

Investigation of serum magnesium, ferritin, and vitamin B12 levels in restless legs syndrome

Huzursuz bacak sendromunda serum magnezyum, ferritin ve vitamin B12 düzeylerinin araştırılması

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Abstract

Purpose: To study magnesium, ferritin, and vitamin B12 levels in patients with restless legs syndrome and assess the relationship between the disease progression and age.

Materials and methods: The retrospective data of 40 restless legs syndrome patients from 2024–2025 were analyzed. Those with chronic diseases (diabetes mellitus, chronic kidney failure, and oncological diseases) were excluded from the study. Before that, serum magnesium, ferritin and vitamin B12 levels were measured. Age was calculated, and Pearson correlation analysis was performed. Patients were followed up for 3 months.

Results: Serum magnesium levels were 2.09 ± 0.24 mg/dL (median: 2.05 mg/dL), ferritin levels were 59.01 ± 43.76 ng/mL (median: 49.88 ng/mL), and vitamin B12 levels were 384.88 ± 108.72 pg/mL (median: 375.50 pg/mL). None of these biochemical parameters showed a statistically significant correlation with age (all $p > 0.05$).

Conclusion: It was evaluated that biochemical imbalances in the restless legs syndrome symptomatology may be independent of the age factor, and that especially changes in the levels of ferritin and magnesium could be due to the pathophysiological process of the disease.

Keywords: Restless legs syndrome, age, magnesium, ferritin, vitamin B12.

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Öz

Amaç: Huzursuz bacak sendromu hastalarında magnezyum, ferritin ve B12 vitamini düzeylerini incelemek ve hastalığın ilerlemesi ile yaş arasındaki ilişkiyi değerlendirmektir.

Gereç ve yöntem: 2024-2025 yılları arasında 40 huzursuz bacak sendromu hastasının retrospektif verileri analiz edildi. Kronik hastalığı olanlar (diyabetes mellitus, kronik böbrek yetmezliği ve onkolojik hastalıklar) çalışmadan dışlandı. Çalışma öncesinde serum magnezyum, ferritin ve B12 vitamini düzeyleri ölçüldü. Yaş hesaplandı ve Pearson korelasyon analizi yapıldı. Hastalar 3 ay boyunca takip edildi.

Bulgular: Hastaların ortalama yaşı $47,9 \pm 12,4$ yıl olup, serum magnezyum düzeyi $2,09 \pm 0,24$ mg/dL (medyan: 2,05 mg/dL), ferritin düzeyi $59,01 \pm 43,76$ ng/mL (medyan: 49,88 ng/mL) ve B12 vitamini düzeyi $384,88 \pm 108,72$ pg/mL (medyan: 375,50 pg/mL) olarak bulundu. Serum magnezyum, ferritin ve B12 vitamini düzeyleri ile yaş arasında istatistiksel olarak anlamlı bir korelasyon saptanmadı ($p > 0,05$).

Sonuç: Huzursuz bacak sendromu semptomatolojisindeki biyokimyasal dengesizliklerin yaş faktöründen bağımsız olabileceği, özellikle ferritin ve magnezyum düzeylerindeki değişikliklerin hastalığın patofizyolojik sürecinden kaynaklanabileceği değerlendirildi.

Anahtar kelimeler: Huzursuz bacak sendromu, yaş, magnezyum, ferritin, B12 vitamini.

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Introduction

Restless Legs Syndrome (RLS) is a neurologic sensory-motor disorder. One of the most difficult symptoms of this disease is the spontaneous movement of the legs, which is accompanied quite frequently by some uncomfortable sensations; essentially, it is caused by rest or lack of movement, and it is usually worse in the evening or at night. Besides that, along with the patients' quality of life getting lower, this disorder is also linked to several comorbidities [1, 2].

The etiology of RLS is complicated, and a significant amount of evidence indicates that brain iron deficiency is the main factor leading to hypoadenosinergic, hyperglutamatergic, and hyperdopaminergic states. These states consequently result in the typical sensorimotor symptoms and arousal disturbances of the disorder [3]. One of the findings that provides evidence for this argument is the close relationship between low serum ferritin levels and the severity of the symptoms [4]. However, the detailed mechanisms by which central iron deficiency induces and eventually brings about dopaminergic dysfunction in RLS are still quite unclear, and there are often discrepancies between the findings of imaging studies and those of post-mortem analyses [2, 5]. Iron is the key factor in the one single most important step of dopamine production, which is the rate-limiting step; therefore, the reduction of iron available may cause the reduction of tyrosine hydroxylase activity. However, various studies have indicated that the correlation is not always direct [6, 7].

