

Is anemia in children with sleep disordered breathing actually a consequence of chronic disease?

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ABSTRACT

Objectives. We aimed to investigate iron metabolism and laboratory findings of anemia in children undergoing adenotonsillectomy for sleep disordered breathing. **Methods.** Consecutive children undergoing adenoidectomy/adenotonsillectomy for sleep disordered breathing between January 2013 and January 2015 were investigated. Routine preoperative blood tests including blood count and iron studies were analyzed. Subgroup analyses were performed addressing to the severity of sleep disordered breathing, age and duration of symptoms. Results were compared between subgroups and normal values. **Results.** The study included 171 children. The mean age was 5.44 ± 2.62 years. The mean hemoglobin level was 11.87 ± 1.125 gr/dL and 24 (14%) out of 171 patients had anemia (< 11 gr/dL). The mean ferritin levels were 23.23 ± 17.27 μ g/L and 21.27 ± 15.44 μ g/L in patients with anemia and non-anemic patients, respectively ($p = 0.572$). Ferritin levels decreased in only 8 (33%) out of 24 patients with anemia. The mean age, body mass index, hematocrit, mean corpuscular volume, unsaturated iron binding capacity and serum iron levels decreased in patients with anemia. The rate of anemia significantly increased in children less than or equal to 3 years of age ($p = 0.020$). There was no significant association between hemoglobin levels and sleep disordered breathing clinical score or duration of symptoms. **Conclusion.** The association between low iron status and sleep disordered breathing has previously published. Unfortunately, the type of anemia is still unclear. Our results supposed that the anemia of chronic disease secondary to chronic inflammatory process might play a role in pathogenesis of anemia in patients with sleep disordered breathing.

Eur Res J 2018;4(3):220-226

Keywords: Sleep disordered breathing, adenotonsillectomy, anemia, iron deficiency, anemia of chronic disease

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Received: October 30, 2017; Accepted: December 4, 2017; Published Online: January 25, 2018

Introduction

Sleep disordered breathing (SDB) is one of the most common childhood disorder with the range from simple snoring to obstructive sleep apnea (OSA) [1]. Approximately 2-3% of children are affected with SDB which may lead to behavioral, cognitive and growth abnormalities [1, 2]. The most common cause of SDB in childhood is upper airway obstruction due to adenotonsillar hypertrophy. Many hypotheses were promoted to clarify pathogenesis of adenotonsillar hypertrophy such as: allergic hypothesis, disordered lymphoproliferation and biofilm models [3, 4]. Unfortunately, there is not enough data to explain pathogenesis of adenotonsillar hypertrophy despite these hypotheses.

SDB is associated with many co-morbid diseases which is one of the current research topic. SDB might have an impact on iron metabolism. Healthy iron metabolism has a critical importance for normal cognitive and motor development in infancy [5, 6]. Furthermore, healthy iron metabolism is essential for immune system [7, 8]. Zilberman *et al.* [9] has published the first paper addressing to association of SDB and impaired iron metabolism. They showed the iron deficiency with SDB in chronic heart failure patients. The other researchers support this finding. The improvement of day-time sleeping in patients with SDB has been published after correcting iron status and anemia [10].

The literature is indicating the increased incidence of iron deficiency in patients undergoing adenotonsillectomy [3, 11, 12]. Unfortunately, these studies mostly included patients operated for recurrent infections. Everland *et al.* [11] reported anemia rate of 56.3% in patients undergoing adenotonsillectomy because of recurrent infection and upper airway obstruction. Kerstein *et al.* [13] evaluated the iron status of children diagnosed with SDB undergoing adenotonsillectomy. They reported low iron status in particular children under 6 years of age. This study concluded the low impaired iron status as an iron deficiency anemia. However, this impaired iron metabolism might be associated with chronic inflammatory process accompanied to SDB. The literature is supporting the increased pro-inflammatory cytokines (IL-6, THF- α , C reactive protein) and decreases IL-10 which is an anti-inflammatory cytokine [14-17]. Iron deficiency anemia is associated with low hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), serum iron level and

serum ferritin levels. But, anemia of chronic disease is associated with low serum iron, iron binding capacity and normal or high ferritin levels [18]. Ferritin is a positive acute phase reactant that explains the normal or high ferritin levels in anemia of chronic disease. Everland *et al.* [11] reported normal ferritin levels in 57% of children with anemia that is not surprising.

