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Restless legs syndrome in children with celiac disease: associations with vitamin D and iron deficiency and the role of gluten-free diet adherence

Ayşegül Cebe Tok[1*], Mehmet Tolga Köle[2], Deniz Güven[2], Ali Kansu Tehçi[2] and İbrahim Kandemir[3]

Abstract

Background Celiac disease (CD) is a systemic autoimmune disorder frequently associated with micronutrient deficiencies and extraintestinal manifestations, including neurological complications. Restless Legs Syndrome (RLS) is a sensorimotor disorder linked to dopaminergic dysfunction and iron and vitamin D deficiency, both of which are common in pediatric CD.

Objective To evaluate the prevalence and severity of RLS in children with CD and to investigate the associations between RLS symptoms and serum vitamin D and iron parameters, as well as the potential effect of gluten-free diet (GFD) adherence.

Methods This prospective cross-sectional study included 67 children with CD (aged 10–18 years) and 68 age- and sex-matched healthy controls. RLS was assessed using the International Restless Legs Syndrome Study Group rating scale. Demographic, anthropometric, clinical, and biochemical data—including serum iron, ferritin, folate, vitamin B12, and 25-hydroxyvitamin D—were recorded. Group comparisons were performed using appropriate parametric or non-parametric tests. Associations were evaluated using Spearman correlation and Bayesian correlation analyses.

Results RLS scores were significantly higher in the CD group compared with controls (median 6 [0–13] vs. 0 [0–0]; $p < 0.001$), and RLS duration was also longer in children with CD ($p < 0.001$). Serum vitamin D levels showed a significant negative correlation with RLS scores ($r = -0.251$, $p < 0.05$). RLS duration demonstrated a strong positive correlation with RLS severity ($r = 0.838$, $p < 0.001$). Transglutaminase IgA levels were inversely correlated with ferritin ($r = -0.417$, $p < 0.001$) and folate levels ($r = -0.332$, $p < 0.05$), while transglutaminase IgG levels were negatively correlated with ferritin ($r = -0.285$, $p < 0.05$) and vitamin D ($r = -0.304$, $p < 0.05$). Bayesian correlation analysis revealed no strong associations between Marsh classification and most clinical or biochemical variables, except for a strong association between RLS duration and severity ($BF_{10} > 100$). Adherence to a gluten-free diet was not significantly associated with RLS severity ($p > 0.05$).

*Correspondence:
Ayşegül Cebe Tok
ayse.cb@gmail.com

Full list of author information is available at the end of the article

Conclusions Children with celiac disease exhibit significantly higher RLS symptom severity than healthy peers. Lower serum vitamin D levels and reduced iron stores appear to be associated with increased RLS severity, regardless of Marsh stage or dietary adherence. These findings highlight the potential value of screening for RLS and monitoring vitamin D and ferritin levels in pediatric patients with celiac disease.

Keywords Celiac disease, Children, Restless Legs Syndrome (RLS), Iron deficiency, Vitamin D deficiency

Introduction

Restless Legs Syndrome (RLS) is a chronic and progressive sensorimotor neurological disorder characterized by an urge to move the legs accompanied by uncomfortable and abnormal sensations, which typically occur or worsen at rest [1–3]. RLS symptoms most commonly intensify during the evening and nighttime hours, become more pronounced during periods of immobility, and are partially or completely relieved by movement; consequently, the condition frequently leads to sleep disturbances [4]. RLS can affect both adults and children, with a reported prevalence of approximately 5–10% in European and North American populations, whereas lower prevalence rates have been observed in Asian populations [5]. Although the exact pathophysiology of RLS has not yet been fully elucidated, genetic predisposition, disturbances in iron metabolism, dopaminergic dysfunction, and alterations in the central opioid system are considered to contribute to its clinical manifestation [6]. While the majority of cases are classified as primary (idiopathic) RLS, secondary RLS may develop in association with certain conditions, particularly systemic diseases characterized by iron deficiency and malabsorption; notably, an association with celiac disease (CD) has been reported [7].

