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RESTLESS LEGS SYNDROME IN PATIENTS ON HEMODIALYSIS

SINDROM NEMIRNIH NOGU KOD BOLESNIKA NA HEMODIALIZI

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Abstract

Patients with restless legs syndrome experience an overwhelming urge to move their legs that is greater during inactivity and at night, and may be idiopathic or secondary. The diagnosis of restless legs syndrome is based on the diagnostic criteria established by the International Group for the Study of Restless Legs Syndrome.

Although the pathophysiology of restless legs syndrome is still partially understood, the most accepted pathophysiological mechanisms include genetic variants, abnormal iron metabolism, dopaminergic dysfunction, and the central opiate system.

In patients with chronic renal failure, restless legs syndrome is presented as one of the most significant forms of the secondary type, with a frequency of 6.6% to 80%. To prevent restless legs syndrome, it is recommended to reduce the use of provocative agents such as tricyclic antidepressants, selective serotonin reuptake inhibitors, dopamine antagonists, correction of anemia, and use of levodopa or dopamine. The symptoms of restless legs syndrome disappear after kidney transplantation, which is a confirmation that terminal renal insufficiency has a decisive role in the etiology of secondary restless legs syndrome.Even though restless legs syndrome is difficult to recognize in hemodialysis patients, this phenomenon is widespread but rarely thought about. Pathogenesis is complex and insufficiently clear, current theories suggest that dopamine and iron play an important role in subcortical neurons. This leads us to the necessary therapy with erythropoietin replacement and the use of dopaminergic agents, and the most successful form of treatment is kidney transplantation.

INTRODUCTION

Current international guidelines define chronic kidney disease as reduced function characterized by markers of kidney damage, glomerular filtration rate less than 60 ml/min per 1.73 m², or both for at least 3 months, regardless of etiology.In the United States, the prevalence is estimated at 13.1% among the adult population, which has increased over time.Global health estimates by the World Health Organization in 2012 state that 864.226 deaths can be attributed to chronic kidney disease. As the leading cause of death, chronic kidney disease is in fourteenth place, accounting for 12.2 deaths per 100,000 people, with the projection that the death rate from chronic kidney disease will continue to rise to reach 14 deaths per 100.000 people by 2030.100.000 people. Kidney disease increases the risk of major non-communicable diseases such as ischemic heart disease, stroke and peripheral vascular disease, diabetes, and cancer and is also significantly associated with the occurrence of restless legs syndrome (RLS) [1, 2].

History

The symptoms of RLS were first described by Sir Thomas Willis in 1672. For more than 4 centuries, the syndrome was largely ignored, appearing only in literature, notably in Anton Chekhov's The Wedding Proposal. It was not until 1945 that Carl Ekbom comprehensively described the symptom complex that characterizes RLS [3, 4, 5, 6].

Definition and pathophysiology of restless legs syndrome

According to the International RLS Study Group, restless legs syndrome is defined as an unpleasant feeling at rest, which prompts the patient to move his legs, while movement alleviates this feeling. Even though it can appear in other parts of the body, it is most often manifested in the lower limbs. Patients sometimes describe this feeling as something crawling on their skin or a feeling of bone pain in one limb. Restless legs syndrome worsens with relaxation, so periodic movements of the extremities occur most often in the evening [7]. When the symptoms are mild and non-specific, they are diagnosed late [8]. Restless legs syndrome is most likely a consequence of the reduction of dopaminergic modulation of intracortical excitability, with reduced supraspinal inhibition and increased excitability of the spinal cord [9], which is manifested by pronounced circadian rhythmicity because it is a phenotype with an unusual combination of sensory and motor symptoms. Inactivity and rest provoke symptoms, while movement and external stimuli cause temporary relief [10]. The quality of life of the disease is markedly reduced, with pronounced depression, anxiety, and mood swings [11].

The single diagnostic standards for RLS were established by the 2012 International RLS Study Group consensus, which included a large international body of clinical and research experts on RLS/Willis-Ekbom disease (RLS/VED). The International RLS Study Group tried to avoid three problems. First, the strong interdisciplinary nature of RLS/VED specialists reduces the possibility that diagnostic criteria will be subtly distorted to fit the framework developed for any particular discipline. Second, the diversity and global nature of the International RLS Study Group reduces the risk of cultural bias that could limit generalizability across racial and ethnic groups. Third, a conservative evidence-based approach avoids arbitrary and negative influence on the validity or significance of previous RLS/VED studies [12].

