

Supplementary material

Restless legs syndrome associated with major diseases: a systematic review and new concept

Methods

Definition of inclusion and exclusion criteria for topics

For the current analysis we included only major diseases from internal medicine, sleep medicine, and neurology that have been attributed to RLS in the past. Given the need to focus this review we excluded psychiatric disorders such as depression and anxiety disorders. The same applies for drug-induced RLS and RLS in special populations such as children and patients with cognitive impairments, as well as RLS in pregnancy and during lactation.¹ Review articles without original data and treatment trials in idiopathic and secondary RLS were also not considered.

Literature search: Search strategy and selection criteria

We systematically searched PubMed on August 13 2014 using the following search terms: anemia, apnea, ataxia, cardiovascular, chronic obstructive pulmonary disorders, dialysis, endocrine, endocrinology, gastrointestinal, headache, heart insufficiency, hepatitis C, hypertension (arterial), hypoxia, inflammation, iron deficiency, kidney disease, migraine, multiple sclerosis, multiple system atrophy, muscle disorder, narcolepsy, neuropathy, Parkinson disease, polyneuropathy, radiculopathy, stroke, thyroid, uremia, varicose veins, vascular disease AND RLS. In addition, we also searched the references of major review articles. We only included full peer-reviewed original articles in English, and excluded all case reports and cohort studies with a baseline group of less than five patients (see table e-1 for an overview of studies included). We also included studies that supported or excluded the association of RLS with any disease by investigating possible major pathophysiological mechanisms.

Articles were classed by medical disorder, and evidence level and data were extracted into tables (see table e-1) by the authors. A total of 494 articles were screened, following initial screening 112 studies were excluded as they did not meet the abovementioned inclusion criteria, and a further 115 articles were eliminated following in-depth review. A total of 267 studies were finally reviewed, certain studies were reviewed more than once as they covered more than one medical disorder/condition.

Medical disorders

Varicose veins

The potential association of varicose veins and RLS remains inadequately studied. Six studies examined the association with RLS, but the majority evaluated “restless legs” as one of several “symptoms of varicose veins”, and not according to formal standard criteria, therefore, no conclusions can be drawn.²

Gastrointestinal and inflammatory diseases

Eight studies investigated Crohn’s disease, irritable bowel syndrome, and bacterial overgrowth in association with RLS. In two studies there was an increase of RLS in patients with celiac disease compared to controls (31% versus 4%,³ and 30% versus 9%)⁴ and in one study a possible increase for irritable bowel syndrome.⁵ In one study with Sjögren syndrome an increase in RLS has been observed.⁶

Endocrine disorders: thyroid and other

Two studies addressed thyroid function and RLS. One manuscript covering two epidemiological studies reported an OR for incident RLS of 0.74 in one study and 1.63 in the other.⁷ Another study contrasted RLS-like symptoms versus true RLS, and demonstrated that RLS-like symptoms (meeting only three out of four criteria), but not RLS, was increased in patients with thyroid disorders.

Endocrine disorders: diabetes

For type-2 diabetes (T-2D) 15 studies looked into the prevalence of RLS both in observational studies and clinical trials. Two large population-based studies investigated incident cases for RLS and found an OR for diabetes as a single disease and RLS of 2.21 and 2.47,⁷ in the RLS cohort, the OR for diabetes was 1.97 and 2.04.⁸ Several studies used a cross-sectional approach in clinical populations of diabetes patients. RLS was diagnosed through interviews, and an overall increased prevalence of RLS up to 28.7% was found compared to 7.1% in controls in Iran,⁹ and even in Korea the prevalence of RLS in diabetic neuropathy was increased: 8% versus 3.5% in an osteoarthritis population.¹⁰ One study found the increased prevalence of RLS in T-2D restricted to polyneuropathy,¹¹ the other studies could not confirm these associations. Therefore, it remains uncertain if diabetes itself

and its metabolic changes, or diabetic neuropathy may lead to an increased manifestation of RLS symptoms.

Obstructive sleep apnea

Only one study compared the prevalence of RLS in obstructive sleep apnea with spouses as controls, finding a prevalence of 8.3% versus 2.5% respectively, and did not differ significantly.¹²

Chronic obstructive pulmonary disease (COPD)

A few studies reported higher prevalence of RLS in COPD patients, pointing to a possible association (see e-table 1).^{13, 14} Other studies compared COPD with and without RLS and reported increased prevalence¹⁵ and an association with severity.¹⁶ In a small group of exacerbated COPD patients, a very high prevalence of RLS was reported compared to healthy controls, however, the study was retrospective and numbers were small.¹⁷ In a population-based study self-reported obstructive lung disease was found to be a predictor for RLS.¹⁸

Narcolepsy

Few studies reported increased prevalence of RLS in narcolepsy, and only two had adequate control groups. In these two studies, RLS prevalence was 14.7% compared to 3% in controls,¹⁹ and 18% versus 5%²⁰ presented mostly mild symptom severity.^{19, 20}

Hereditary ataxia

Four publications investigated the manifestation of RLS in patients with spinocerebellar ataxias (SCA) types 1, 2, 3, and 6, one of which also analyzed Friedreich's ataxia (FA) finding a 50% prevalence of RLS.²¹ In these small cohort studies, none of which had a control population, the prevalence of RLS varied from 23% to 50% in spinocerebellar ataxias type 3 patients with²² or without²³ association to neuropathy, although no association of RLS and CAG repeat length in SCA forms was detected.²⁴ Two of five patients with SCA 6 showed RLS symptoms.²⁵ As SCA patients suffer from both various sleep disorders and neuropathy, larger cohorts are needed to confirm the suspected association of hereditary ataxias and RLS.

Multiple system atrophy (MSA)

Both types of MSA, Parkinson as well as cerebellar subtypes, have been investigated for additional RLS symptoms. Overall, the three, mostly small studies, do not allow any conclusion to be drawn: only a single multicenter study included a control group²⁶ and documented an increased prevalence of RLS in MSA (28% vs. 14% in PD patients and 7% in controls.²⁶ A recent study found eight of 30 MSA patients suffering from RLS associated with excessive daytime sleepiness.²⁷

Other diseases of the peripheral neuromuscular system

Eleven reports of RLS in muscle disease encompass small studies on rare diseases, some claiming increased prevalence up to, for example, 100% in post-polio syndrome.²⁸ No conclusions can be drawn in this group at present. There is some evidence that fibromyalgia may accompany increased RLS prevalence up to 33%,²⁹ but symptomatology of RLS and fibromyalgia mostly overlap. Still, prevalence of RLS in muscle disease in general and fibromyalgia cannot be provided by the current publications.

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