The Egyptian Journal of Hospital Medicine (January 2018) Vol. 70 (7), Page 1169-1173

Evaluation of Patients with Iron Deficiency Anemia

Mohannad Ali S Alomari [1], Sultan Ali M Alshehri [2] , Ehab Osama Mugharbal [3] , Yousef Mohammed Alhazmi [4] , Mohammed Ammar A Almoabadi [5] , Maram Adnan Rawah [6] , Ayat Essam Shaban [7] , Rabab Abdulrazaq S Makkawi [8] , Leena Abdulaziz Y Alsaiari [5] , Mohammed Adil H Alqadheeb [9] , Naif Enad Alanazi [10] , Mohammed Yarub Hafez [11]

1- Najran University Hospital, 2- Almujardah General Hospital, 3- Ohud Hospital, 4- Al Amal Mental Health Complex, 5- King Abdulaziz University, 6- Jeddah Eye Hospital, 7- Al Nahdah PHC, 8- MCH PHC , 9- Imam Abdulrahman Bin Faisal University , 10- King Salman Hospital -Riyadh, 11- Jeddah Alsulimania PHC

ABSTRACT

Objectives: We aimed to assess the effect of anemia on subjective sleep quality in patients with iron deficiency anemia (IDA).

Methods: The present study is a prospective and cross-sectional study which has been carried out at King Abdulaziz hospital between November 2016 and April 2017. Fifty-two patients diagnosed with iron deficiency anemia and 40 healthy individuals, who are gender and age matched, were involved in the study. All participants were requested to fill 3 forms: a socio-demographic form (age, gender, marital status, income level and educational status), hospital anxiety and depression (HAD) scale and Pittsburgh sleep quality index (PSQI).

Results: According to the HAD scale, the average anxiety score was found 9.31±2.41 in patients and 7.62± 2.11 in controls. And, the average depression score was 7.49±2.08 in patients and 6.39±2.73 in controls. The total sleep quality score was 6.68±2.99 in patients and 4.27±1.71 in controls. There was a statistically significant difference in terms of anxiety, depression and sleep quality scores. Linear regression analysis showed no association between anxiety and depression with poor sleeping.

Conclusion: IDA affects sleep quality irrespective of psychological symptoms such as depression and anxiety.

Keywords: Iron deficiency anemia, sleep quality, anxiety, depression.

INTRODUCTION

After a negative iron balance in the body as a result of increased iron demand, chronic blood loss, and absorption disorder, hemoglobin synthesis is compensated by mobilization of iron from stores and when the stores of iron fail to release adequate iron, iron deficiency anemia (IDA) develops [(1)]. Just like in KSA, iron deficiency is the most common cause of anemia in the world and is more prevalent in women than men [(2, 3)]. It has been known that more than 30% of those attending to hospitals in developed countries are anemic and the said ratio is much higher in developing countries[(3)].

In developed countries, 3% of adult males, 20% of adult females and 50% of pregnant women have iron deficiency anemia [(4)]. Loss of appetite, tiredness, lethargy, pale skin, headache, tinnitus and impairments in cognitive and intellectual functions can be perceived in IDA. Iron plays a key role in the metabolism of monoamines in the brain, accordingly, iron deficiency leads to symptoms, for instance, drowsiness, apathy, irritability and lack of attention arise as a result of impaired monoamine oxidase activity [(5)]. Patients affected from iron deficiency display many behavioral and emotional signs and have symptoms comparable to the ones in depressive individuals. Sleep is the period of physiological, periodic and reversible changes in consciousness and behavior [(6)]. It is defined as a reversible state where interaction of the organism with the environment is lost temporarily, partially and periodically. Almost 30–33% of the society has a significant sleep problem. The said ratio is higher in older adults, those having a psychiatric disorder and specific groups with learning difficulties [(7, 8)]. In numerous studies, stress, advanced age, depression, female gender, alcohol, anxiety, substance abuse and physical diseases are the main factors causing sleep disorders [(9)].

As a result of the key role of iron in the metabolism of monoamines in the brain and the role of the same monoamines in sleep physiology, we specified that sleep quality might deteriorate in IDA. In this context, studies regularly have been performed in pediatric populations. Therefore, we intended evaluating sleep quality in adult patients diagnosed with iron deficiency anemia.

