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Prevalence of Restless Legs Syndrome (RLS) in children with Thalassemia Major in Ali Asghar Hospital in Zahedan

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Abstract

Introduction: Thalassemia major is one of the most debilitating chronic and inherited diseases caused by impaired hemoglobin production. To improve the quality of life in the long-term treatment of thalassemia patients, it is necessary to pay special attention to sleep-related disorders such as restless legs syndrome. The present study, thus, attempts to determine the frequency of restless legs syndrome in children and adolescents with thalassemia major.

Methods: This study was performed on 302 patients with thalassemia major with an age range of 5-20 years in Ali Asghar Hospital in Zahedan in 2018. After obtaining the patients' consent and their information including age, sex, underlying disease, history of drug use, Insomnia, splenectomy, oral and injectable iron depletion, and serum ferritin levels, as well as restless legs syndrome were recorded. Then the data were analyzed by SPSS statistical software. Chi-square and T-test were used to compare the data.

Results: The results of this study revealed that the prevalence percentage of Restless Legs Syndrome in children and adolescents with thalassemia major was 17.2%. In addition, it had a direct and significant relationship with vitamin D (p-value=0.008) and calcium (p-value<0.001) intake by patients; and it was higher in patients with Insomnia (p-value=0.004). However, there was no significant relationship between this syndrome and the age, underlying disease, the use of cardiac drugs and growth hormone, splenectomy, iron depletion or serum ferritin level. (p-value>0.05)

Conclusion*:* Due to the high prevalence of RLS in patients with thalassemia major, especially in patients with a history of vitamin D and calcium intake, screening for RLS is necessary. In this way, taking medical measures can help improving the quality of life among these patients.

Keywords: Children, Restless legs syndrome, Thalassemia major

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Introduction

Thalassemia major is one of the most debilitating chronic and inherited diseases caused by impaired hemoglobin production. Sistan and Baluchistan province in the southeastern region of Iran has the highest rate of this disease in the country. (1 and 2) The chronicity of this disease and the need for lifelong treatment leaves negative impacts on the physical and mental health of these children. To improve the quality of life in the long-term treatment of thalassemia patients, it is necessary to pay special attention to sleep-related disorders such as restless legs syndrome. (3) Restless Legs Syndrome (RLS) is a common sensorimotor neurological syndrome in children and adults. (4-6) Recent studies in Iran have had contradictory reports in regard to the presence and prevalence of RLS and its associated factors. For example, Jamalnia (7) reported an RLS rate of 50%, with a mean score of 12.02, and found no difference between men and women in this disorder. Hosseini et al. (8) reported a prevalence of 27.9% for this syndrome in cardiovascular patients and Molahosseini et al. (9) reported a prevalence of 61.5% in hemodialysis patients in Yazd. RLS has many complications and causes a decrease in the quality of life, sleep disorder, increased risk of cardiovascular disease and even death; and is closely associated with depression disorder (10,11). This disease can affect all parts of the body but often manifests itself with a feeling of discomfort in the lower extremities. (11)

There are two types of this syndrome: primary and secondary. In the primary type, the disease is not caused by another disorder and often occurs with a positive family history. In contrast, secondary types occur in conditions such as pregnancy, renal failure, iron deficiency anemia, diabetes, rheumatoid arthritis, and neuropathy. (12) Evidence suggests that the pathological mechanism in the primary type is associated with dopaminergic dysfunction and iron deficiency, while the secondary type mechanism is more associated with impaired serum phosphorus and calcium. (13) Some recent studies have shown the role of genetics in RLS (14), while other studies have suggested the role of infectious inflammatory factors and abnormal immune responses (15).

This syndrome can manifest itself in varying degrees of severity from mild to severe. (16) Exacerbation of symptoms occurs more in the evening and night, which reflects the circadian changes of dopamine in the black body. (17) The syndrome is associated with sleep disorders, hyperactivity, behavioral disorders, growth disorders and decreased ferritin levels. In addition, it can affect the daily functioning of social activities and quality of life (9). Due to the importance of quality of life in patients, we decided to conduct this study with the aim of determining the frequency of restless legs syndrome in children and adolescents with thalassemia major.