CD is an autoimmune enteropathy triggered by gluten intake in genetically susceptible individuals and has a global prevalence of approximately 1% [8]. The pathogenesis of the disease is characterized by gluten-induced inflammatory responses leading to villous atrophy, crypt hyperplasia, and disruption of microvillus integrity in the small intestinal mucosa [7]. Although CD was traditionally regarded as a disorder confined to the gastrointestinal system, accumulating evidence indicates that it may present with a wide range of extraintestinal manifestations beyond gastrointestinal symptoms. In this context, neurological involvement has attracted increasing attention, and a potential association with sensorimotor disorders such as RLS has become a subject of growing interest [9].

Vitamin D deficiency and iron deficiency are among the most common micronutrient deficiencies observed in CD, and these deficiencies have been reported to contribute to the severity of neurological and sensorimotor symptoms associated with the disease [7, 10, 11]. Vitamin D plays an important role in the regulation of the dopaminergic system and in maintaining brain iron homeostasis [12, 13]. Current evidence suggests that low serum vitamin D levels are associated with dopaminergic dysfunction and are linked to increased severity of RLS symptoms [4, 12]. Iron deficiency also plays a critical role in the pathophysiology of RLS. Iron is essential for dopamine synthesis and dopaminergic neurotransmission, and iron deficiency has been associated with worsening RLS symptoms; in particular, brain iron deficiency is widely emphasized in the literature as a key neurological component of RLS [9, 14]. In individuals with CD, intestinal iron malabsorption may lead to persistent iron deficiency, which has been reported to be associated with increased severity of RLS symptoms [15, 16]. Indeed, studies have shown that vitamin D and iron deficiencies may persist in children with CD despite adherence to a gluten-free diet, and that this persistence may be associated with greater RLS symptom severity [17, 18].

The aim of this study was to evaluate the prevalence and symptom severity of RLS in children diagnosed with CD and to investigate the relationship between vitamin D and iron deficiencies and RLS symptom severity in this patient population. In addition, the potential effects of adherence to a gluten-free diet on the presence and severity of RLS symptoms in children with CD were examined.

Materials and methods

Study design and participants

This prospective cross-sectional study was conducted between December 2024 and December 2025 and included 67 patients aged 10–18 years who were followed with a diagnosis of celiac disease (CD) at the Pediatric Gastroenterology, Hepatology, and Nutrition Clinic of Ankara Etlik City Hospital, as well as 68 healthy children of comparable age and sex who presented to the Pediatric Outpatient Clinics.

Sample size calculation was performed assuming a type I (α) error rate of 0.05, a statistical power (1–β) of 0.80, an effect size (Cohen's d) of 0.5, and a 1:1 group allocation ratio. Based on these parameters, a minimum total sample size of 128 participants (64 patients and 64 controls) was required. Sample size estimation was conducted using the G*Power software (version 3.1).

Inclusion criteria: Being between 10 and 18 years of age, agreeing to participate in the study, and having no accompanying chronic or acute disease.

Table 1 International Restless Legs Syndrome Rating Scale (IRLS)

Item No	Content Assessed	Score Range
1	Intensity of RLS discomfort	0–4
2	Need or urge to move	0–4
3	Relief by movement	0–4
4	Sleep disturbance due to RLS	0–4
5	Daytime tiredness/sleepiness	0–4
6	Severity of RLS symptoms overall	0–4
7	Frequency of RLS symptoms	0–4
8	Duration of symptoms during the day	0–4
9	Impact on daily activities	0–4
10	Impact on mood	0–4
Score	**Severity**	
0	None	
1–10	Mild	
11–20	Moderate	
21–30	Severe	
31–40	Very severe	

Table 2 Marsh's histological classification

Marsh Type	Histology
0	Normal mucosa
1	Increased IEL
2	Crypt hyperplasia
3a	Partial villous atrophy
3b	Subtotal villous atrophy
3c	Total villous atrophy

Exclusion criteria: Not providing consent to participate in the study; children with chronic diseases (including neurological, hematological, metabolic, rheumatological, or psychiatric disorders); those with a history of acute infection or antibiotic use within the preceding two months; and those outside the 10–18-year age range were excluded from the study.

After obtaining written informed consent, the concept and symptoms of Restless Legs Syndrome were explained to both the families and the children in age-appropriate language.

Restless Legs Syndrome (RLS) was evaluated according to the 2014 diagnostic criteria defined by the International Restless Legs Syndrome Study Group(3). All participants were interviewed face-to-face by the investigator. The five essential diagnostic criteria were systematically assessed. Particular attention was given to the fifth criterion to exclude mimicking conditions such as leg cramps, positional discomfort, peripheral neuropathy, arthritis, or other neurological symptoms.