Magnesium is an indispensable component of the body, which is the primary factor responsible for regulating nerve and muscle functions, nerve transmission, and muscle relaxation. Deficiency of it may lead to nerve cells' hyperexcitation, muscle cramps, and a few types of involuntary movements. Hence, magnesium levels are seen as being associated with the occurrence of Neuropathic Legs Syndrome symptoms. Only a handful of clinical trials have indicated that the blood magnesium concentration of RLS patients is lower than that of the control group [8-10]. Besides these, it is

also mentioned that magnesium intake causes some beneficial effects, mainly on sleep quality and night leg movements [11, 12].

Vitamin B12 (cobalamin) is one of the vital elements needed for the nervous system to be healthy and for the myelin production process to be a part of its function. Insufficient vitamin B12 may result in peripheral neuropathy, paresthesia, sensory loss, and symptoms of neuromuscular irritability. As a result, the association between low vitamin B12 levels and RLS has been, in large part, a matter of debate and research in the last couple of years. While the connection of vitamin B12 to RLS is not entirely obvious, a few studies have indicated that a lack of vitamin B12 may exacerbate the dysfunction of the dopaminergic system and thus cause the development of RLS symptoms. One of the nutrients that is required for methylation processes, which are cofactors for dopamine synthesis, is vitamin B12; therefore, a lack of it can lead to a reduction of dopamine activity [13-15].

This study aims to find out the association between serum magnesium, ferritin, and vitamin B12 levels and age in patients diagnosed with RLS. The study goal is to determine whether changes in the biochemical parameters that co-migrate with RLS symptoms are caused by age-dependent mechanisms or by age-independent (disease-specific) mechanisms.

Materials and methods

This retrospective study involved 40 patients who were diagnosed with RLS at the Neurology Clinic between 2024 and 2025. Permission was obtained from the Pamukkale University Non-Interventional Clinical Research Ethics Committee for the study. The mean age of the patients was 47.9 ± 12.4 years, with an age range of 22 to 72 years. The number of female patients was significantly more than male patients (females 70%, males 30%). All patients underwent follow-up in the neurology outpatient clinic, and almost all of them reported long-lasting or recurrent symptoms. Patients suffering from chronic diseases (diabetes mellitus, chronic kidney disease, cancer) were excluded from the research. The patients were followed up

after three months of treatment initiation. Those who had borderline values were additionally supplemented with ferritin, vitamin B12, and magnesium. Besides that, the administration of pramipexole or gabapentin was mainly chosen as the accompanying therapy. The connections between age and biochemical parameters have been analyzed with Pearson correlation analysis. A p -value of <0.05 was considered statistically significant. All patients included in the study were diagnosed with Restless Legs Syndrome based on the diagnostic criteria established by the International Restless Legs Syndrome Study Group (IRLSSG).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ standard deviation (SD), median, and minimum–maximum values, while categorical variables were summarized as numbers and percentages.

The distribution of continuous variables was assessed for normality prior to statistical testing. The associations between age and serum magnesium, ferritin, and vitamin B12 levels were examined using Pearson's correlation analysis when the assumptions for parametric testing were satisfied. The relationships between age and each biochemical parameter were additionally visualized using scatter plots with fitted linear regression lines. Pearson's correlation coefficients (r) and corresponding p -values were reported to indicate the strength and direction of the associations. All statistical tests were two-sided, and a p -value <0.05 was considered statistically significant.

Results

The difference between age and magnesium, ferritin, or vitamin B12 levels was not statistically significant ($p>0.05$). Even though there was a little positively directed tendency for vitamin B12 levels and age, the difference was still not significant ($r=0.245$; $p=0.132$) (Table 1).

Table 1. Correlation of biochemical parameters

Biochemical parameter	Correlation Coefficient (r)	p -value	
Magnesium	-0.00	0.998	No association was found with age
Vitamin B12	+0.245	0.132	A mild positive tendency was observed
Ferritin	-0.027	0.868	No association was found with age

The mean serum magnesium level was 2.09 ± 0.24 mg/dL, with a median value of 2.05 mg/dL (range: 1.47–2.70 mg/dL). Most patients had serum magnesium levels within the normal reference range (1.7–2.4 mg/dL); however, hypomagnesemia (<1.7 mg/dL) was observed in a small number of patients (Figure 1).

The mean serum ferritin level was 59.01 ± 43.76 ng/mL, with a median value of 49.88 ng/mL (range: 3.39–167.50 ng/mL). Ferritin levels were within the low-normal range in some patients (Figure 2).

