The relationship between Willis-Ekbom disease and serum ferritin levels among children in Northwestern Turkey

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ABSTRACT

الأهداف : لدراسة حالات متلازمة تململ الساقين (RLS) بين الأطفال الذين يعانون من نقص الحديد ، أو أنيميا نقص الحديد ، أو كليهما ، والعلاقة بين انتشار RLS ومستويات المصل فيريتين .

الطريقة : أجريت هذه الدراسة المحتملة ، مستعرضة للرقابة من يناير ويونيو 2013م ، وشملت 200 طفل حُولوا إلى قسم الأعصاب والأطفال في كلية الطب في جامعة بزمي عالم ، اسطنبول ، تركيا .

النتائج : كان مجموعة من مستويات نطاق الفيرتين12-0.01 ملغ/ مل في المرضى بينما كان 12.3-91.8 ملغ/مل في المجموعة الضابطة . تم الكشف عن متلازمة تململ الساقين في 61.2% من الأطفال الذين يعانون من أنيميا نقص الحديد ، وفي 37.3% من الأطفال الذين يعانون من القيم الكيميائية الحيوية العادية . وجدت علاقة إحصائية مهمة بين مستويات مصل فيريتين RLS . المرضى الذين يعانون من مستويات فيريتين المصل أعلى من 50 نانوغرام / مل ، كان 92.3% بدون RLS ، بينما 55.2% من المرضى الذين يعانون من مستويات المصل فيريتين أقل من 50ng / مل RLS . المرضى الذين يعانون من مستويات المصل فيريتين >50ng كان لديهم نسبة أعلى بكثير من RLS . وكانت مستويات مصل فيريتين مختلفة اختلافا كبيراً بين المجموعتين .

الخاتمة : إن نسبة الإصابة RLS ، المعروف أيضاً بمرض Willis-Ekbom ، عالية لدى الأطفال الذين تتراوح أعمارهم بين 8-18 سنوات والذين يعانون من نقص الحديد ، أو أنيميا نقص الحديد ، أو كليهما . ويؤيد هذا الاكتشاف أهمية العلاج ببدائل الحديد خصوصاً خلال نمو وتطور الأطفال .

Objective: To examine the incidence of restless legs syndrome (RLS) among children with iron deficiency, or iron deficiency anemia, or both, and the relationship between RLS prevalence and serum ferritin levels.

Methods: This prospective, cross-sectional, case controlled study was carried out between January and June 2013, and included 98 iron deficiency and/or iron deficiency anemia, and 102 healthy children referred to the Neurology and Pediatric Departments of the Medical Faculty of Bezmialem Vakif University, Istanbul, Turkey. Both groups were evaluated according to the International Restless Legs Syndrome Study Group diagnostic criteria.

Results: The range of ferritin levels was 0.01-12 mg/ml in patients while it was 12.3-91.8 mg/mL in the control group. Restless legs syndrome was detected in 61.2% of children with iron deficiency anemia, and in 37.3% of children with normal biochemistry values. A statistically significant correlation was found between serum ferritin levels and frequency of RLS. In patients with serum ferritin levels higher than 50 ng/ml, 92.3% had no RLS, while 55.2% of patients with serum ferritin levels lower than 50ng/ml had RLS. The patients with serum ferritin levels of >50ng/ml had a significantly higher incidence of RLS. Serum ferritin levels were significantly different between the 2 groups.

Conclusion: The incidence of RLS, also known as Willis-Ekbom Disease, is high in children aged between 8-18 years with iron deficiency, or iron deficiency anemia, or both. This finding supports the importance of iron replacement therapy especially during the growth and development of children.