Subsequently, the International Restless Legs Syndrome Rating Scale (IRLS) questionnaire was administered to all participants under the supervision of a pediatrician and a pediatric gastroenterologist. The IRLS scoring form is presented below (Table 1) [19].

The diagnosis of celiac disease was established according to the 2020 ESPGHAN criteria, requiring serological positivity for anti–tissue transglutaminase IgA (> 20 IU/L) and confirmation by duodenal biopsy findings [20].

Duodenal biopsy specimens were evaluated by an experienced pathologist and classified according to the modified Marsh classification (Marsh–Oberhuber classification) [21] (Table 2).

Data collection

Demographic data including age, sex, height, weight, and body mass index (BMI) were recorded. Laboratory parameters included complete blood count, serum iron, ferritin, folate, vitamin B12, 25-hydroxyvitamin D, calcium, phosphorus, magnesium, parathyroid hormone (PTH), serum tissue transglutaminase IgA and IgG, and total serum IgA levels.

Disease duration and adherence to a gluten-free diet (GFD) were determined through structured interviews conducted by a dietitian. Patients with celiac disease were categorized into three subgroups: newly diagnosed patients, patients adherent to a gluten-free diet, and patients non-adherent to a gluten-free diet.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics (version 22; IBM Corp., Armonk, NY, USA). Bayesian correlation analyses were conducted using the JASP software. The distribution of continuous variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Normally distributed data are presented as mean ± standard deviation (SD), whereas non-normally distributed data are expressed as median (minimum–maximum or interquartile range, IQR). Categorical variables are presented as counts and percentages (%).

Comparisons of continuous variables between the celiac disease and control groups were performed using Student's t test, Welch's t test, or the Mann–Whitney U test, depending on data distribution. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. All tests were two-tailed, and a p value < 0.05 was considered statistically significant.

In the celiac disease group, associations between transglutaminase antibodies (anti-tTG IgA and anti-tTG IgG), RLS scores, Marsh classification, and clinical, anthropometric, and biochemical parameters were evaluated using Spearman's rank correlation analysis. Correlation coefficients (r) and corresponding p values were reported.

In addition to classical correlation analyses, Bayesian correlation analysis was applied to assess relationships between Marsh classification and ordinal RLS scores and clinical and biochemical variables. Evidence strength was interpreted using Bayes factors (BF_{10}). A $BF_{10} < 0.33$ was

Table 3 Baseline demographic and clinical features of celiac patients and healthy controls

Variable	CD group (*n* = 67)	Control group (*n* = 68)	*p* value
Age (years)	—	—	0.08[a]
Female sex, n (%)	48 (71.6%)	34 (50.0%)	0.01[b]
Height (cm)	149.8 ± 16.0	159.8 ± 10.1	<0.001[c]
Weight (kg)	43.2 ± 17.2	53.8 ± 13.2	<0.001[d]
BMI (kg/m^2)	18.7 ± 4.9	21.0 ± 4.5	0.005[c]
RLS duration (months)	4 (0–12)	0 (0–0)	<0.001[a]
RLS score	6 (0–13)	0 (0–0)	<0.001[a]

Data are presented as mean ± standard deviation or median (minimum–maximum)

[a]Mann–Whitney U test

[b]Chi-square test

[c]Student's t test

[d]Welch t test

RLS Restless Legs Syndrome, *BMI* Body Mass Index. A *p* value < 0.05 was considered statistically significant

considered strong evidence in favor of the null hypothesis, BF_{10} values between 0.33 and 3 indicated weak or inconclusive evidence, and $BF_{10} > 3$ was interpreted as evidence supporting the alternative hypothesis. The Bayesian approach was particularly employed to evaluate weak associations between Marsh classification and laboratory and clinical parameters.

Comparisons of RLS scores between the celiac disease and control groups were performed using the Mann–Whitney U test. The relationship between RLS duration and RLS scores was assessed using Spearman's correlation analysis.

All statistical analyses were conducted using two-tailed p values; $p < 0.05$ was considered statistically significant, and $p < 0.001$ was considered highly significant.