MATERIALS AND METHODS

The present study is a prospective and cross-sectional study which has been carried out at King Abdulaziz hospital between November 2016 and April 2017. Fifty-two patients diagnosed with IDA and gender and age matched 40 healthy individuals were involved in the study. Loss of appetite and

Received: 18/12/2017
Accepted: 28/12/2017
DOI: 10.12816/0044545

tiredness were the most common presentations. It was confirmed that there were no accompanying neurological or endocrinal diseases in patients with IDA.

The diagnosis of IDA was made by assessing the levels of hemoglobin, transferrin saturation - calculated by the ratio of serum iron to serum iron binding capacity- and ferritin. Hemoglobin level below 13 g/dL in men and 12 g/dL in women, transferrin saturation ratio below 15%, and ferritin level below 15 ng/mL indicated IDA. The control group was composed of healthy volunteers who were regular blood donors in the hospital. Those having systemic diseases for example, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure, rheumatoid arthritis, coronary artery disease, systemic lupus erythematosus and ankylosing spondylitis and any medication use were excluded from the study. The participants were asked to complete a socio-demographic form (age, gender, marital status, income level and educational status), hospital anxiety and depression scale and Pittsburgh sleep quality index.

Anxiety and depression parameters were tested by the hospital anxiety and depression scale (HAD). As the scores increase, depression and anxiety increase [(10)]. The Pittsburgh sleep quality index (PSQI) was utilized to measure sleep disturbance. It is consisted of 19 items and over 7 domains that contain habitual sleep efficiency, subjective sleep quality, sleep latency, sleep disturbance, sleep duration, use of sleep medications and daytime dysfunction. Greater PSQI scores show worse sleep quality. A global sum of 6 or greater indicates a poor sleeper [(11)].

SPSS 15.0 statistical program (SPSS, version 15.0 for Windows; SPSS, Chicago, IL, USA) was utilized for statistical analysis. Continuous variables are presented as means ± SDs, and categorical variables are presented as percentages. Independent-sample t- test were utilized to compare patients and healthy individuals with regard to the study variables. Chi-square tests were utilized to compare data presented as percentages. Correlation analysis was performed using Pearson's coefficient of correlation. Linear regression analysis was utilized to assess the contributions of age, anxiety, and depression to poor sleeping.

RESULTS

The patient population (average age: 33.5 ±9.9 years) were composed of 52 patients [40 (76.9%) female and 12 (23.1%) male]. The control group (average age: 29.8 ± 9.8 years) had similar socio-demographic characteristics and were composed of 40 healthy individuals [30 (75%) female and 10 (25%) male]. In terms of age and gender distribution, there was no statistically significant difference between the groups . The socio-demographic characteristics of the study groups are given in Table 1.

Table 1: Socio-demographic characteristics of the study groups

	Patients		Controls		p value
	N	%	N	%	
Gender					
Female	40	76,9%	30	75,0%	>0.05
Male	12	23,1%	10	25,0%	
Educational status					
Primary school	16	30,8%	13	32,5%	
Secondary school	10	19,2%	8	20,0%	>0.05
High school	18	34,6%	14	35,0%	
University	8	15,4%	5	12,5%	
Marital status					
Married	33	63,5%	27	67,5%	>0.05
Single	19	36,5%	13	32,5%	
Income status					
Low-income	13	25,0%	10	25,0%	<0.001
Middle-income	33	63,5%	25	62,5%	
High-income	6	11,5%	5	12,5%	

In terms of hemoglobin, hematocrit and MCV values, there was a statistically significant difference between the groups (P<0.001; P<0.001; P<0.001, respectively). The other hemogram parameters did not show any differences between the groups. The detailed hemogram values of the groups are shown in Table 2.

In the patient group, the average serum ferritin level and total iron binding capacity were measured as 7.21±5.31 and 409.10±59.8, respectively. In HAD scale, the average anxiety score was 9.31±4.41 in patients and 7.62±4.11 in controls (P>0.05). The average depression score was 7.49±4.08 in patients and 6.39±2.73 in controls (P>0.05). There was not any statistically significant difference in terms of anxiety and depression scores. The number of patients who had an anxiety level above the cut-off score was 22 (42.2%) and it was 11 (27.5%) in the control group (P>0.05). The number of patients who had a depression score above the cut-off score was 25 (48%) and it was 13 (32.5%) in the control group (P>0.05).