We analyzed the iron metabolism and effects of SDB in patients undergoing adenotonsillectomy for upper airway obstruction.

Methods

A retrospective clinical trial was conducted in an academic tertiary referral center between January 2013 and January 2015 after obtaining local Medical Ethics Committee approval. A total of 186 adenoidectomy, tonsillectomy and adenotonsillectomy case files were reviewed retrospectively and subjects were included in the study if they operated for SDB. Patients were excluded from the study if they met any of following: 1) nasal septal deviation, 2) history of recurrent tonsillitis, 3) history of anemia treatment in the past 3 months, 4) the other causes of anemia; recurrent epistaxis, bleeding disorders, surgical operations in the past 3 months, 5) history of chronic diseases.

We use a standard questionnaire for SDB preoperatively that include; mouth breathing during sleep, daytime mouth breathing, apnea, snoring, cough, rhinorrhea and restless sleep. Scoring is used for each of above; 0: never, 1: occasionally, 2: frequently and 3: always [19, 20]. Patients were categorized into 3 subgroups according to these questionnaire score; mild: 1-7, moderate: 8-14 and severe: 15-21. Age groups were conducted as ≤ 3 years, >3 years - ≤ 6 years and > 6 years of age. Duration of primary symptoms were categorized as ≤ 12 months, > 12 months - ≤ 24 months and > 24 months.

All patients were analyzed for Hb, Hct, MCV, ferritin, unsaturated iron binding capacity, serum iron, aPTT and INR. Results were compared to the World Health Organizations (WHO) normal range.

Statistical Analysis

Continuous data were summarized as mean \pm standard deviation and categorical data were presented as frequency and percent. Distribution of continuous variables were controlled with Shapiro-Wilks test.

Comparisons for continuous variables were done using independent samples t test for two groups and one-way ANOVA followed by Tukey HSD post hoc test for three and more groups. Categorical data were analyzed by Pearson chi-square or Fisher's exact tests. Statistical analyses were performed with SPSS v.23 statistical package and statistical significance level was considered as $\alpha = 0.05$.

Results

One hundred and eighty patients undergoing adenoidectomy, tonsillectomy, adenotonsillectomy for SDB were analyzed. The study included 171 patients with sufficient laboratory data. The mean age was 5.44 ± 2.62 years. Tonsilla platina size was assessed by using the Brodsky grading scale [21]. The adenoid tissue volume was graded from 1 to 4 with flexible endoscopy findings depending on choanal opening [22].

The mean Hb level was 11.87 ± 1.125 gr/dL and

24 (14%) out of 171 patients had anemia (Hb < 11 gr/dL). The mean ferritin level was 22.28 ± 17.16 μ g/L. Forty-seven (27%) patients had low ferritin levels (< 16 μ g/L). The mean age ($p < 0.001$), BMI ($p = 0.021$), Hct ($p < 0.001$), MCV ($p = 0.013$) and serum iron ($p = 0.038$) levels was lower in patients with anemia. Unsaturated iron binding capacity level was lower in anemia patients but the difference was not statistically significant. Table 1 summarizes the laboratory findings in patients with anemia and normal Hb levels. Ferritin levels were decreased in only 8 (33%) patients with anemia. Furthermore, the mean ferritin levels were 23.23 ± 17.27 μ g/L and 21.27 ± 15.44 μ g/L in patients with anemia and non-anemic patients respectively. The increased ferritin levels in patients with anemia documented but the difference was not statistical significant (Table 1).

