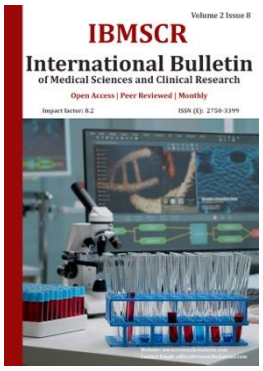

RISK FACTORS ASSOCIATED WITH RESTLESS LEGS SYNDROME

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Abstract

Restless legs syndrome (RLS) is a neurosensorimotor disorder manifested by unpleasant sensations in the lower limbs at rest, which compel the patient to move in order to relieve them. Despite the wide prevalence of the disease, systematizing the risk factors for its development remains a relevant task.

This paper presents an analysis of 19 scientific publications aimed at identifying and assessing the main risk factors for RLS. The pathogenetic mechanisms of the disease are examined, including the role of dopaminergic dysfunction and iron deficiency as a key cofactor in dopamine synthesis. The primary (idiopathic) and secondary (symptomatic) forms of RLS are described, along with their clinical manifestations.

Based on the results of the analysis, the following risk factors for the development of RLS were established: female sex, older age, number of births, tobacco smoking, depression, iron deficiency, excess body weight, and Parkinson's disease.

Keywords: restless legs syndrome, Ekbom disease, risk factors.

Introduction

Restless legs syndrome (RLS, also known by the eponym Ekbom disease) is a neurosensorimotor disorder characterized by unpleasant sensations in the lower limbs that occur at rest (more often at night) and are temporarily relieved by movement. The diagnosis is established when four mandatory criteria are present:

1. an urge to move the legs
2. worsening of symptoms at rest
3. a feeling of relief with movement
4. peak discomfort during the evening and night hours

Subjectively, patients describe the discomfort in quite varied terms: as itching, burning, a crawling "pins-and-needles" sensation, or a specific feeling as though blood were boiling in the veins.

Classification

According to the classification, RLS is divided into two types — primary (idiopathic) and secondary (symptomatic) — which occur with approximately equal frequency [2].

Hereditary predisposition plays a key role in the development of idiopathic RLS: 25% to 75% of patients report a family history, confirming a substantial contribution of genetic factors.

The secondary form of RLS arises against the background of various somatic and neurological conditions. The most common causes are iron-deficiency anemia, pregnancy, chronic kidney disease, and polyneuropathies [2]. In addition, cases of secondary RLS have been described in diabetes mellitus, hypothyroidism and thyrotoxicosis, rheumatoid arthritis, multiple sclerosis, deficiency of vitamin B12, folic acid, thiamine, and magnesium, as well as in COPD [2].

The main cause of RLS during pregnancy is a decrease in iron levels in the body, together with hormonal shifts — elevated levels of prolactin, progesterone, and estrogens [2].

Iron is an obligatory cofactor of tyrosine hydroxylase, the key enzyme that catalyzes the conversion of tyrosine to DOPA in the dopamine synthesis pathway. When iron is deficient, the activity of this enzyme decreases, leading to reduced dopamine synthesis and a subsequent disruption of dopaminergic transmission at the synapse.

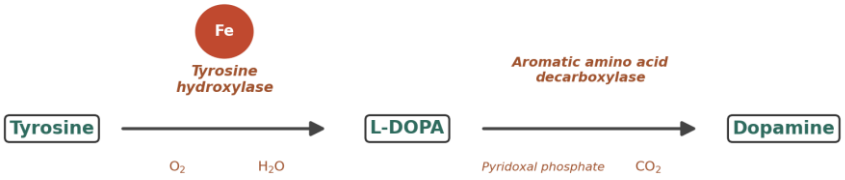

Figure 1. Dopamine synthesis under normal conditions

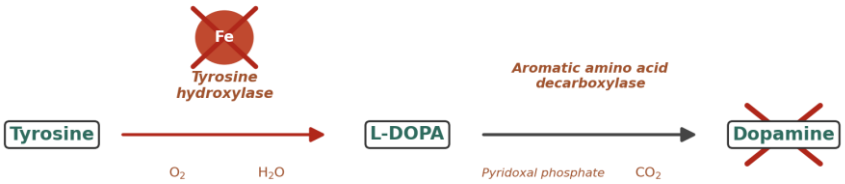

Figure 2. Impaired dopamine synthesis under iron deficiency

The higher prevalence of RLS during pregnancy may be related to a threefold increase in iron requirements: the placenta increases iron uptake at the expense of maternal stores, leading to maternal iron deficiency [4].

Clinical Picture

The diagnosis of RLS is based on four criteria:

1) presence of an urge to move the legs, usually accompanied by unpleasant sensations
2) worsening of symptoms at rest
3) relief with movement
4) worsening of symptoms in the evening and night hours [6, 7, 48]

The discomfort is localized mainly deep within the calves and is described by patients in various ways: itching, burning, a feeling of distension, “pins and needles,” “legs being twisted,” or “blood boiling in the veins” [7].