Ethical approval

The study was approved by the Institutional Ethics Committee of Ankara Etlik City Hospital (Approval No: AEŞH-BADEK_2024-939; Date: 25/12/2024). Written informed consent was obtained from the parents or legal guardians of all participants, and assent was also obtained from children aged 12 years and older. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

A total of 67 children with celiac disease (CD) and 68 healthy controls were included in the study. There was no statistically significant difference between the groups in terms of mean age (p = 0.08). However, the proportion of female participants was significantly higher in the CD group compared with the control group (71.6% vs. 50.0%, p = 0.01). Anthropometric assessment revealed that height, weight, and body mass index (BMI) values were

Table 4 Comparison of hematological and biochemical parameters between the celiac and control groups

Variable	Celiac (*n* = 67)	Control (*n* = 68)	*p* value
Hemoglobin (g/dL)	13.8 ± 1.1	14.1 ± 1.4	0.335[c]
Hematocrit (%)	43.0 ± 2.8	42.9 ± 3.4	0.136[b]
Platelet count (×10^3/μL)	311.8 ± 81.9	309.0 ± 154.9	0.827[c]
MPV (fL)	10.2 ± 0.8	10.1 ± 0.8	0.363[b]
Phosphorus (mg/dL)	4.5 ± 0.7	4.4 ± 0.7	0.736[b]
Magnesium (mg/dL)	2.1 ± 0.2	2.0 ± 0.2	0.833[b]
Calcium (mg/dL)	9.7 ± 0.4	9.8 ± 0.3	0.212[b]
Iron (μg/dL)	82.4 ± 35.8	75.9 ± 34.7	0.288[b]
Vitamin B12 (pg/mL)	411 ± 118	360 ± 110	<0.001[c]
Vitamin D (ng/mL)	16.6 ± 7.1	18.8 ± 8.0	0.102[b]
Zinc (μg/L)	820 ± 83	740 ± 114	0.129[b]
Ferritin (ng/mL)	33.7 ± 33.9	33.9 ± 19.9	0.700[a]
Parathyroid hormone (pg/mL)	33.6 (27.9–45.7)	33.6 (27.9–45.7)	0.895[a]

Data are presented as mean ± standard deviation or median (interquartile range)

[a]Mann–Whitney U test

[b]Student's t test

[c]Welch t test

MPV Mean Platelet Volume, A *p* value < 0.05 was considered statistically significant

significantly lower in the CD group than in the control group ($p < 0.001$, $p < 0.001$, and $p = 0.005$, respectively).

When Restless Legs Syndrome (RLS)-related parameters were evaluated, both RLS duration and RLS scores were significantly higher in the CD group compared with the control group (both $p < 0.001$). In addition, the use of iron supplementation was more common among children with CD than in controls (16.4% vs. 2.9%, $p = 0.009$) (Table 3).

With respect to hematological parameters, no significant differences were observed between the two groups in terms of hemoglobin, hematocrit, platelet count, or mean platelet volume (all $p > 0.05$). Similarly, serum phosphorus, magnesium, calcium, iron, zinc, ferritin, and parathyroid hormone levels were comparable between groups. In contrast, vitamin B12 levels were significantly higher in the CD group than in the control group (411 ± 118 vs. 360 ± 110 pg/mL; $p < 0.001$). Although serum vitamin D levels did not differ significantly between groups ($p = 0.102$), they tended to be lower in the CD group (Table 4).

Correlations between transglutaminase antibodies and clinical, anthropometric, and biochemical parameters in the CD group are presented in Table 5. A strong and statistically significant positive correlation was observed between transglutaminase IgA and transglutaminase IgG levels (r = 0.601, $p < 0.001$). Transglutaminase IgA levels were negatively correlated with ferritin (r = –0.417, $p < 0.001$) and folate levels (r = –0.332, $p < 0.05$). Similarly, transglutaminase IgG levels showed negative correlations

Table 5 Correlations between transglutaminase antibodies and clinical, anthropometric, and biochemical parameters among celiac group

