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CLINICAL REVIEW

When gender matters: Restless legs syndrome. Report of the "RLS and woman" workshop endorsed by the European RLS Study Group

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SUMMARY

Sleep is an essential human behavior that shows prominent gender differences. Disturbed sleep, in particular, is much more prevalent in females than males. Restless legs syndrome (RLS) as one cause of disturbed sleep was observed to be somewhat more common among women than men in Ekbom's 1945 seminal series of clinical cases with the disease. He, however, reported this gender difference mainly for those with more severe symptoms. Since then numerous studies have reported that women are affected by RLS about twice as often as males for mild as well as moderate to severe RLS. The present review focuses on RLS in females from the perspectives of both epidemiology and pathophysiology. RLS will generally become worse or might appear for the first time during pregnancy. Parity increases the risk of RLS later in life suggesting that pregnancy is a specific behavioral risk factor for developing RLS. Some evidence suggests that dysfunction in iron metabolism and high estrogen levels might contribute to RLS during pregnancy. But, menopause does not lower the incidence of RLS nor does hormone replacement therapy lead to an increase, suggesting a quite complex uncertain role of hormones in the pathophysiology of RLS. Therefore, further, preferably longitudinal studies are needed to unravel the factors causing RLS in women. These studies should include genetic, clinical and polysomnographic variables, as well as hormonal measures and variables assessing iron metabolism.

Introduction

In surveys on subjectively disturbed sleep, there is overwhelming evidence for a clear-cut preponderance of females,[1] particularly beyond the age of 40. The underlying causes are still under investigation, but some contributing factors are known: insomnia is tightly linked to depression which is much more prevalent in women compared to men.[2] Night time care of children and other family members, tasks more commonly performed by women, increases their vulnerability to disturbed night sleep.[3] Hormonal changes, related to the menstrual cycle, pregnancy and ageing are prominent additional challenges to women's sleep. The influence of female steroidal sex hormones on sleep is, however, complex.[4] In healthy women, for example, polysomnographically recorded sleep is remarkably stable across the menstrual cycle,[5] whereas subjective reports of sleep disturbances are both frequent for women in the late luteal phase and associated with depressed mood, affective lability, anxiety and other emotional symptoms known as premenstrual dysphoric disorder.[4] Of course, the cessation of ovarian endocrine function during menopause also influences sleep and it is not surprising that during the 4th and 5th decade of life the prevalence of sleep problems in women increases to up to 25%.[6] However, hormonal changes are unlikely to be the only cause of this increase, because hormonal replacement therapy (HRT) is not able to entirely reverse these age-related changes.[4] Finally, pregnancy and delivery result in profound changes in

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Abbreviations

AC	active controlled
CO	crossover
CSF	cerebrospinal fluid
DB	double blind
FMT	female-to-male transsexuals
HRQoL	health related quality of life
HRT	hormone replacement therapy
IQR	interquartile range
IRLSSG	international restless legs syndrome study group
MFT	male-to-female transsexuals
MRI	magnetic resonance imaging
PC	placebo controlled
PG	parallel group
PLM	periodic leg movements
R	randomized
REST	RLS epidemiology, symptoms and treatment
RLS	restless legs syndrome
RLSQoL	restless legs syndrome quality of life
SD	standard deviation
SF-36	short form (36) health survey

hormonal secretion. Sleep problems start quite early in pregnancy indicating endocrine causes and tend to increase as the pregnancy progresses, suggesting that particularly in late pregnancy mechanical aspects might also contribute.[7]

The last trimester of pregnancy is also a time of increased prevalence of restless legs syndrome (RLS), which may occur in up to 30% of pregnant women. In those women affected, the typical symptoms of the disorder including unpleasant sensations in the legs and an almost mandatory drive to move, tend to further aggravate the sleep problems occurring in late pregnancy.[8] Additional evidence reviewed below shows that even in non-pregnant women RLS might be about twice as frequent as in males.

Hence the female side of RLS seems quite important and our effort in this paper is to review for the first time the epidemiological data and the evidence explaining the increased prevalence of RLS in general and under specific conditions in females. Of course, the interaction of hormones and RLS will be a major topic of this review, but also iron metabolism, which is closely linked to RLS and consistently affected by pregnancy, will be discussed.[9] The present review was endorsed by the European RLS Study Group and written by the participants of the workshop on "RLS and women" which took place in Munich, Germany (December 2009).