The diagnosis can be made if all 5 diagnostic criteria adopted by the International RLS Study Group [13] are met:

1. The need to move the legs usually accompanied by unpleasant, unpleasant sensations in the legs.

2. Symptoms are exclusively present or worsen during periods of inactivity/rest.

3. Partial or complete relief of symptoms by movement, such as walking or stretching, at least while the activity lasts.

4. Symptoms are generally worse or occur exclusively in the evening or during the night.

5. The occurrence of the above features is not considered only as primary symptoms of another medical or behavioral condition (eg, myalgia, venous stasis, leg edema, arthritis, leg cramps, postural discomfort, habitual foot tapping).

The etiology of uremic RLS is still unclear. Evidence supporting a link between renal insufficiency and restless legs syndrome is sparse and mostly shows an association of RLS with decreased urine output in dialysis patients. Restless legs syndrome negatively affects outcomes in chronic hemodialysis patients, reduces sleep quality and quality of life, and increases mortality. Even though patients with end-stage renal disease have a permanent state of chronic inflammation, and systemic inflammation is associated with poor sleep quality, there is still no evidence of a direct correlation between restless legs syndrome and inflammation. Multiple mechanisms have been implicated as the cause of RLS in uremic patients. In addition to dopamine recycling, an intracellular enzymatic reactionthat requires iron as a cofactor, iron deficiency in the central nervous system may be the cause of secondary RLS. This may explain the occurrence of secondary RLS in anemic hemodialysis patients. Restless legs syndrome can also be associated with oxidative stress, higher serum ferritin, and lower transferrin saturation, and the role of parathyroid hormone and hyperphosphatemia has also been mentioned [12].

The results of studies examining the association of RLS with the gender of hemodialysis patients, age, duration of dialysis, time of hemodialysis, history of type 2 diabetes, cardiovascular disease, and body mass index are, unfortunately, inconsistent and contradictory [14].

Peripheral neuropathy is also associated with RLS. Although electrophysiological studies of the median, ulnar, and sural nerves have shown no correlation with RLS in patients with chronic renal failure, an isolated small loss of sensory fibers, undetectable in routine nerve conduction studies, could be an interesting theoretical possibility in this setting. at least for some patients [15].

Frequency of restless leg syndrome in hemodialysis patients

The prevalence of restless legs syndrome is significantly higher in the CKD population than in the general population, ranging from 6.6% to 80% in hemodialysis patients and 7%–24.1% in the non-dialysis population. Restless legs syndrome is often neglected in clinical practice, which negatively affects the physical and psychological health of patients and leads to a reduced quality of life. There is an association of RLS with sleep disturbance, severe anxiety, depression, sexual dysfunction, and fatigue. Restless legs syndrome is also a risk factor for increased cardiovascular morbidity and mortality [16, 17, 18].

Risk factors and complications of restless legs syndrome

Restless legs syndrome is a neurological sensorimotor disorder associated with iron deficiency in the motor and sensory areas of the brain, but other biological systems, dopaminergic, oxygen-sensitive system, opioid, glutamatergic, and serotonergic systems are not excluded [14].

Identification of RLS in dialysis patients is important because it can cause significant subjective complaints. In a survey of the general population, it was found that women are affected twice as often as men, most likely as a result of the influence of sex hormones. The association between RLS and increasing duration of dialysis may be explained by the accumulation of intermediate molecules in a process similar to beta 2-microglobulin, as well as the accumulation of amyloid [19, 20].

Restless legs syndrome has a negative impact on the quality of life, contributes to drowsiness, affects poor sleep quality, fatigue and depression, and atrophy of the thigh muscle can be verified [7, 14, 21].

Types of restless legs syndrome

Restless legs syndrome is etiologically divided into two types, type I or idiopathic RLS, which usually follows a familial and genetic pattern, and type II, which is associated with other disorders, including pregnancy, iron deficiency, peripheral neuropathy, radiculopathy, rheumatoid arthritis, and uremic syndrome [12].

Primary RLS is strongly associated with a genetic background: about 60% of patients have a family history of RLS. Secondary RLS is more common in people with end-stage renal disease, iron deficiency, pregnancy, and Parkinson's disease [14].

The negative effects of this syndrome worsen the individual's performance and affect professional and social activities, family life, and communication problems with others [20].