Variable	Transglutaminase IgA	Transglutaminase IgG	RLS Score	Marsh classification
Anti-TG IgG	0.601***	—		
RLS score	0.044	0.156	—	
Marsh classification	0.055	0.15	0.042	—
Age (months)	-0.005	-0.03	0.133	0.048
Height (cm)	0.01	-0.079	0.165	0.13
Weight (kg)	0.189	0.122	0.141	0.109
BMI (kg/m^2)	0.201	0.134	0.123	0.09
RLS duration (months)	0.012	0.094	0.838***	-0.02
Hemoglobin (g/dL)	-0.206	-0.168	0.029	0.124
Hematocrit (%)	-0.182	-0.237	0.04	0.107
Platelet count (×10^3/μL)	-0.043	0.011	0.048	-0.063
MPV (fL)	-0.001	0.01	0.157	-0.22
Phosphorus (mg/dL)	0.196	0.05	-0.074	-0.024
Magnesium (mg/dL)	0.208	0.001	-0.08	-0.147
Calcium (mg/dL)	-0.116	-0.052	-0.072	-0.226
Iron (μg/dL)	-0.16	-0.067	0.051	0.189
Parathyroid hormone (pg/mL)	0.168	0.124	-0.181	-0.044
Ferritin (μg/L)	-0.417***	-0.285*	-0.083	-0.183
Folate (μg/L)	-0.332*	-0.166	0.027	-0.104
Vitamin B12 (pg/mL)	-0.129	0.089	0.009	-0.237
Vitamin D (25-OH, ng/mL)	-0.118	-0.304*	-0.251*	-0.082
Zinc (μg/L)	-0.8	-0.1	-0.154	0
Total IgA (g/L)	0.077	0.058	0.027	-0.082

Values in the table represent Spearman correlation coefficients (r). *$p < 0.05$ was considered statistically significant; ***$p < 0.001$ indicated highly significant correlation

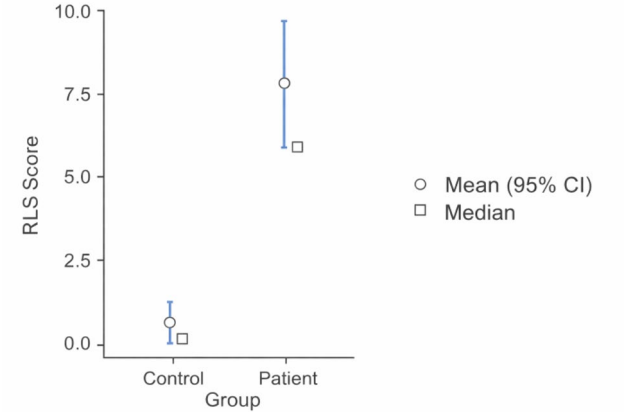

Fig. 1 Comparison of Restless Legs Syndrome (HBS) scores between patient and control groups

with ferritin (r = −0.285, $p < 0.05$) and vitamin D (r = −0.304, $p < 0.05$).

A significant negative correlation was also found between RLS scores and vitamin D levels (r = −0.251, $p < 0.05$). In contrast, RLS duration demonstrated a strong positive correlation with RLS scores (r = 0.838, $p < 0.001$). No significant correlations were observed between transglutaminase antibody levels and anthropometric variables (height, weight, BMI) or hematological parameters (hemoglobin, hematocrit, platelet count, MPV).

RLS scores were significantly higher in the CD group compared with the control group (Fig. 1). While the mean RLS score in the control group remained below 1, the mean score in the CD group was approximately 7–8, with a median value of 6 ($p < 0.001$, Mann–Whitney U test).

According to the correlation analyses, the associations between Marsh classification and clinical, anthropometric, and biochemical variables in patients with celiac disease were generally weak. No significant relationship was identified between Marsh classification and transglutaminase antibodies (anti–tTG IgA and anti–tTG IgG), with correlation coefficients of r = 0.037 and r = 0.119, respectively. Similarly, no significant associations were observed between Marsh stage and child age (r = 0.113), sex (r = −0.018), body mass index (r = 0.094), or dietary adherence (r = −0.070; moderate evidence, $BF_{10} < 0.33$) (Table 6).

A strong positive correlation was detected between RLS duration and ordinal RLS scores (r = 0.736, $BF_{10} > 100$), indicating a high level of evidence based on the Bayes factor. Apart from this finding, no significant correlations were observed between Marsh classification and hematological parameters (hemoglobin, hematocrit, platelet count, mean platelet volume) or biochemical markers (calcium, magnesium, phosphorus, iron, ferritin, folate, vitamin B12, vitamin D, and zinc), with moderate evidence supporting the absence of association ($BF_{10} < 0.33$) (Table 6).