Method

This descriptive cross-sectional study was performed on all children and adolescents with thalassemia major with an age range of 5 to 20 years, referred to Ali Asghar Clinic in Zahedan in 2018. Patients were evaluated for symptoms of Restless Legs Syndrome based on revised IRLSSG criteria, and then all patient information including age, sex, underlying disease, history of drug use, insomnia, splenectomy, oral and injectable iron depletion, and Serum ferritin levels were recorded in information forms. Demographic information of patients was completed through their history and records. History of drug use including calcium, vitamin D, insulin, growth hormone and cardiac drugs were also asked. Information including serum ferritin level, type of iron depletion, splenectomy

as well as a history of heart disease and hypoparathyroidism were also extracted from the patients' records. Besides, the existence of sleep problems was confirmed through history. This study was approved by the University Ethics Committee with the code IR.ZAUMS.REC.1396.34. Inclusion criteria included informed consent to enter the project, age between 5 and 20 years, and cooperation required to obtain a history. Exclusion criteria were kidney failure and diabetes. The data were analyzed by SPSS statistical software. The characteristics of the two groups with RLS and non-RLS were compared by t-test. A significance level of 0.05 was considered.

Criteria considered for diagnosing Restless Legs Syndrome, based on the criteria revised by the IRLSSG in 2012 (18) were as follows:

1. A constant urge to move the legs is usually unpleasant and uncomfortable. This feeling is usually in the lower limbs. Sometimes other parts of the body, such as the arms, are also involved.

2. Symptoms begin during periods of inactivity or rest.

3. Complete or partial relief with movement, at least as long as it lasts.

4. The symptoms of the disease only get worse or appear in the evening or at night.

5. The above criteria should not be the only main symptoms of another disease.

Results

From among the 302 patients who were admitted to the study according to the inclusion and exclusion criteria, 150 (49.7%) were male and 152 (50.3%) female. Of these patients, 52 patients (17.2%) had restless legs syndrome. The results of our study showed that the mean age and standard deviation in thalassemia patients with restless legs syndrome were 3.95±11.79 years and in the group without restless legs syndrome were 4.19±12.09, which did not have a statistically significant difference. Likewise, the mean ferritin levels in the group with RLS and non-RLS did not differ significantly. (Table 1)

Table 1- Frequency of age and sex in patients with thalassemia major based on restless legs syndrome

Restless Leg Syndrome (RLS)			No	Yes	All	P-Value
Age	Less than 10 year	Number	75	18	93	0.23
		Percentage	80.6	19/4	100/0	
	10 to 14.9 year	Number	118	18	136	
		Percentage	86.8	13/2	100/0	
	15 and over	Number	57	16	73	
		Percentage	78.1	21/9	100/0	
	All	Number	250	52	302	
		Percentage	82.8	17/2	100/0	
Sex	Male	Number	124	26	150	0.958
		Percentage	82/7	17/3	100/0	
	Female	Number	126	26	152	
		Percentage	82/9	17/1	100/0	
	All	Number	250	52	302	
		Percentage	82/8	17/2	100/0	

Table 2 shows the frequency of drug use and oral and injectable iron deprivation based on Restless Legs Syndrome. As can be seen in the table, the prevalence of Restless Legs Syndrome in children who consumed calcium was significantly higher than children who did not consume calcium. The incidence of restless legs syndrome was also significantly higher in children who took vitamin D than in children who did not take vitamin D, but there was no statistically significant difference in heart medications, insulin, and growth hormone. (Table 2)

Table 2 - Frequent use of drugs and oral and injectable iron depletion based on restless legs syndrome