Table 2: Hemogram values

	Patients	**Controls**	
	mean ± SD	mean ± SD	P
Haemoglobin (g/dl)	10.10 ± 1.45	13.08 ± 0.81	<0.001
Hematocrit (%)	31.98 ± 3.59	35.98 ± 3.18	<0.001
MCV (μm^3)	69.97 ± 7.76	84.89 ± 3.71	<0.001
White Blood Cell (thousand/mm^3)	6.28 ± 1.35	6.07 ± 1.51	>0.05
MCH (pg/RBC)	22.02 ± 3.51	21.76 ± 3.28	>0.05
MCHC (g/dl)	29.98 ± 3.31	30.95 ± 3.58	>0.05

In PSQI, 35 (67.3%) patients and 16 (40.5%) controls reported a bad sleep quality. The number of patients who reported a bad sleep quality were statistically significantly higher than the controls (P<0.01). The total sleep quality score was 6.68±2.99 in patients and 4.27±1.71 in controls. In terms of total PSQI score, there was a statistically significant difference between the groups (P<0.001).

With respect to the subscales of PSQI, subjective sleep score was 1.29±0.79 in patients and 0.88±0.61 in controls, so, we have found a statistically significant difference between groups (P<0.01). Sleep disorder score was 1.59±0.81 in patients and 0.89±0.61 in controls, so, we have found a statistically significant difference between groups (P<0.001). PSQI subscale scores of the groups are given in Table 3. In the regression analysis, we assessed whether the presence of sleep disorder is related with depression and anxiety. Linear regression analysis showed no association of anxiety (partial correlation coefficient: −0.181; P>0.05) and depression (partial correlation coefficient: −0.084; P>0.05) with poor sleeping.

Table 3: PSQI subscales

	Patients	**Controls**	**Column2**
	(mean ± SD)	(mean ± SD)	P
Subjective sleep quality	1.29 ± 0.29	0.88 ± 0.31	<0.01
Sleep latency	1.29 ± 0.29	0.81 ± 0.31	<0.01
Sleep duration	0.67 ± 0.19	0.53 ± 0.11	>0.05
Habitual sleep efficiency	0.58 ± 0.21	0.41 ± 0.19	>0.05
Sleep disturbances	1.59 ± 0.21	0.89 ± 0.11	<0.001
Use of sleep medication	0.03 ± 0.001	0.00 ± 0.00	>0.05
General dysfunction	1.22 ± 0.21	0.71 ± 0.19	<0.01
Total sleep disorder	5.68 ± 1.97	4.08 ± 1.59	<0.01

DISCUSSION

Iron deficiency has been described to cause behavioral and developmental symptoms by affecting transmitters, for instance, myelination, noradrenaline and dopamine, serotonin, and the metabolic activity in the neurons [12]. It has been likewise stated that brain functions such as cognition and learning are affected in patients with IDA [13]. Peirano et al. [14] described that relative to controls, children with IDA showed longer duration of REM sleep episodes in the first third and shorter in the last third; more REM sleep episodes in the first third and fewer in the second third; and shorter latency to the first REM sleep episode and shorter NREM stage 2. Thus, their outcomes display that IDA is allied with long-lasting alterations in the temporal organization of sleep patterns. Peirano et al. [14] recommended that the changes in the neurotransmitter metabolism caused by iron deficiency, psychological status or a likely restless leg syndrome (RLS) influences sleep negatively. These outcomes might be clarified by some mechanisms. One possible explanation for the differences that long-lasting effects of iron deficiency on the developing dopamine (DA) system are a promising example [15].