However, a weak negative correlation was observed between vitamin D levels and Marsh classification (r = −0.194, $BF_{10} = 2.155$). This finding suggests that increasing mucosal damage in celiac disease may be associated with decreasing vitamin D levels. Overall, no strong or statistically significant associations were identified between Marsh stage and laboratory or clinical parameters (Table 6).

Regarding dietary adherence, 44.8% of patients ($n = 30$) were compliant with a gluten-free diet, 35.8% ($n = 24$) were non-compliant, and 19.4% ($n = 13$) were newly diagnosed.

Discussion

This study is among the limited number of investigations evaluating the prevalence and symptom severity of Restless Legs Syndrome (RLS) in children diagnosed with celiac disease (CD), as well as its relationship with serum vitamin D and iron levels. Our findings demonstrate that

Table 6 Bayesian correlation analysis between marsh classification and clinical and biochemical parameters

	Marsh classification		HBS ordinal score	
Variable	**r**	**BF_{10}**	**r**	**BF_{10}**
HBS ordinal score	0.035	0.173	—	
Anti-TG IgG	0.105	0.343	0.119	0.43
Anti-TG IgA	0.037	0.175	0.037	0.175
Follow-up duration	-0.079	0.247	0.045	0.183
Dietary adherence	-0.093	0.293	-0.07	0.224
Child age (months)	0.038	0.176	0.113	0.39
Sex	-0.073	0.231	-0.018	0.163
BMI (kg/m^2)	0.061	0.208	0.094	0.296
HBS duration	-0.02	0.163	0.736	>100
Hb (g/dL)	0.093	0.293	0.023	0.166
Hct (%)	0.079	0.247	0.035	0.174
PLT (10^3/μL)	-0.051	0.192	0.037	0.176
MPV (fL)	-0.169	1.163	0.12	0.436
Phosphorus (mg/dL)	-0.02	0.163	-0.045	0.183
Magnesium (mg/dL)	-0.11	0.364	-0.065	0.216
Calcium (mg/dL)	-0.169	1.142	-0.062	0.209
Iron (μg/dL)	0.137	0.586	0.034	0.174
Parathyroid hormone	-0.038	0.179	-0.125	0.465
Ferritin (μg/L)	-0.14	0.619	-0.059	0.204
Folate (μg/L)	-0.087	0.268	0.013	0.171
Vitamin B12 (ng/L)	-0.173	1.315	-0.006	0.16
Vitamin D (μg/L)	-0.063	0.211	-0.194	2.155
Zinc (μg/L)	0	0.526	-0.105	0.54
IgA (g/L)	-0.063	0.212	0.015	0.165

Values are presented as Spearman's correlation coefficients (r) and Bayes factors (BF_{10})

HBS Restless Legs Syndrome, *BMI* Body Mass Index, *Hb* Hemoglobin, *Hct* Hematocrit, *PLT* Platelet count, *MPV* Mean Platelet Volume, *PTH* Parathyroid Hormone, *IgA* Immunoglobulin A

RLS scores are significantly higher in children with CD, that RLS scores are negatively correlated with vitamin D levels, and that there is a strong positive association between RLS duration and symptom severity. In addition, the inverse relationship between elevated transglutaminase antibody levels and ferritin and folate concentrations supports an association between intestinal damage and micronutrient deficiencies in celiac disease.

It is well established that celiac disease is not solely a gastrointestinal disorder but may also be accompanied by neurological, endocrine, and psychiatric complications [7, 8]. The combination of chronic intestinal inflammation, micronutrient malabsorption secondary to villous atrophy, and autoimmune mechanisms may lead to dopaminergic dysfunction within the central nervous system [11]. In a study conducted by Işıkay et al. [22], although the prevalence of RLS in children with CD was reported to be similar to that of the control group (approximately 3.5%), RLS symptoms were shown to begin at an earlier age and to be more severe in the CD group. In the same study, negative correlations were demonstrated between RLS severity and serum ferritin, folate, and 25(OH)D levels [22]. These findings are consistent with the results of the present study.