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Willis-Ekbom disease (WED), also known as restless legs syndrome (RLS), is a sensory-motor disorder affecting patients' sleep quality, cognition, and quality of life.[1] Studies have shown that genetic factors, dopaminergic dysfunction, and low serum iron levels play an important role in the pathogenesis of WED/RLS.[2,3] Iron deficiency is one of the most important nutritional problems throughout the world. Anemia prevalence due to iron deficiency is high among underdeveloped and developing countries, while it is relatively low in developed countries.[4-6] The anemia prevalence is still high in Turkey although some progress has been made.[7,8] Two studies[7,8] on the incidence of WED/RLS frequency in iron deficiency among adults showed an incidence rate of approximately 40%; however, there is a lack of data on the incidence of WED/RLS among children. The WED/RLS can be seen among all age groups, and diagnosis depends on subjective complaints. Unfortunately, there is no specific biological marker for the diagnosis of this disease. Our knowledge of WED/RLS among children is limited, and diagnosis cannot be made without polysomnography (PSG), especially among infants and preschool ages. The incidence of WED/RLS is approximately 2-4% among school aged children and adolescents.[3,9,10] Four mandatory clinical features to establish the diagnosis of WED/RLS were first described by The International Restless Legs Syndrome Study Group (IRLSSG), namely: (i) an urge to move the legs, usually accompanied, or caused by uncomfortable and unpleasant sensations in the legs; (ii) these symptoms begin or worsen during periods of rest or inactivity, such as lying or sitting; (iii) are partially or totally relieved by movement; and (iv) symptoms are worse in the evening or nighttime.[11] In 2013, special considerations of WED/RLS for children were determined.[12] According to these considerations: (i) a child should be able to describe its symptoms in his/her own words; (ii) the person to diagnose WED/RLS in children and adolescents should be aware of the typical words used for the definition of disease; (iii) language and cognitive development rather than child's age is important for WED/RLS diagnosis; (iv) the WED/RLS of children leads to behavioral and educational changes unlike adults; (v) periodic limb movements may be seen prior to WED/RLS diagnosis in some instances. We aimed to study the incidence of WED/RLS among children with iron deficiency, or iron deficiency anemia, or both and the relationship between WED/RLS prevalence and serum ferritin levels in this study. Our hypothesis was that WED/RLS frequency was much higher among children with iron deficiency than the normal population.

Methods.

Study design and study population. In this prospective, cross-sectional controlled study, a total of 200 consecutive children with iron deficiency and/or iron deficiency anemia were referred to the Neurology and Pediatrics Departments of the Medical Faculty of Bezmialem Vakıf University, Istanbul, Turkey between January and June 2013. The Ethics Committee of the Faculty of Medicine of Istanbul University approved the study, and informed consent was obtained from the all participants.

Inclusion criteria. Children between the ages of 8-18 years in whom blood tests revealed iron deficiency and/or iron deficiency anemia were included in the study. The control group consisted of volunteers between 8-18 years old who had no medical problem.

Exclusion criteria. Patients aged <8 years with a limited expressive capability of thoughts and language or >18 years, patients unwilling to participate in the study, patients with an underlying disease other than iron deficiency, such as uremia, cancer, peripheral vascular disease, rheumatoid arthritis, hypothyroidism, polyneuropathy, lumbosacral radiculopathy, myelopathy, multiple sclerosis, and poliomyelitis. Patients using neuroleptic and antiepileptic drugs, and those with local and systemic infectious disease, chronic hepatitis, high serum transaminases (more than twice), serum C-reactive protein and sedimentation rates, portal hypertension, collagen tissue disease, hematologic malignancies, hemolytic anemia, and inflammatory bowel disease were also excluded.

Patient assessment. All participants were questioned regarding their medical family history and drug usage. All patients and controls underwent systemic physical examination. Blood and urine analysis were performed to diagnose co-morbid diseases. Both the study and control groups were evaluated by pediatric and neurology residents with face to face questionnaires

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according to the IRLSSG diagnostic criteria.[11,12] Patients' complaints, in their own words, were taken into consideration. All patients meet the 4 essential diagnostic criteria for WED/RLS.