Restless Leg Syndrome (RLS)			**No**	**Yes**	**All**	**P-Value**
Cardiac Drugs	No	Number	214	40	254	0/119
		Percentage	84/3	15/7	100/0	
	Yes	Number	36	12	48	
		Percentage	75/0	25/0	100/0	
Insulin	No	Number	245	50	295	0/346
		Percentage	83/1	16/9	100/0	
	Yes	Number	5	2	7	
		Percentage	71/4	28/6	100/0	
Growth Hormone	No	Number	245	52	297	0/592
		Percentage	82/5	17/5	100/0	
	Yes	Number	5	0	5	
		Percentage	100/0	0	100/0	
Calcium	No	Number	162	18	180	<0/001
		Percentage	90/0	10/0	100/0	
	Yes	Number	88	34	122	
		Percentage	72/1	27/09	100/0	
Vitamin D	No	Number	222	39	261	0/008
		Percentage	85/1	14/9	100/0	
	Yes	Number	28	13	41	
		Percentage	68/3	31/7	100/0	
Iron Celator	PO	Number	6	0	6	0/305
		Percentage	100/0	0	100/0	
	IV	Number	239	52	291	
		Percentage	82/1	17/9	100/0	
	No	Number	5	0	5	
		Percentage	100/0	0	100/0	
	All	Number	250	52	302	
		Percentage	82/8	17/2	100/0	

In patients, the only statistically significant variable was sleep disturbance, so that the frequency of restless legs syndrome in children with sleep problems was significantly higher than children without sleep problems. Also, the incidence of restless legs syndrome in children with sleep problems was significantly higher than the others (30.8% vs. 14.4%). (Table3)

Table 3 - Frequency of Restless Legs Syndrome by Underlying Disease, Sleep Disorder and Splenectomy

Restless Leg Syndrome (RLS)			No	Yes	All	P-Value
Cardiac Disease	No	Number	228	44	272	0/149
		Percentage	83/8	16/2	100/0	
	Yes	Number	22	8	30	
		Percentage	73/3	26/7	100/0	
Hypoparathyroidism	No	Number	244	49	293	0/194
		Percentage	83/3	16/7	100/0	
	Yes	Number	6	3	9	
		Percentage	66/7	33/3	100/0	
Sleep Disorder	No	Number	214	36	250	0/004
		Percentage	85/6	14/4	100/0	
	Yes	Number	36	16	52	
		Percentage	69/2	30/8	100/0	
	All	Number	250	52	302	
		Percentage	82/8	17/2	100/0	
Splenectomy	No	Number	240	50	290	0/959
		Percentage	82/8	17/2	100/0	
	Yes	Number	10	2	12	
		Percentage	83/3	16/7	100/0	
	All	Number	250	52	302	
		Percentage	82/8	17/2	100/0	

Discussion

The aim of this study was to evaluate the frequency of restless legs syndrome in patients with thalassemia major. Restless Legs Syndrome is a common movement disorder, and these patients can hardly describe a vague sensory problem deep in their legs, and most patients can hardly fall asleep or wake up frequently. Diagnosis and treatment of these disorders improves quality of life. (19)

From among the 302 patients included in the study, 150 were male and 152 were female. Of these 302 patients, 52 patients (17.2%) had restless legs syndrome. This study showed that the variables of age, sex, underlying disease, use of cardiac drugs, insulin and growth hormone, splenectomy, iron depletion and mean serum ferritin level in patients with thalassemia major are not influential factors on RLS, since there was not a significant difference between the RLS patients and those without RLS. Furthermore, it was found that the incidence of restless legs syndrome in children who consumed calcium was significantly higher than children who did not consume calcium (27.9% vs. 10%). It was also found that the incidence of restless legs syndrome in children who consumed vitamin D was significantly higher (31.7% vs. 14.9%). Also, the incidence of restless legs syndrome in children with sleep problems was significantly higher than the others (30.8% vs. 14.4%).