Studies examined the association of end-stage renal disease with sex, age, duration of dialysis, history of type 2 diabetes, history of cardiovascular disease, body mass index, serum hemoglobin level, serum iron level, serum ferritin level, transferrin saturation, parathyroid hormone level, but unfortunately, the results of these studies were inconsistent or conflicting [14].

Restless legs syndrome is associated with an increased incidence of stroke, hypertension, and death in hemodialysis patients [21]. Even though the etiology of RLS has not yet been clarified, the most probable mechanism goes in the direction of the already mentioned disproportion of dopamine levels in the central nervous system and the peripheral nervous system [7, 22].

RESTLESS LEGS SYNDROME THERAPY

Pharmacologic Treatment

Given that dopamine dysfunction and CNS iron deficiency have been proposed as the most likely mechanisms to explain the pathophysiology of RLS, dopamine agonists, levodopa, and iron supplements are suggested for therapy. Opioids and benzodiazepines are also mentioned as another option. Clinical trials evaluating the effectiveness of gabapentin showed significant improvement in symptoms after six weeks of use. Unfortunately, there are no adequate studies evaluating the use of opioids for the treatment of RLS in dialysis patients [7].

Non-pharmacological treatment

Some studies have found significant improvement in RLS severity after parathyroidectomy. The use of cold dialysate for hemodialysis can also help relieve symptoms of RLS by improving the removal of toxins from the blood and reducing creatinine and urea levels. Stretching exercises in dialysis patients have shown a significant improvement in RLS and a positive effect of exercise on fatigue, depression, and sleep quality in hemodialysis patients [23]. There are data on the impact of aromatherapy, as well as infrared light, on reducing RLS symptoms. In hemodialysis patients, RLS symptoms decrease after kidney transplantation and kidney function normalizes. Reportedly, both olive oil and lavender oil massage, after dialysis sessions in RLS patients, can be used as a complementary therapy as they significantly improve symptoms. There are also data on the positive impact of vibrations on the reduction of RLS symptoms in hemodialysis patients [7].

CONCLUSION

RLS in hemodialysis patients must be thought about intensively because it significantly reduces the quality of life and can also increase the mortality rate. RLS is two to three times more common in CKD compared to the general population. The diagnosis can be challenging because the pathophysiological mechanism is very complex and still insufficiently clear, and the treatment can be pharmacological and non-pharmacological. Dopaminergic drugs and replacement with erythropoietin stimulators help treat RLS, and there is evidence that aerobic exercise, lavender oil massage, aromatherapy, and infrared light can improve symptoms.

Declaration of conflicting interests

The authors declared no conflicts of interest concerning the authorship and/or publication of this article.

Sažetak

Pacijenti sa sindromom nemirnih nogu doživljavaju ogromnu potrebu za pomeranjem nogu koja je veća tokom neaktivnosti i noću, može biti idiopatska ili sekundarna. Dijagnoza sindroma nemirnih nogu zasniva se na dijagnostičkim kriterijumima koje je ustanovila Međunarodna grupa za proučavanje sindroma nemirnih nogu. Iako je patofiziologija sindroma nemirnih nogu još uvek delimično shvaćena, najprihvaćeniji patofiziološki mehanizmi uključuju genetske varijante, abnormalni metabolizam gvožđa, dopaminergičku disfunkciju i centralni opijatni sistem. Kod pacijenata sa hroničnom bubrežnom insuficijencijom, sindrom nemirnih nogu je predstavljen kao jedan od najznačajnijih oblika sekundarnog tipa, sa učestalošću od 6,6% do 80%. Kao vid prevencije sindroma nemirnih nogu, preporučuje se smanjenje upotrebe provokativnih agenasa kao što su triciklični antidepresivi, selektivni inhibitori preuzimanja serotonina, antagonisti dopamina, korekcija anemije i upotreba levodopa ili dopamina. Simptomi sindroma nemirnih nogu nestaju nakon transplantacije bubrega, što je potvrda da terminalna bubrežna insuficijencija ima odlučujuću ulogu u etiologiji sekundarnog sindroma nemirnih nogu. Iako je sindrom nemirnih nogu teško prepoznati kod pacijenata na hemodijalizi, ova pojava je vrlo česta, ali se o njoj retko razmišlja. Patogeneza je složena i nedovoljno jasna, sadašnje teorije sugerišu da dopamin i gvožđe igraju važnu ulogu u subkortikalnim neuronima. To nas dovodi do neophodne terapije zamenom eritropoetina i upotrebom dopaminergičkih sredstava a najuspešniji oblik lečenja predstavlja transplantacija bubrega.

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