Evaluation of the laboratory results. Serum ferritin levels measured by Advia centaur classic, IIA (Centaur Chemiluminescent Enzyme Immunoassay Analyzer, Siemens, 2006, Germany). Serum ferritin levels of below 12 ng/ml was accepted as indicating iron deficiency.[13]

Statistical analysis. Sample size. We did not calculate sample size before starting the study; however, the power analysis performed after completion of study was 90%. Statistical analysis was performed with SPSS for Windows (Version 13.0, SPSS Inc., Chicago, IL, USA). Descriptive data were expressed as mean±standard deviation (SD) for continuous variables, and n (%) for categorical variables. Demographic characteristics were compared between the patients (serum ferritin level lower than12 ng/ml) and controls (serum ferritin level higher than 12 ng/ml). Categorical variables were compared using the chi-squared test, while continuous variables were compared using Mann-Whitney U tests as variables did not show normal distribution. Multivariate analysis was performed to find independent predictors for the occurrence of RLS by using a binary logistic regression analysis (enter method). A *p*-value less than 0.05; 95% confidence intervals was considered statistically significant.

Results. Ninety-eight patients with anemia (88 female and 10 male patients) as the patient group, and 102 patients without anemia (51 female and 51 male) as the control group were included in the study. Demographic and clinical characteristics of the patients were shown in **Table 1**. There was a statistically significant difference between patients and controls with regard to age (the patient group was older), gender, ferritin levels, and presence of RLS p=0.000. The frequency of RLS was found higher in patient group than control group (p=0.001).

We also compared the frequency of WED/RLS between children with serum ferritin levels below and over 50 ng/ml. There were 26 children whose ferritin levels were over 50 ng/ml. The WED/RLS was not found in 92.3% (n=24) of these children, while 7.7% (n=2) of them had the diagnosis. There were 174 (89.4%) patients who had serum ferritin levels below 50 ng/ml (**Table 2**). The frequency of WED/RLS was significantly higher among the group with serum ferritin levels under 50 ng/ml (p<0.01). Also, there was a significant difference regarding serum ferritin levels between the WED/RLS positive and negative group (p<0.001). The multivariate logistic regression model showed that

Table 1 - Demographic and clinical characteristics of Turkish pediatric patients with and without anemia.

Variables	Patients with anemia	Patients without anemia	*P*-value
Number of patients	98	102	
Age (years) (mean±SD)	15.4±1.9	11.5±2.5	0.000
Gender (female/male) (n)	88/10	51/51	0.000
Ferritin, µg/ml (mean±SD)	6.01±3.4	36.9±19.4	0.000
Presence of RLS n (%)	60 (61.2)	38 (37.3)	0.001

SD - standard deviation, n - number of patients, RLS - Restless Leg Syndrome

Table 2 - Presence of RLS in Turkish pediatric patients with ferritin levels above and below 50 ng/dl.

Variables	Presence of RLS/ WED	Absence of RLS/ WED	Total	*P*-value
	n (%)			
Patients with ferritin levels more than 50ng/mL	2 (7.7)	24 (92.3)	26 (11.6)	0.000
Patients with ferritin levels less than 50ng/mL	96 (55.2)	78 (44.8)	174 (89.4)	

RLS - Restless Leg Syndrome, WED - Willis-Ekbom Disease

Table 3 - Multivariate logistic regression analysis of potential risk factors for presence of RLS among Turkish pediatric patients.

Variable	OR	95% CI	*P*-value
Age (years)	0.98	0.87-1.1	0.78
Gender	0.85	0.39-1.82	0.68
Ferritin (ng/ml)	0.95	0.93-0.97	0.000

OR - odds ratio, CI - confidence interval, RLS - Restless Leg Syndrome

RLS was not associated with age or gender. This model indicated that decreasing ferritin levels (odds ratio 0.95; p=0.000; 95% confidence interval: 0.93 - 0.97) were independent risk factors for RLS (**Table 3**).