Vitamin D plays a crucial role in the maintenance of dopaminergic system function. The high density of vitamin D receptors in the substantia nigra, its ability to increase the activity of tyrosine hydroxylase—the key enzyme involved in dopamine synthesis—and its anti-neuroinflammatory effects provide a biological explanation for this association [12]. Cederberg et al. [23] reported that vitamin D deficiency is common in individuals with RLS and that low 25(OH)D levels are associated with increased symptom severity. Similarly, a recent meta-analysis by Xu et al. [24] reported that vitamin D deficiency is frequently observed in individuals with RLS; however, the available evidence does not conclusively demonstrate that vitamin D supplementation leads to significant improvement in RLS symptom severity. Vitamin D deficiency is frequently observed in celiac disease due to impaired fat absorption. Kreutz et al. [18] reported that vitamin D levels may remain low in children even with long-term adherence to a gluten-free diet (GFD). In our study, vitamin D levels tended to be lower in the CD group and showed a negative correlation with RLS scores. This finding suggests that vitamin D deficiency may exacerbate RLS symptoms by contributing to dopaminergic dysfunction. The combined role of vitamin D and iron in the pathogenesis of restless legs syndrome (RLS) has become increasingly evident. Beyond these neurobiological observations, growing evidence indicates that vitamin D plays a critical regulatory role in iron homeostasis through direct modulation of the hepcidin–ferroportin axis. Zughaier et al. [28] demonstrated that active vitamin D suppresses hepcidin expression while upregulating ferroportin in monocytes, thereby facilitating cellular iron export and increasing functional iron bioavailability. This mechanism provides a biological framework linking vitamin D status to iron availability at both systemic and tissue levels. Iron deficiency–related alterations in dopaminergic neurotransmission constitute a central neurobiological mechanism underlying RLS. In this context, Connor et al. [29] demonstrated that reduced D2 dopamine receptor levels in the putamen were correlated with RLS severity, while increased tyrosine hydroxylase expression in the substantia nigra was observed in animal and autopsy models of iron insufficiency, suggesting compensatory dopaminergic upregulation secondary to impaired iron availability.

Iron is an essential cofactor for the enzyme tyrosine hydroxylase and is required for dopamine biosynthesis. Brain iron deficiency is widely accepted as a fundamental pathophysiological mechanism underlying RLS [9, 25]. Dosman et al. [26] reported that in children diagnosed

with RLS, elemental iron supplementation at a dose of 3–6 mg/kg/day for three months may be beneficial when ferritin levels are below 50 µg/L. In patients with celiac disease, the primary cause of iron deficiency is impaired absorption secondary to duodenal villous damage. Montoro-Huguet et al. [16] reported that iron deficiency is observed in 40–80% of individuals with CD. Although ferritin levels in our study were comparable between the CD and control groups, the inverse correlation between transglutaminase antibody levels and ferritin suggests that the severity of mucosal damage adversely affects iron stores. Erdem et al. [27] emphasized that deficiencies in iron, zinc, and vitamins in celiac disease may negatively impact neurological function, supporting the notion that iron deficiency may indirectly exacerbate RLS symptomatology.

The combined role of vitamin D and iron in the pathogenesis of restless legs syndrome (RLS) has become increasingly evident. Beyond these neurobiological observations, growing evidence indicates that vitamin D plays a critical regulatory role in iron homeostasis through direct modulation of the hepcidin–ferroportin axis. Zughaier et al. [28] demonstrated that active vitamin D suppresses hepcidin expression while upregulating ferroportin in monocytes, thereby facilitating cellular iron export and increasing functional iron bioavailability. This mechanism provides a biological framework linking vitamin D status to iron availability at both systemic and tissue levels. Iron deficiency–related alterations in dopaminergic neurotransmission constitute a central neurobiological mechanism underlying RLS. In this context, Connor et al. [29] demonstrated that reduced D2 dopamine receptor levels in the putamen were correlated with RLS severity, while increased tyrosine hydroxylase expression in the substantia nigra was observed in animal and autopsy models of iron insufficiency, suggesting compensatory dopaminergic upregulation secondary to impaired iron availability.

Furthermore, evidence from clinical studies indicates that modulation of iron-regulatory pathways is closely linked to symptom improvement. Following 12 weeks of dopaminergic therapy, a reduction in serum hepcidin levels was associated with a significant decrease in RLS severity and an improvement in quality of life [30]. These findings support the hypothesis that vitamin D enhances neuronal iron bioavailability by upregulating ferroportin expression, thereby facilitating dopaminergic function. Accordingly, the study by Im et al. [30] indicates that hepcidin could play a role both as a regulator of iron metabolism and as a potential biomarker of therapeutic response in RLS.