Iron has a complex effect on dopaminergic function. It is a cofactor for tyrosine hydroxylase and is integral to D2 receptor function [16]. Neuromodulation by the DA system plays an important role in sleep regulation, comprising the modulation of REM sleep quality, quantity, and timing [17]. **Holst *et al.*** [18] studied sleep-wake regulation in humans and combined

pharmacogenetic and neurophysiologic methods to analyze the effects of the 3′-UTR variable-number-tandem-repeat polymorphism of the gene (DAT1, SLC6A3) encoding dopamine transporter. Their results recommended that the dopamine transporter contributes to homeostatic sleep-wake regulation in humans. Fifel *et al*. [19] examined alterations of circadian rhythms in non-human primate models following lesion of the dopaminergic nigro-striatal system. Their outcomes are of clinical significance and stress that sleep/wake disturbances allied with DA loss can be more severely affected than earlier thought, in specific in sub-optimal lighting conditions. The dynamic balance amid neurotransmitter systems is another important consideration. The ultradian alternation of NREM sleep/REM sleep seems to be controlled by a permanent interacting balance amid brainstem aminergic and cholinergic neuronal discharges. A further clarification could be differing amounts of sleep alterations. In specific, RLS and periodic limb movements throughout sleep have been connected with conditions characterized by compromised iron status [20]. It has been recognized that iron deficiency plays a vital role in the physiopathology of the RLS characterized by an irresistible urge to move legs as well as motor restlessness.

Iron treatment has been believed to increase sleep quality of the patients by decreasing RLS complaints. In a study of Allen et al. [21], pervasiveness of clinically significant RLS (RLS sufferers) was 23.9% in 251 patients with IDA, nine times higher than the general population. In another study, the said ratio was reported as 40% [22]. Patients with RLS were excluded from this study. In the current study, nearly 68% of the patients with IDA were shown to have an impaired sleep quality. Our findings support the idea that sleep quality is impaired in a significant portion of patients with IDA.

Depression and anxiety disorders are among the psychological disorders that affect sleep quality negatively. In a study conducted by **Onder *et al.*** depressive disorder was found to be a common disorder in patients with anemia [23]. In the present study, comparable to the literature, a major portion (almost 45%) of the patients had high anxiety and depression scores. Son et al. reported that cognitive functions were worse in anemia patients when compared to healthy controls, which was shown to be associated with depressive disorder [24]. In the current study, logistic regression analysis showed that anemia affected sleep quality irrespective of the psychological symptoms.

We have found no significant relation between the sleep quality and laboratory values of the patients. In the present study, lack of significant correlation between laboratory values and sleep quality scores was not an expected result. **Shariatpanaahi *et al*.** [25] stated that there was a weak correlation between serum ferritin level and depression. In another study, it was shown that serum ferritin and hemoglobin levels had no significant relation with depression level. Similar to the results of the previous studies, the results of the current study showed that the sleep quality level could not be evaluated through hemogram, serum iron and ferritin levels in patients with IDA.

CONCLUSION

Subjective sleep quality was assessed in patients with IDA in the current study. The results showed that IDA affects sleep quality irrespective of psychological symptoms such as depression and anxiety. And similarly, it was shown that subjective sleep quality was worse in patients with IDA when compared to the healthy controls. The effects of anemia treatment on sleep quality were not assessed as a result of the cross-sectional nature of the study. Additional studies are required where anemia patients ought to be followed-up for an extended period of time and evaluated by polysomnography.

REFERENCES

1. **Demir eksikliği anemisi Dündar S, Yasavul Ü, Çelik İ, Arıcı M(2004):** Hacettepe İç Hastalıkları kitabı. 2B. Ankara: Hacettepe Üniversitesi Yayınları. www.istanbulsaglik.gov.tr/w/tez/pdf/.../serap_yavuz_gulertan.pdf
2. **De Falco L, Sanchez M, Silvestri L, Kannengiesser C, Muckenthaler MU, Iolascon A et *al.*(2013):** Iron refractory iron deficiency anemia. Haematologica,98:845–853.
3. **Turgut B(1995):** How Important is Anemia for the Clinician? Balkan Med J.,27:31–34.
4. **Beutler E, Lichman M A, Coller B S(1995):** Iron deficiency. In: Williams E, editor. Hematology. fifth edition. Philadelphia. pp. 4905–4911.
5. **Shoham S, Youdim MBH(2000):** Iron involvement in neural damage and microgliosis in models of neurodegenerative diseases. Cell Mol Biol (Noisy-le-grand) ,46:743–760.
6. **Kryger MH, Roth T, Dement WC(2005):** Principles and Practice of Sleep Medicine. 4th ed. Philadelphia: W.B. Saunders Company.
7. **Wallander MA, Johansson S, Ruigómez A, García Rodríguez LA, Jones R(2007):** Morbidity associated with sleep disorders in primary care: a longitudinal cohort study. Prim Care Companion. J Clin Psychiatry,9:338–345.
8. **Senthilvel E, Auckley D, Dasarathy J(201):** Evaluation of sleep disorders in the primary care setting: history taking compared to questionnaires. J Clin Sleep Med., 7:41–48.