Among the biochemical disturbances seen in RLS, iron deficiency holds a central place. Iron deficiency is one of the most important factors in the development of the disease; analysis of blood ferritin level is considered the most reliable indicator [6]. In clinical observations, iron-deficiency anemia was diagnosed in 49% of patients with idiopathic RLS.

Risk Factors

Sex

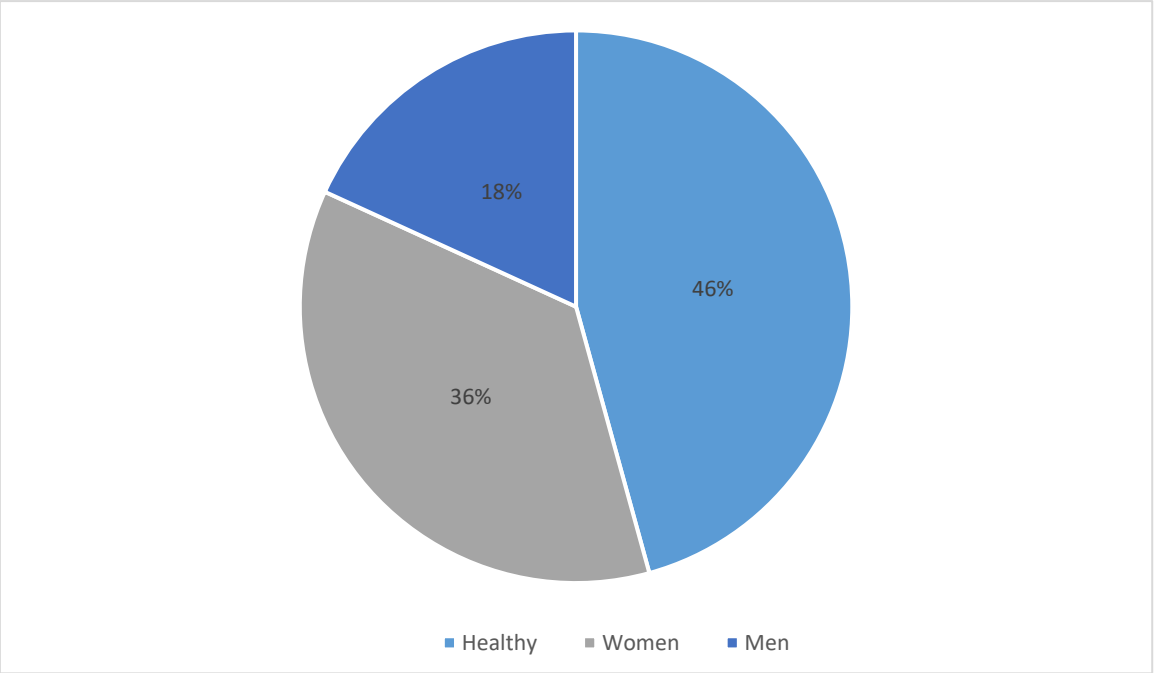

Figure 3. Effect of sex on the risk of developing RLS

The severity of restless legs syndrome was higher in women, whereas the rate of periodic limb movements during sleep was higher in men [7].

Age

Although RLS occurs in patients of all ages, one of the factors positively associated with restless legs syndrome is older age (hazard ratio [HR] = 1.13; 95% confidence interval [CI] = 1.04–1.24) [10].

Number of Births

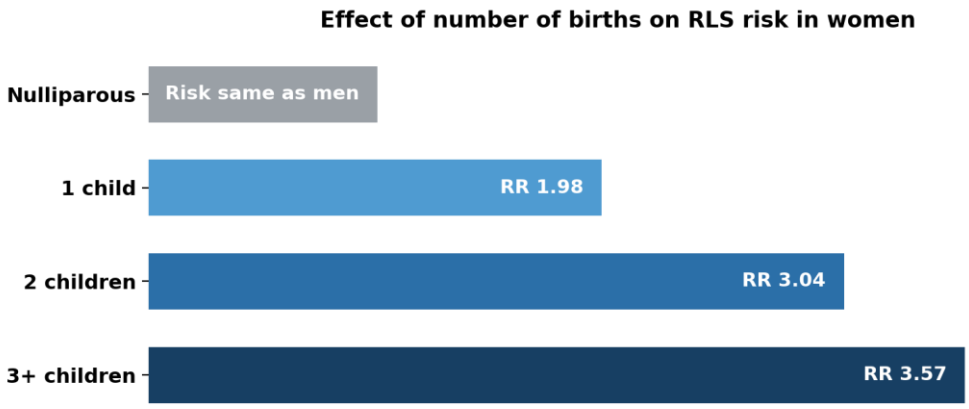

Figure 4. Effect of number of births on the risk of developing RLS

In a study involving 4,310 people aged 20 to 79 years, RLS was identified in 10.6% of participants, with women affected twice as often as men. Although the prevalence among

nulliparous women was similar to that among men up to age 64, the risk of developing restless legs syndrome increased progressively among women with:

one child (RR 1.98; 95% CI 1.25–3.13)

two children (RR 3.04; 95% CI 2.11–4.40)

three or more children (RR 3.57; 95% CI 2.30–5.55) [5].

