of RLS in controls (%)
Auger (2005) [26]	200/100	PtQ	37.5	16
Manconi (2007) [27]	156/-	Int, NeurEx.	32.7	NA
Gómez-Choco (2007) [38]	135/118	Int	13.3	9.3
Manconi (2008) [28]	861/649	Int,	19	4.2
Moreira (2008) [29]	44/-	PtQ,	27	NA
Deriu (2009) [30]	202/212	PtQ, Int,	14.6	2.8
Douay (2009) [33]	242/-	PtQ	18	NA
Aydar (2011) [32]	98/129	Int	27.6	10.1
Fragoso (2011) [31]	80/180	Int	57.5	18.3
Vávrová (2012) [35]	765/-	Int	32	NA
Li (2012) [36]	264/65280	PtQ	15.5	6.4
Miri (2012) [34]	205/-	Int	27.8	NA
Shaygannejad (2013) [37]	126/126	PtQ	65.1	12.7

PtQ: patient-filled questionnaire; Int: interview; NeurEx: neurological examination.