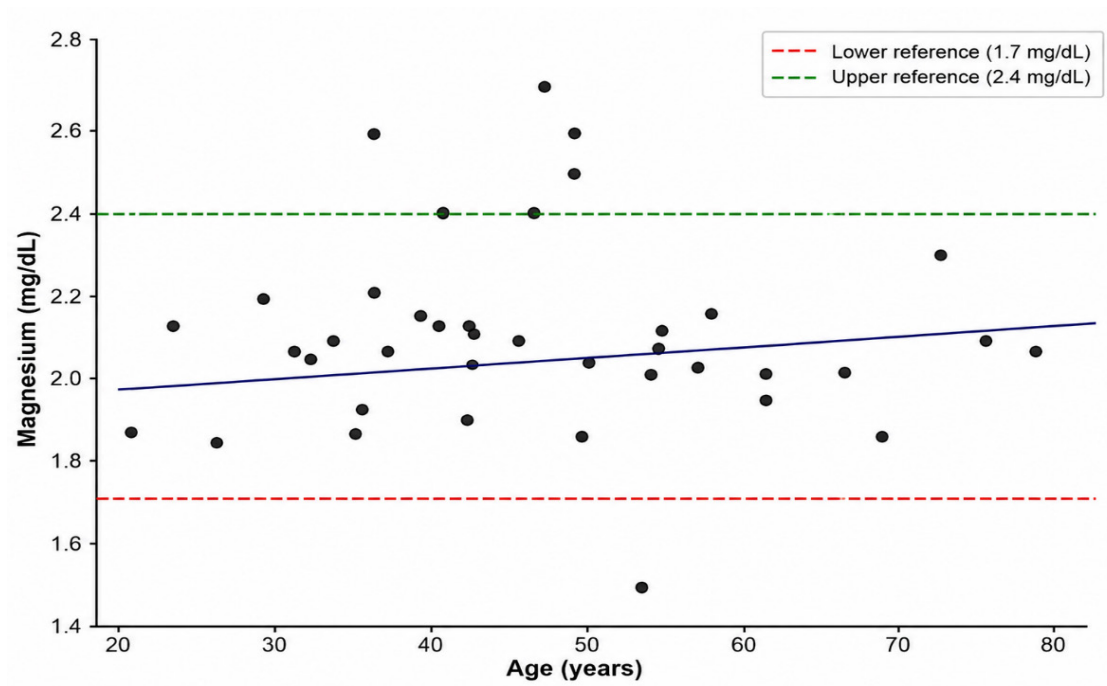


Figure 1. The relationship between age and magnesium

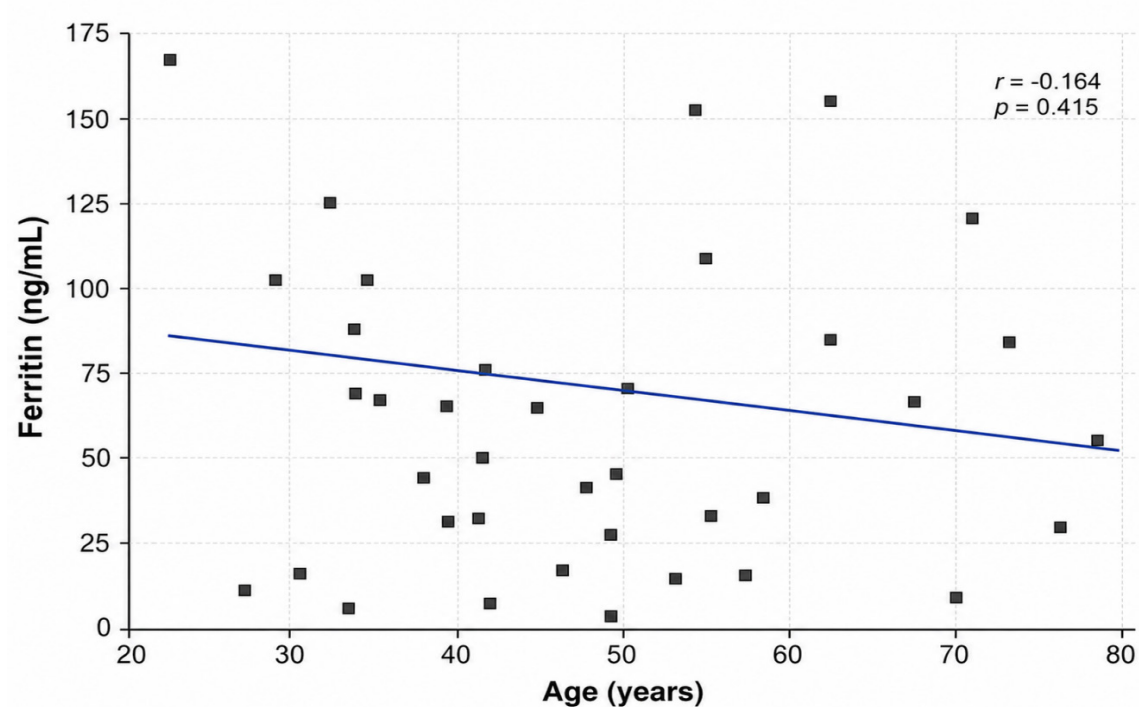


Figure 2. The relationship between age and ferritin

The mean serum vitamin B12 level was 384.88 ± 108.72 pg/mL, with a median value of 375.50 pg/mL (range: 193–658 pg/mL). Vitamin B12 concentrations were generally

within the reference range; however, marginally low values (200–250 pg/mL) were observed in some patients (Figure 3).

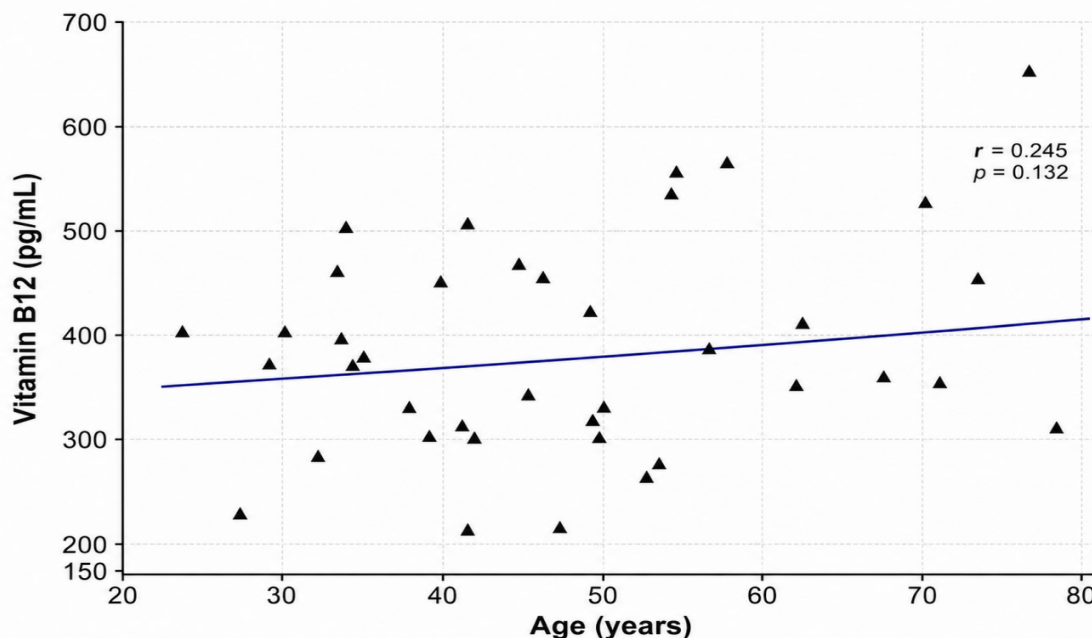


Figure 3. The relationship between age and vitamin B12

Discussion

The study question was to determine if there is a connection between magnesium, ferritin, and vitamin B12 levels and age in 40 patients with RLS. The outcome of the research indicated that none of the three parameters had a statistically significant correlation with age ($p > 0.05$). Vitamin B12 levels showed a slight positive tendency, but the difference was not statistically significant. The results indicate the potential for the biochemical imbalances behind RLS to become age independent.

The pathophysiology causing RLS is complicated. It is proposed that changes in brain iron metabolism lead to alterations of the dopaminergic system, which in turn is considered to be the main source of RLS symptoms [1, 4, 16]. On the other hand, we found in our study that ferritin levels were not correlated with age, which implies that systemic iron status may be dependent on the pathophysiological process of the disease rather than age. This agrees with

the literature cited, which also points to the fact that iron deficiency is not an age-related condition [17, 18].