Table 2 summarizes the demographics according to SDB severity. There were 7 (3%) patients in mild SDB, 91 (49%) patients in moderate SDB and 88 (48%) patients in severe SDB groups. The mean ages were 5.86 ± 1.49 years, 5.91 ± 2.77 years and $4.93 \pm$

Table 1. Comparison of anemic and non-anemic patients

	Hb < 11 g/dL (n = 24)	Hb \geq 11 g/dL (n = 147)	<i>p</i>
BMI	15.96 \pm 1.74	17.04 \pm 2.77	0.021
Mean age (year)	4.00 \pm 1.84	5.69 \pm 2.68	< 0.001
Ferritin μg/L	23.23 \pm 17.27	21.27 \pm 15.44	0.572
Hct (%)	33.12 \pm 4.46	38.45 \pm 2.17	< 0.001
MCV (fL)	74.25 \pm 10.33	79.94 \pm 3.75	0.013
UIBC (μmol/L)	236.27 \pm 90.04	259.82 \pm 64.79	0.145
SI (μmol/L)	53.59 \pm 29.13	67.39 \pm 28.20	0.038

BMI = body mass index, Hb = hemoglobin, Hct = hematocrit, MCV = mean corpuscular volume, SI = serum iron, UIBC = unsaturated iron binding capacity

Table 2. Demographics according to severity of SDB

	Mild (0-7) (n = 7)	Moderate (8-14) (n = 91)	Severe (15-21) (n = 88)	<i>p</i>	General
Mean age (year)	5.86 \pm 1.49	5.91 \pm 2.77	4.93 \pm 2.44	0.038	5.44 \pm 2.62
\leq 3 years	0 (0.0%)	19 (20.9%)	30 (34.1%)		49 (26.3%)
> 3 - \leq 6 years	6 (85.7%)	34 (37.4%)	37 (42.0%)	0.013	77 (41.4%)
> 6 years	1 (14.3%)	38 (41.8%)	21 (23.9%)		60 (32.3%)
Female	5 (71.4%)	44 (48.4%)	44 (50.0%)	0.570	93 (50.0%)
Male	2 (28.6%)	47 (51.6%)	44 (50.0%)		93 (50.0%)
Duration of symptoms	14.29 \pm 9.98	25.15 \pm 17.97	23.76 \pm 14.90	0.233	24.09 \pm 16.40

SDB = sleep disordered breathing

Table 3. Laboratory findings in comparison with severity of SDB

	Mild (0-7) (n = 7)	Moderate (8-14) (n = 84)	Severe (15-21) (n = 80)	<i>p</i>
Hb < 11 g/dL	0 (0.0%)	13 (15.7%)	11 (13.6%)	0.524
Ferritin < 16 µg/L	1 (16.7%)	23 (27.3%)	23 (28.75%)	0.713
Hct (%)	37.04 ± 1.85	37.86 ± 3.86	37.59 ± 2.46	0.736
MCV (fL)	82.16 ± 2.41	78.96 ± 6.42	79.07 ± 4.62	0.337
UIBC (µmol/L)	216.00 ± 65.61	250.75 ± 62.76	263.64 ± 75.98	0.239
SI (µmol/L)	82.60 ± 50.30	71.31 ± 27.88	57.78 ± 24.92	0.007

Hb = hemoglobin, Hct = hematocrit, MCV = mean corpuscular volume, SDB = sleep disordered breathing, SI = serum iron, UIBC = unsaturated iron binding capacity