Smoking

In multivariate analysis, tobacco smoking (RR 1.28, 95% CI 1.07–1.53; p = 0.008) and anxiety (RR 1.34–1.42; p < 0.05) were associated with persistent restless legs syndrome [6].

Depression

Individuals with restless legs syndrome showed significantly more symptoms of depression than individuals without RLS, according to the Beck Depression Inventory (mean difference [MD] = 6.58, 95% CI = 5.54–7.62, p < 0.01). Similarly, results from the Beck Anxiety Inventory showed that individuals with RLS had significantly more pronounced anxiety symptoms than those without RLS (MD = 9.30, 95% CI = 7.65–10.94, p < 0.01) [8].

In addition to RLS contributing to the development of depression, depression itself is also a risk factor for the development of RLS (HR = 1.71; 95% CI = 1.26–2.32) [10].

In a 6-year study involving 56,399 women (mean age = 68 years) who had no symptoms of depression at baseline, the authors identified 1,268 cases of clinical depression over 300,155 person-years of follow-up. Women with RLS at baseline had a higher probability of developing clinical depression (multivariable-adjusted HR = 1.5, 95% CI: 1.1–2.1; P = 0.02) than women without RLS [9].

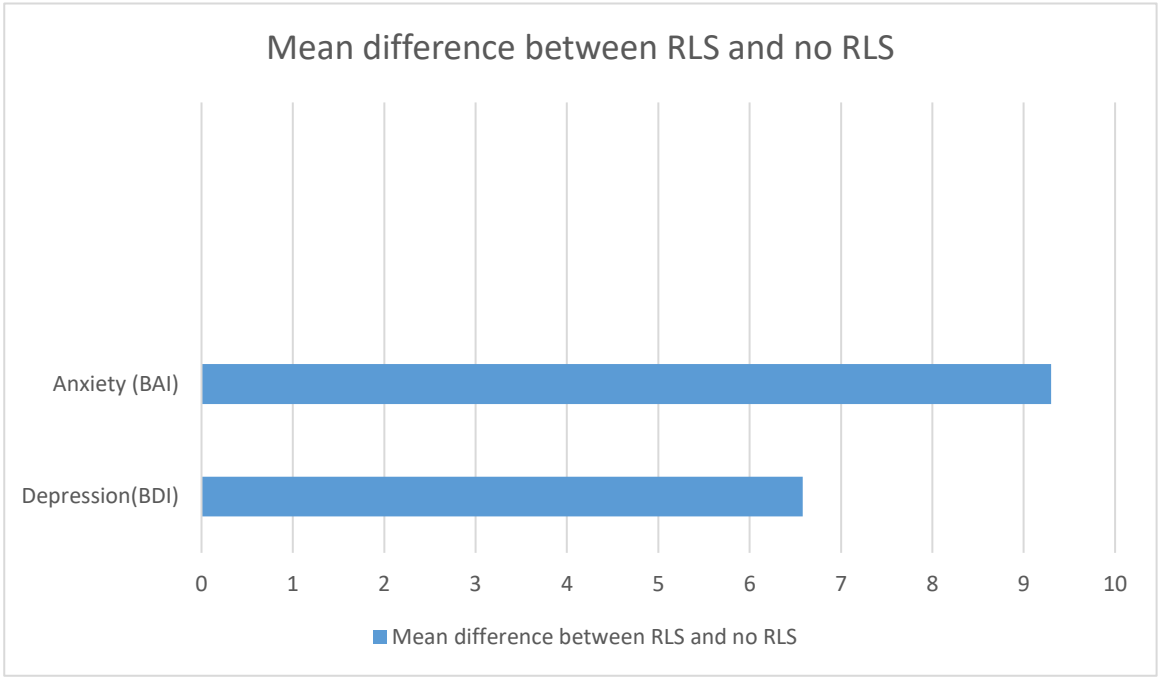

Figure 5. Mean difference in anxiety and depression scores between patients with RLS and controls, using the Beck scales

Low Socioeconomic Development

Prevalence was similar in regions with a high socioeconomic development index (7.29%; 95% CI = 5.04–10.41) and a low socioeconomic development index (7.10%; 95% CI = 5.16–9.70), although most cases occurred in countries with a low socioeconomic development index (323.06 million, 90.73%) [10].

