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Association of Restless Legs Syndrome and Migraine

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Abstract The article presents the results of an analysis of global studies that have shown that the prevalence of restless legs syndrome is higher in patients with migraine compared to people without migraine. A higher prevalence of migraine has also been reported in patients with restless legs syndrome. According to global research, the prevalence of restless legs syndrome in patients with migraine is about 13.7–25%, and the prevalence of migraine with restless legs syndrome is about 12.6–53.2%, which is significantly lower than in healthy individuals. Our analysis showed that the association between migraine and restless legs syndrome may be due to a family history and the effects of serotonergic drugs, which may disrupt the balance between dopaminergic and serotonergic pathways.

Keywords Restless legs syndrome, Migraine, Dopaminergic connection, Genetic predisposition

1. Introduction

Restless legs syndrome (RLS) is a circadian sensorimotor disorder manifested by unpleasant sensations and an irresistible desire to move the legs [2,3,12]. The incidence of restless legs syndrome in adults is 2-15%, in children aged 8-17 years in 1.9 – 2% of cases, in the elderly – up to 8% [3,4,13,26]. Due to the uncertain symptoms and similarities with other diseases, it is increasingly difficult for primary care physicians to diagnose this disorder correctly and in a timely manner, which leads to a lack of proper treatment and a significant decrease in their quality of life [8,17].

Restless legs syndrome is represented by two types – primary and secondary. Primary RLS may be sporadic or have a genetic predisposition. Secondary RLS can coexist with various conditions such as diabetes mellitus, iron deficiency anemia, depression, anxiety, Parkinson's disease, kidney disease, pregnancy, rheumatoid arthritis, polyneuropathies, lumbosacral radiculopathy, etc. [3,6,14,17]. To date, the pathophysiology of RLS is still not fully understood [14,17,26]. It is believed that genetic aspects, abnormal iron metabolism, dopaminergic dysfunction, and the central opioid system play a major role in the manifestation of RLS [1,5,24,25].

Some scientists associate the development of RLS with migraine [21], which is a common primary disorder affecting approximately 10% to 20% of the population, mainly women. It manifests itself mainly in the form of unilateral, pulsating headaches that respond to movement and cause sensitivity to afferent signals such as visual and auditory stimuli. Migraines significantly affect a person's quality of life during their peak productive years. Research shows that many disorders such as anxiety and depressive disorders, cardiovascular diseases, and pain syndromes are associated with migraines. In addition, the prevalence of RLS is higher in patients with migraines compared to people without migraines. A higher prevalence of migraine has also been reported in patients with RLS [20]. According to global research data, the prevalence of restless legs syndrome in patients with migraine is about 13.7–25%, and the prevalence of migraine in restless legs syndrome is about 12.6–53.2%, which is significantly higher than in healthy individuals [22].

The mechanism of migraine comorbidity and restless legs syndrome is currently unclear. Thus, Young W.B. et al. Based on the IRLSSG criteria, restless legs syndrome was detected in 34% of 50 patients with primary non-curable headache. In turn, d'Onofrio et al. An examination of 200 patients with migraine revealed a high prevalence of RLS in patients with headache compared with the control group (22.4 vs. 8.3%, p = 0.002) [18].

Didriksen M. et al. The associations between RLS and migraines with and without aura were studied using multifactorial logistic regression analysis. The results of their study showed that there were 1091 patients with restless legs syndrome among the participants of 4,827 with migraines. Individuals with restless legs syndrome had an increased risk of migraine compared to individuals without restless legs syndrome, with odds ratio (OR) = 1.52 (95% confidence interval: 1.33–1.73). For the studied subtypes of migraine, this relationship was found to be OR = 1.55 (1.31–1.83) for migraine with aura and OR = 1.29 (1.09–1.52) for migraine without aura [11].

Our analysis has once again proved that these two diseases have common pathophysiological mechanisms in the form of dopaminergic imbalance, iron metabolism disorders, genetic mutations, serotonergic disorders, sleep disorders, anxiety

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and depression, as well as structural imaging [7,15,21,23].

As noted earlier, dopamine plays an important role in the development of RLS, which is also involved in the pathogenesis of migraine, as evidenced by data on hypersensitivity of dopamine receptors in patients with migraine. As stated by Cannon P.R. et Larner A.J., the administration of low doses of dopamine agonists can provoke attacks of precursor symptoms in patients with migraine. When the dopamine antagonist droperidol was being tested in acute migraine, a frequently reported side effect was "acute drug akathisia," which may have been restless legs syndrome [9], Young W.B. et al. It was also found that patients with headache and restless legs syndrome had a significantly increased risk of developing drug-induced akathisia when treated with intravenous dopamine receptor blockers [26]. Cologno C. et al. It was found that patients suffering from migraine and RLS have a higher prevalence of dopaminergic symptoms accompanying their migraine attacks, in contrast to patients without RLS (47.6 vs. 13.1%, $p < 0.001$), which confirms the influence of dopaminergic imbalance on the pathogenic relationship between migraine and RLS [10].

In turn, Sabayan et al. It has been hypothesized that migraine and restless legs syndrome may have a common origin, which has been confirmed by the identical genetic origin of migraine without aura and restless legs syndrome on chromosome 14q21, which encodes protein 1 interacting with survival motor neurons (SIP1) and plays a role in both diseases; correlation of both restless legs syndrome and migraines with fibromyalgia; changes in the excitability of the cerebral cortex in both migraine and restless legs syndrome [19].

Restless Legs Syndrome (RLS) is a circadian sensorimotor disorder characterized by unpleasant sensations and an irresistible urge to move the legs. The prevalence of RLS is 2-15% in adults, 1.9-2% in children aged 8-17, and up to 8% in elderly populations. Due to non-specific symptoms and similarity to other conditions, primary healthcare providers increasingly struggle to diagnose this disorder accurately, leading to inadequate treatment and significant quality of life reduction.

RLS is presented in two types – primary and secondary. Primary RLS can be sporadic or have genetic predisposition. Secondary RLS may coexist with various conditions such as diabetes, iron-deficiency anemia, depression, anxiety, Parkinson's disease, kidney diseases, pregnancy, rheumatoid arthritis, polyneuropathies, lumbosacral radiculopathy, and others. The pathophysiology of RLS remains incompletely understood. It is believed that genetic aspects, abnormal iron metabolism, dopaminergic dysfunction, and the central opioid system play primary roles in RLS manifestation.

2. Conclusions

Thus, our analysis showed that the relationship between migraine and restless legs syndrome may be due to a family predisposition and the action of serotonergic drugs, possibly disrupting the balance between dopaminergic and serotonergic pathways. However, it is obvious that more scientific and practical research is needed in this area to answer many unresolved questions and help improve the management of such patients.

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