Discussion. This study aimed to show the frequency of WED/RLS among children who had iron deficiency with, or without anemia. There are 2 important findings: 1) Frequency of WED/RLS among children with iron deficiency anemia may be much higher than adults (61.2% in children and 40% in adults,[7,8] and many patients of this group are already taking iron replacement therapy; 2) WED/RLS was found in half (55.2%) of the children with serum ferritin levels below 50 ng/dl. Also, the WED/RLS frequency dramatically decreased in patients with serum ferritin levels over 50 ng/dl (only 7.7%). The prevalence of WED/RLS among school aged children, and adolescents is 2-4% according to studies in Turkey and other countries.[3,9,10] Turkdogan et al[9] found that 15.4% of these patients had also attention deficit and hyperactivity. However, there is not enough data on the etiology of the WED/RLS among this age group.

Iron deficiency anemia is accepted as the most important cause of WED/RLS throughout the world, and several treatment strategies have been suggested. Iron plays an important role in oxygen transport, energy metabolism, and brain development and children are more prone to the effects of iron deficiency because of their fast growth and development. Even in the presence of solely iron deficiency without anemia, the long-term negative effects may be seen in mental, psychomotor, and behavioral development.[14,15] The WHO reported that RLS/WED was seen in 37.3% of children without iron deficiency anemia (serum ferritin level of higher than 12 ng/dl). Our study result is actually very different from other prevalence studies.[3,7,8] But when we divided the patient group into 2 groups according to serum ferritin levels below or over 50 ng/dl, the results decreased to 7.7%. Our study result is also different from 2 previously reported Turkish studies.[9,10] We suggest that this difference may be because of several reasons. One of the previously reported studies was among adolescents, and the other among patients aged between 10-19 years.[10] Our study covered a wider range of ages compared with the other studies, and younger age groups are more sensitive to serum ferritin levels. The previous studies were community based, whereas our study was performed among children referred to hospital, which is the most probable explanation of our higher results. Our study also covers a smaller number of patients. However, we suggest that iron deficiency either directly or with WED/RLS affect routine life and sleep, which causes impairment of growth and development of school aged children and adolescents.

The RLS/WED has many etiologies. Although it is not fully understood, the dopaminergic system and iron metabolism have been suggested to be the basic mechanisms.[14] The presence of low ferritin and high transferrin values in the CSF of WED/RLS patients support the suggestion that symptoms arise from dopaminergic dysfunction due to low iron levels in the brain.[14] It has been reported that the WED/RLS symptoms worsen when serum ferritin levels drop under 50 ng/dl.[16,17] Iron replacement therapy is suggested for children with serum ferritin levels less than 50 ng/dl.[18] A significant correlation was previously reported between serum and CSF ferritin levels.[19]

As our study group consisted of many younger aged patients, we could not conduct a severity evaluation. Hence, we were unable to evaluate the relationship between the level of serum ferritin levels and severity of WED/RLS symptoms. However, we found that almost half of our study group with ferritin levels less than 50 ng/dl had WED/RLS, and so suggest to maintain serum ferritin levels of children at over 50 ng/dl or even higher. Our study also indicated a negative correlation between serum ferritin levels and the presence of WED/RLS. As ferritin levels increased, the frequency of WED/RLS decreased in our study group.

Iron is the co-factor of thyrosine-hydroxylase, which is essential for synthesis of dopamine, and its deficiency disturbs normal dopamine synthesis. Both levels of iron and dopamine show a circadian rhythm, and lowest levels are seen during night time when WED/RLS symptoms are reported to be increased.[20-22] An increase in WED/RLS symptoms causes an increase in sleep latency, sleep disturbances, and shortening of total sleep time in children.

One of the limitations of our study was the relatively small study population size. Other limitations were that we could not provide age- and gender -matching between patients and controls, and we did not perform polysomnography examination in the patients.

In conclusion, we demonstrated that the incidence of RLS/WED is high in children aged between 8-18 years with iron deficiency and/or iron deficiency anemia. The frequency of RLS/WED is higher if ferritin levels below 50 ng/ml. Iron replacement therapy is very important in these children in order to avoid growth and developmental retardation. In order to determine the lower cut-off level of ferritin levels among children, more studies with larger groups of patients are needed.

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