Low Iron Levels

Reduced iron stores are also a risk factor for the development of RLS, as confirmed in studies with a combined total of 213 participants [6, 11, 12, 13, 16].

Patients with restless legs syndrome showed significantly lower iron indices:

mean serum ferritin level (88.4 ± 25.6 ng/mL vs. 126.7 ± 30.1 ng/mL)

transferrin saturation (16.3 ± 4.7% vs. 22.1 ± 5.6%)

and serum iron (48.2 ± 11.4 µg/dL vs. 64.7 ± 13.1 µg/dL) [12].

The development of anemia is not a necessary criterion for reduced iron stores in RLS ($p < 0.01$) [15]. Women with iron deficiency without anemia were significantly more prone to RLS: RR = 5.51 [19].

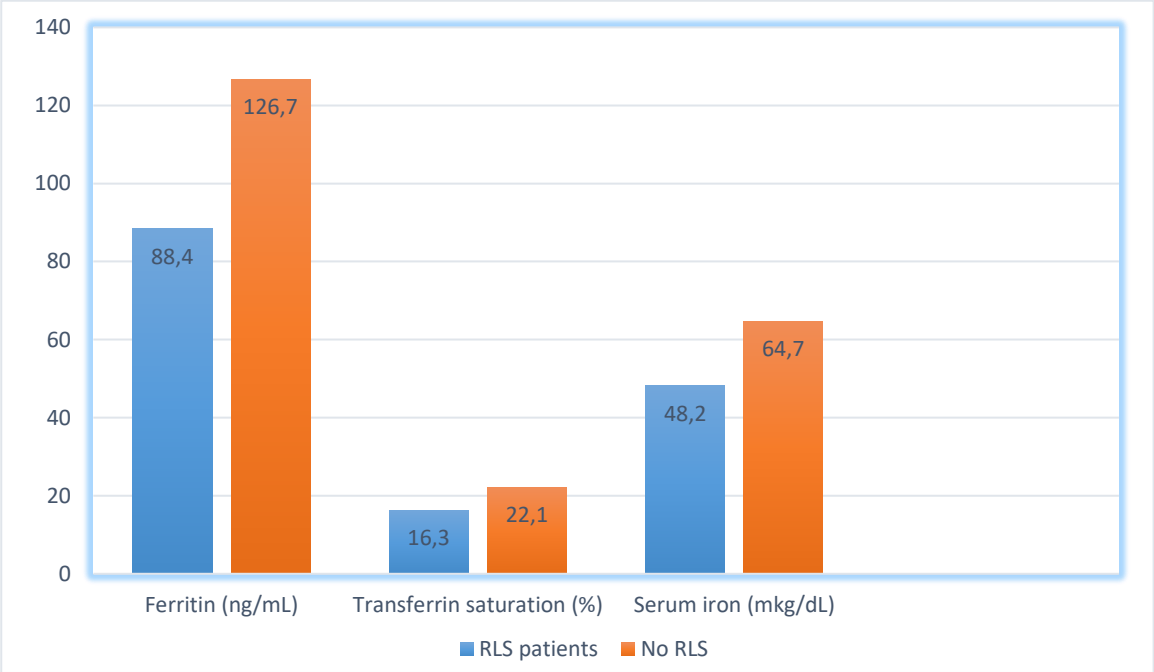

Figure 6. Comparison of biochemical iron markers

Excess Body Weight

In a study of 1,008 people, an association was demonstrated between the development of RLS and excess body weight (RR = 1.77; 95% CI 1.05–2.99) [14].

Parkinson's Disease

The prevalence of restless legs syndrome associated with Parkinson's disease exceeds the rates reported in the general population, indicating a relationship between the two disorders [17]. This is most likely due to impaired dopamine synthesis.

The presence of restless legs syndrome was associated with more than a twofold increase in the risk of developing Parkinson's disease (HR = 2.57, 95% CI: 1.95–3.39) compared with patients without restless legs syndrome [18].

Conclusions

As a result of the analysis of 19 articles, the following risk factors for the development of RLS were identified:

– Sex

– Older age (HR = 1.13; 95% CI = 1.04–1.24)

– Births [one (RR 1.98; 95% CI 1.25–3.13), two (RR 3.04; 95% CI 2.11–4.40), three or more (RR 3.57; 95% CI 2.30–5.55)]

– Tobacco smoking (RR 1.28, 95% CI 1.07–1.53; p = 0.008)
– Depression (HR = 1.71; 95% CI = 1.26–2.32)
– Low socioeconomic development index (7.10%; 95% CI = 5.16–9.70)
– Low iron levels in the body
– Excess body weight (RR = 1.77; 95% CI 1.05–2.99)
– Parkinson's disease (HR = 2.57, 95% CI: 1.95–3.39)

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