Meta-regression results showed that there was a significant negative relationship between the prevalence of RLS and the sample size, year of publication, and mean age of the subjects. This means that the

smaller the sample size, mean age, and publication of articles, the higher the prevalence of RLS in Iranian society. Abdi et al. (20) reported an 18.5% prevalence (95% CI: 16.05-12.02) of RLS in Asian pregnant women and also found that there is no significant relationship between the prevalence of RLS in patients with the year of publication (p= 0.939), sample size (p= 0.161) and mean age of the samples (p= 0.105). In European and American societies, it has been reported that the prevalence of RLS in the general population has increased with ageing but in Asian countries, there have been no changes in the prevalence of this disorder with aging (20,21).

In a study conducted by Çurgunlu et al., evaluating the relationship between serum ferritin levels and RLS, it was found that most patients with RLS had less than 50 ferritin levels. The results had shown an inverse relationship between RLS severity and ferritin levels (22) but in our study there was no significant relationship between RLS and serum ferritin levels.

In another study conducted by Roohangiz Sorkhabi et al., in 2010, the relationship between RLS and thalassemia major was investigated. They had reported a prevalence of 24% for RLS; and it was not found to be related to serum ferritin level, which is completely consistent with the findings of our study (23). In another study by Mehdizadeh in 2016, 39 children with thalassemia and 39 healthy children were included in a case-control study to evaluate the association between RLS and thalassemia major. The prevalence of RLS in girls and thalassemia patients was higher than the control group, but there was no significant relationship between RLS and serum ferritin level and the prevalence of RLS in this study was twice more than in our study. (24)

A study by Gulistan Halac et al., evaluated the incidence of RLS in children with iron deficiency in Istanbul in 2013. It showed that 6.2% of children with iron deficiency anemia and 37.3% of children with normal anemia had RLS. Moreover, they had found a significant positive correlation between ferritin level and RLS frequency. According to the results of this study, RLS was not found in 92.3% of the patients with ferritin levels above 50 mg / ml, while 55.2% of patients with ferritin levels below 50 had RLS. It was found that RLS is significantly more common in people with ferritin levels below 50 (25). However, in our study, the prevalence of restless legs syndrome in children with thalassemia major was 17.2%, which is much lower. The reason for this difference may be due to differences in the sample size, differences in inclusion and exclusion criteria, differences in demographic indicators of patients, differences in the type of drugs used and the type of underlying disease.

In another study conducted by Salimipour et al., in Bushehr on 130 dialysis patients and published in 2009, it was found that 33.1% of patients had RLS. Based on the results of this study, serum ferritin level did not show a significant relationship with RLS and only a positive family history showed a significant difference between patients with RLS and others (26).

In a 2018 study by Dimitriadou et al., the association between RLS and thalassemia was investigated. 114 beta thalassemia patients participated in this cross-sectional descriptive study. The patients were evaluated for RLS based on international RLS diagnostic criteria. The prevalence of RLS in this sample of beta thalassemia patients was zero. Quality of life scores were low, but iron and ferritin levels were in the normal range. It was concluded that dequate levels of iron and ferritin, which are often seen in these patients, may be the reason for the absence of RLS symptoms (27).

Due to the high prevalence of RLS in patients with thalassemia major, especially in patients with a history of vitamin D and calcium intake, screening for RLS is essential. In this way, taking medical measures can help improving the quality of life among these patients.

Study Limitations

Patients' unwillingness to participate in the study and incomplete patients' recorded information

Conclusion

Sleep disorder is a common problem in major thalassemia patients and RLS is the most common underlying etiology for their sleep disturbances. However, RLS was not significantly correlated with the variables of age, sex, underlying disease, the use of cardiac drugs and growth hormone, splenectomy, iron depletion and serum ferritin level.

Due to the high prevalence of RLS in patients with thalassemia major, especially in patients with a history of vitamin D and calcium, screening for RLS is necessary. In this way, taking medical measures can help improving the quality of life among these patients.

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