Consistent with this mechanistic framework, Xu et al. [18] reported an association between low vitamin D levels and restless legs syndrome (RLS), suggesting a potential interplay between vitamin D status and iron metabolism. Experimental studies indicate that vitamin D may regulate iron homeostasis via the hepcidin–ferroportin axis; however, these mechanisms remain incompletely elucidated. Collectively, these observations support the hypothesis of a vitamin D–iron–dopamine interaction in RLS pathophysiology, although causality cannot be established based on current evidence. Notably, a randomized controlled trial by Siraj Omar Wali et al. reported that vitamin D replacement was not superior to placebo in reducing RLS symptom severity, further indicating that the relationship between vitamin D status and clinical improvement remains uncertain [31].

Accordingly, patients with concurrent deficiencies in both vitamin D and ferritin may be more likely to experience more severe RLS symptoms. In our study, vitamin D levels were low, and ferritin levels were inversely associated with disease activity, a pattern that appears broadly consistent with observations reported in the literatüre [18, 30].

A gluten-free diet may promote villous healing and improves micronutrient absorption in celiac disease. However, several studies have reported that full adherence to a GFD does not always normalize vitamin and mineral deficiencies [11, 18]. Mager et al. [17] demonstrated that vitamin D and iron deficiencies may persist even in children receiving long-term GFD. In our study, no significant difference was observed between GFD adherence and RLS severity; nevertheless, dietary compliance might contribute indirectly to improvement of neurological symptoms. Consequently, monitoring and, if necessary, replacing micronutrients could be considered an important adjunct to dietary management.

This study underscores the importance of evaluating vitamin D and iron levels together when assessing RLS symptoms in children with celiac disease. Low serum 25(OH)D and ferritin levels are associated with increased RLS symptom severity. Although vitamin D and iron supplementation have been proposed as potential interventions in RLS, current evidence does not conclusively support their effectiveness, and further randomized controlled trials are required [3, 12, 24]. Accordingly, routine follow-up of children with celiac disease may benefit from screening for RLS, periodic monitoring of serum ferritin and vitamin D levels, and consideration of supplementation when indicated.

The cross-sectional design of this study limits the ability to establish causal relationships. In addition, RLS diagnosis was based on self-reported measures, and objective sleep assessments were not performed. Nevertheless, the observed correlations are robust and indicate that RLS represents a clinically relevant neurological complication that should not be overlooked in children with celiac disease.

An additional limitation of the present study is the absence of systematically collected data regarding family history of Restless Legs Syndrome. Given the well-established hereditary contribution to pediatric RLS, particularly in early-onset cases, the lack of family history data limits our ability to determine the relative contribution of genetic predisposition versus disease-related micronutrient deficiencies. Future prospective studies incorporating detailed familial assessment are warranted.

In conclusion, this study demonstrates a significant association between celiac disease and RLS in children, mediated by Vitamin D and iron levels. While GFD promotes mucosal healing, it often fails to resolve RLS symptoms without adequate micronutrient replacement. Therefore, routine pediatric follow-up for celiac disease should include RLS screening and the monitoring of serum 25(OH)D and ferritin levels. Addressing these neurological symptoms is vital for overcoming the developmental challenges associated with celiac disease and ensuring optimal health outcomes.

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Authors' contributions
Conceptualization: A.C.T., M.T.K. Data Collection: A.C.T, D.G.,M.T.K. Statistical Analysis: İ.K. Manuscript Drafting: A.C.T., M.T.K.,D.G.,A.K.T. Critical Revision: All authors. Final Approval: All authors.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Institutional Ethics Committee of Ankara Etlik City Hospital (Approval No: AEŞH-BADEK_2024 – 939; Date: 25/12/2024). Written informed consent was obtained from the parents or legal guardians of all participants, and assent was also obtained from children aged 12 years and older. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Conflict of interest
The authors declare no conflicts of interest.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Pediatric Gastroenterology and Hepatology Specialist, University of Health Sciences, AnkaraEtlik City Hospital, Varlık Mahallesi, Halil Sezai Erkut Caddesi, Ankara, Yenimahalle 06170, Türkiye
[2]Department of Pediatrics, University of Health and Sciences, Ankara Etlik City Hospital, Ankara, Türkiye
[3]Department of Pediatrics, Istanbul Health and Technology University, İstanbul, Türkiye

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