Table 4. Laboratory findings in comparison with age groups

	≤ 3 years (n = 41)	> 3 - ≤ 6 years (n = 76)	> 6 years (n = 54)	<i>p</i>
Hb < 11 g/dL	11 (26.8%)	9 (11.8%)	4 (7.4%)	0.020
Ferritin < 16 µg/L	14 (34.1%)	27 (35.1%)	6 (10.9%)	0.005
Hct (%)	35.88 ± 4.29	37.74 ± 2.60	39.02 ± 2.24	< 0.001
MCV (fL)	76.72 ± 8.15	79.36 ± 3.46	80.68 ± 4.86	0.002
UIBC (µmol/L)	260.28 ± 70.32	258.22 ± 70.77	247.40 ± 67.02	0.630
SI (µmol/L)	58.23 ± 23.31	67.49 ± 30.75	69.77 ± 28.24	0.139

Hb = hemoglobin, Hct = hematocrit, MCV = mean corpuscular volume, SI = serum iron, UIBC = unsaturated iron binding capacity

2.44 years in the mild, moderate and severe SDB groups, respectively ($p = 0.038$). The mean age in the severe group was significantly lower than in the mild and moderate group. All patients with anemia were in moderate and severe SDB groups but Hb, Hct, MCV, ferritin, and unsaturated iron binding capacity were not significantly different in these subgroups (Table 3). Serum iron was significantly difference among SDB groups ($p = 0.007$). When we categorize the patients depending on apnea score, as low apnea score (0 or 1) and high apnea score (2 or 3), there were 96 patients with low apnea score and 75 patients with high apnea score. The anemia rates (Hb < 11 g/dL) between the low and high apnea score groups were not different, 11.5% and 17.3%, respectively ($p = 0.272$). However, lower ferritin rate (Ferritin < 16 µg/L) was 20.0% in low apnea score group and 37.0% in high apnea score group, and the difference was statistically significant ($p = 0.013$). The other questionnaires were not significantly associated with anemia when analyzed each of them.

Table 4 summarizes the subgroups according to age. Hb, Hct, MCV and ferritin levels were significantly decreased in small age group (≤ 3 years

of age). The anemia rates (Hb < 11 g/dL) between the ≤ 3years of age and > 6 years of age groups were different, while the > 3 - ≤ 6 years of age group was similar to them. The lower ferritin rates (Ferritin < 16 µg/L) in the ≤ 3 years of age and > 3 - ≤ 6 years of age groups were higher than in the > 6 years of age group. The mean of Hct rates were different in all groups while MCV level in small age group was significantly lower than in the other age groups. There was no significant association for Hb, MCV, serum iron, unsaturated iron binding capacity level and ferritin levels according to duration of symptoms (Table 5). Hct levels were significantly increased in patients with extended duration of symptoms ($p = 0.042$).

Discussion

SDB is a common health problem in children with the estimated incidence of 2-3%. SDB may lead to numerous morbidities such as neurocognitive disorders, craniofacial growth abnormalities, enuresis and cardiovascular problems if not treated [1]. The

Table 5. Laboratory findings in comparison with duration of symptoms

	< 12 months (n = 72)	12-24 months (n = 49)	> 24 months (n = 50)	<i>p</i>
Hb < 11 g/dL	10 (13.9%)	9 (18.4%)	5 (10.0%)	0.487
Ferritin < 16 µg/L	17 (23.0%)	18 (37.5%)	12 (23.5%)	0.229
Hct (%)	37.13 ± 3.47	37.62 ± 3.07	38.60 ± 2.73	0.042
MCV (fL)	79.12 ± 6.06	78.30 ± 6.22	80.02 ± 3.64	0.302
UIBC (µmol/L)	260.03 ± 62.02	249.89 ± 77.43	252.51 ± 73.01	0.739
SI (µmol/L)	61.26 ± 27.43	69.13 ± 34.40	69.83 ± 22.26	0.217