9. **Gulec Cakın T, Yoruk O, Gulec M, Selvi Y, Boysan M, Oral E, Yucel A, Mazlumoglu MR(2013):** Benefits of submucous resection on sleep quality, daytime and dream anxiety in patients with nasal septal deviation. Sleep and Biological Rhythms,11:227–236.
10. **Zigmond AS, Snaith RP(1983):** The hospital anxiety and depression scale. Acta Psychiatr Scand.,67:361–370.
11. **Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ(1989):** The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res.,28:193–213
12. **Beard J(2003):** Iron deficiency alters brain development and functioning. J Nutr., 133:468–472.
13. **Beard JL(1999):** Iron deficiency and neural development: an update. Arch Latinoam Nutr.,493:34–39.
14. **Peirano PD, Algarín CR, Garrido MI, Lozoff B(2007):** Iron deficiency anemia in infancy is associated with altered temporal organization of sleep states in childhood. Pediatr Res.,62:715–719.
15. **Felt BT, Beard JL, Schallert T, Shao J, Aldridge JW, Connor JR *et al*.(2006):** Persistent neurochemical and behavioral abnormalities in adulthood despite early iron supplementation for perinatal iron deficiency anemia in rats. Behav Brain Res., 171:261–270.
16. **Kim J, Wessling-Resnick M(2014):** Iron and mechanisms of emotional behavior. J Nutr Biochem.,25:1101–1107.
17. **Dzirasa K, Ribeiro S, Costa S, Santos LM, Lin S-C, Grosmark A *et al*.(2006):** Dopaminergic control of sleep- wake status. J Neurosci.,26:10577–10589.
18. **Holst SC, Bersagliere A, Bachmann V, Berger W, Achermann P, Landolt HP(2014):** Dopaminergic role in regulating neurophysiological markers of sleep homeostasis in humans. J Neurosci.,34:566–573.
19. **Fifel K, Vezoli J, Dzahini K, Claustrat B, Leviel V, Kennedy H *et al*.(2014):** Alteration of daily and circadian rhythms following dopamine depletion in MPTP treated non-human primates. (9).PLoS One,23(1):e86240.
20. **Sadrzadeh SM, Saffari Y(2004):** Iron and brain disorders. Am J Clin Pathol.,121:64–70.
21. **Allen RP, Auerbach S, Bahrain H, Auerbach M, Earley CJ(2013):** The prevalence and impact of restless legs syndrome on patients with iron deficiency anemia. Am J Hematol.,88:261–264.
22. **Akyol A, Kiylioglu N, Kadikoylu G, Bolaman AZ, Ozgel N(2003):** Iron deficiency anemia and restless legs syndrome: is there an electrophysiological abnormality? Clin Neurol Neurosurg.,106:23–27.
23. **Onder G, Penninx BW, Cesari M, Bandinelli S, Lauretani F, Bartali B, Gori AM, Pahor M, Ferrucci L(2005):** Anemia is associated with depression in older adults: results from the InCHIANTI study. J Gerontol A Biol Sci Med Sci.,60:1168–1172.
24. **Son SJ, Lee KS, Na DL, Seo SW, Kim CH, Kim JH *et al*.(2011):** Anemia associated with depressive symptoms in mild cognitive impairment with severe white matter hyperintensities. J Geriatr Psychiatry Neurol.,24:161–167.
25. **Vahdat S, Vahdat S, Moshtaaghi M, Shahbaazi S, Abadi A(2007):** The relationship between depression and serum ferritin level. Eur J Clin Nutr.,61:532–535.