The fact that dopamine agonists have a very positive effect in therapy and can relieve both sensory and motor symptoms, especially periodic limb movements during sleep, is one of the pieces of evidence that the dopaminergic system is involved in the development of RLS and that a presynaptic hyperdopaminergic state is most likely the case [7]. Nevertheless, the sustainability of dopamine-related drugs is frequently curtailed by augmentation, a condition in which RLS symptoms aggravate or extend to other body parts, thus reflecting a complicated interplay within the dopaminergic system and the likelihood of dopamine receptor desensitization [7]. Such a case emphasizes the need for searching other possible therapeutic targets outside the direct dopaminergic agonism, for example, the influence of glutamatergic, adeno-synergic, or opioid systems [19, 20]. One of the factors

causing sensory disturbances and hyperarousal in patients with RLS is the involvement of the glutamate system, which, when dysregulated, leads to increased excitability and central nervous system sensitization [21].

Among the other factors, the enhanced excitability, in combination with iron dysregulation, may be responsible for the production of abnormal motor movements characteristic of RLS. One of the pivotal hypotheses suggests that a hypo-adenosine-synergic condition, as a consequence of brain iron deficiency, leads to the generalized decrease of adenosine A1 receptors (A1Rs) in the entire brain, which is the ultimate mechanism resulting in hyper-glutamatergic and hyperdopaminergic states in RLS [19, 22, 23].

Such a disturbance of adenosine-synergic modulation may result in an imbalance of the adenosine-dopamine-glutamate axis in the striatum, which is the part of the brain responsible for motor control and sensory processing. Additionally, the finding of increased glutamate concentration in the thalamus of RLS patients correlates with extended duration of wakefulness, thus indicating a presynaptic hyper-glutamatergic state that is leading to the hyperarousal aspect of the syndrome. With such a complicated neurobiological scenario, it is extremely important to have a thorough understanding of the interaction between magnesium, ferritin, and vitamin B12; the lack of these micronutrients may become an additional factor that increases the severity of or modulates the already existing pathophysiological mechanisms in RLS. Also, the evidence that serum magnesium levels have no significant correlation with age is an indication that the neuromuscular and biochemical processes in RLS are associated with neurochemical mechanisms rather than age. Literature sources also indicate that there is no significant correlation between magnesium levels and disease severity; however, it has been suggested that magnesium may be a regulator of motor phenomena in the sleep period as well as muscle excitability [22, 24, 25]. Furthermore, it is emphasized that serum magnesium levels may not be a complete indication of magnesium concentration in the central nervous system. Thus, magnesium involvement in RLS pathophysiology is probably through neurotransmitter-related

mechanisms and needs to be confirmed by sophisticated neurophysiological and metabolic investigations.

While the involvement of vitamin B12 in RLS is not entirely clear, a study has indicated that a lack of vitamin B12 may worsen the dysfunction of the dopaminergic system, which turn could lead to the occurrence of RLS symptoms. Vitamin B12 is involved in methylation processes that are cofactors in the synthesis of dopamine; therefore, a deficiency of this vitamin may result in reduced dopaminergic activity. A few clinical trials have found that the level of vitamin B12 is significantly lower in RLS patients than in the control groups [13, 26]. Moreover, there have been instances where patients have shown a partial improvement in their symptoms after being given vitamin B12 supplementation. On the other hand, some studies have stated that there is no direct correlation between vitamin B12 levels and RLS. The differences in these results point out that vitamin B12 levels could be affected by factors such as the individual's characteristics, food intake, diseases existing together, and especially the increase in supplement consumption with age.

We saw in our patients a small positive trend of vitamin B12 levels with age, but this difference was not statistically significant. The case may be that there is more supplementation and treatment application in the older age group. O'Leary and Samman indeed stated that although dietary vitamin B12 absorption decreases in aged people, absorption from pharmaceutical supplements remains unchanged [27]. Additionally, the literature points out that vitamin B12 deficiency may supercharge dopaminergic system dysfunction and thus cause RLS symptoms [13-15]. So, the differences among individuals in vitamin B12 levels and the rise in vitamin B12 that is related to the treatment are thought to have indirect impacts on the development of RLS.

The relatively small sample size has been one of the major limitations of this study. Pearson correlation analysis was carried out; however, the few patients may have weakened the statistical power, which is necessary to find subtle age and biochemical parameter associations. This aspect should be borne in mind when interpreting the results, and further investigations with bigger cohorts are needed.

Considering that the diagnosis and clinical characterization of Restless Legs Syndrome primarily rely on detailed clinical assessment and symptom-based criteria, the retrospective design of this study limited the availability of standardized data regarding symptom duration and disease severity, which represents an important limitation.

In conclusion, this study shows that magnesium, ferritin, and vitamin B12 levels in RLS are not influenced by age, and biochemical imbalances may be primarily related to the neurometabolic mechanisms of the disease. The results coincide with intricate pathophysiological models for RLS described in the literature and, therefore, require confirmation by more extensive, prospective studies.

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