Female prevalence

In 1945, the Swedish neurologist K.A. Ekbom published his thesis "Restless legs. A clinical study of a hitherto overlooked disease in the legs".[10] Thus Ekbom coined the name of this disorder and wrote what still is considered to be one of the most substantial and comprehensive works on RLS. Ekbom reported a prevalence of 5.2% of restless legs in subjects living in Stockholm. There was a female predominance noted for more severe cases.[10] After Ekbom's report, there have been more than thirty published epidemiological studies focusing on RLS.[11]

Data on the occurrence of RLS are quite variable and this may be due to several reasons. It is important to define the study population, i.e., whether the sample studied represents a clinical patient population or harvested in the general population. Moreover, the instruments used for the diagnosis of RLS vary between different epidemiological studies.

Different strategies of data collection may influence the results. Face-to-face interviews and examinations by trained physicians are the most sensitive and specific way to acquire the data.

In 1995, the International restless legs syndrome study group (IRLSSG) published a consensus report for the diagnosis of RLS.[12] Data from studies performed before 1995, and some studies performed after 1995 as well, used different diagnostic instruments in order to ascertain the population defined as RLS. Thus reports on the occurrence of RLS, not using the criteria from 1995 or the revised criteria from 2003,[13] are not directly comparable to each other or to later studies.

In a recent substantial and comprehensive population-based survey, face-to-face home interviews were conducted in a random sample of 10,263 French adults.[14] The four features defined by the IRLSSG in 1995 were used to assess the prevalence of symptoms consistent with a diagnosis of RLS. The 12-month prevalence of RLS symptoms in the French adult population was estimated to be 8.5%, with a higher prevalence observed in women (10.8%) than in men (5.8%). Prevalence increased with age until 64 years and decreased thereafter in both genders. RLS was often underdiagnosed and few subjects received recommended RLS drug treatment. Accordingly, the prevalence of RLS in the Caucasian population seems so be about 5–15%. What we know from these studies is that there seems to be strong evidence for a female preponderance in the prevalence of RLS and that RLS prevalence increases with age. The female/male ratio is often 2–3/1.[11] Data harvested on the occurrence of RLS from countries outside Europe and USA are still few.

There are very few studies on the occurrence of RLS that did not report a female preponderance in RLS. Table 1 shows the prevalence of RLS in both genders in epidemiological surveys performed on a random sample of the population in different countries by using the IRLSSG definition to diagnose RLS.

Quality of life in women with RLS

One way of defining the concept of health related quality of life (HRQoL) is: "The extent to which one's usual or expected physical, emotional and social well-being are affected by a medical condition". Individual patients with the same objective health status can report dissimilar HRQoL due to unique differences in expectations and coping abilities and it must be measured from the individual's viewpoint.

Previous studies focusing on gender differences in HRQoL have reported consistently worse results for women. This has been a subject of controversy and much is written on the topic. Whether this is attributable to sociocultural, socioeconomic or biomedical factors has not been determined definitively.[15] It is proposed that women have a greater "inclusiveness" of various sources of

Table 1
Studies on the prevalence of RLS performed in random samples of the general population of different countries, using the IRLSSG criteria to assess the diagnosis.

First author, year of publication	Country	Sample size	Total RLS prevalence (%)	Prevalence (%) female/male
Ohayon, 2002[88]	UK, Germany, Italy, Spain, Portugal	18980	5.5	
Sevim, 2003[a,89]	Turkey	3234	3.2	
Berger, 2004[19]	Germany	4310	10.6	
Bjorvatn, 2005[90]	Norway, Denmark	2005	11.5	13.4/9.4
Tison, 2005[a,14]	France	10263	10.3	10.8/5.8
Högl, 2005[a,53]	Austria	701	10.6	14.2/6.6
Hadjigergiou, 2007[91]	Greece	3033	3.9	
Ulfberg, 2007[92]	Sweden	1000	5.0	5.7/3.5
Cho, 2009[a,93]	South Korea	6509	0.9	1.3/0.6

[a] Surveys based on face-to-face interviews.