Hb = hemoglobin, Hct = hematocrit, MCV = mean corpuscular volume, SI = serum iron, UIBC = unsaturated iron binding capacity

impaired iron metabolism is the other effect of SDB. The published literature documented the increased incidence of anemia in patients underwent adenotonsillectomy [3, 12, 13] and improved anemia after operations without any iron supplementation [11]. Unfortunately, there is no enough data to explain pathogenesis of impaired iron metabolism in these patients. There are two potential causes of impaired iron metabolism in SDB; nutritional iron deficiency and anemia of chronic disease secondary to chronic inflammation. Iron deficiency is the commonest nutritional deficiency worldwide according to WHO and affects a significant part of the population [23]. WHO estimates iron deficiency in 2.5% of pediatric population and describes an abnormality if the rate more than 5% [24]. The evaluation iron deficiency starts with measurement of Hb and Hct levels that are non-specific markers. Ferritin, serum iron, total iron binding capacity or unsaturated iron binding capacity are widely used for differential diagnosis and confirmation of iron deficiency. The decreased Hb (< 11 g/dL) and ferritin (< 16 µg/L) levels are important for diagnosis of iron deficiency anemia. Anemia of chronic disease is an iron metabolism disorder that might be associated with neoplastic diseases, chronic immunologic diseases, chronic inflammation and trauma [18]. The main mechanism of anemia of chronic disease is depending on increased levels of IL-1, IL-6, TNF- α and CRP. These cytokines affect the erythropoietin synthesis from kidney that results with decreased erythropoiesis and decreased iron absorption from gastrointestinal system [25]. The increased releasing of Hepsidin in chronic inflammatory process plays an important role of decreased iron absorption from intestine. Patients have normochromic normocytic anemia in early stages that progress to hypochromic microcytic anemia. Ferritin

levels might be normal or increased in these patients, which is an acute phase reactant. Unsaturated iron binding capacity or total iron binding capacity levels were decreased with serum iron. These findings are crucial to differentiate anemia of chronic disease and iron deficiency anemia.

The increased levels of TNF- α , IL-6 and CRP have been reported in patients with OSA [14-16]. The decreased IL-10 levels in non-obese children with OSA was documented that corrected after adenotonsillectomy [17]. IL-10 is an anti-inflammatory cytokine which is negative correlated with OSA severity [26].

We documented anemia (Hb < 11 g/dL) rate in 14% of those patients underwent adenotonsillectomy for SDB. This rate is much more than WHO expectations (2.5%) which is abnormal. Hct, MCV, serum iron and unsaturated iron binding capacity were significantly decreased in patients with anemia. However, only 8 (33%) patients had low ferritin levels in patients with anemia. Additional, 16 (67%) of those patients with anemia had normal ferritin levels. The mean ferritin levels were 23.23 ± 17.27 and 21.27 ± 15.44 µg/L in patients with anemia and non-anemic patients, respectively (Table 1). These findings are supporting the role of inflammatory process in anemia. Louise *et al.* [27] analyzed the association of ferritin with OSA in adults. They did not find an association between apnea-hypopnea index and ferritin levels but they documented the negative correlation between apnea-hypopnea index and ferritin levels in only women patients. The same study is indicating the association of lower minimum oxygen saturation and increased sleep stage shifts (that are correlated with severity of OSA) with increased ferritin levels. There are many publications supporting the chronic inflammatory process and increased ferritin levels in

patients with OSA [28-31]. In our study, all patients with anemia had moderate or severe SDB clinical score (Table 3) but the difference was not significant. Everland *et al.* [11] reported the 57% normal ferritin levels of those patients underwent adenotonsillectomy because of recurrent infection and upper airway obstruction. They indicated the role of chronic inflammatory process in these increased ferritin levels. Unfortunately, they did not do subgroup analysis addressing to the indication of adenotonsillectomy. We include only patients underwent adenotonsillectomy for SDB in the current study. On the other hand, Elverland *et al.* [11] reported the corrected Hb levels and iron metabolism at postoperative 6th month. This result is an important characteristic of anemia of chronic disease. Iron metabolism immediately becomes normal levels when you correct the underlying disease [25]. Chronic inflammation is the main cause of anemia in these patients that corrected after adenotonsillectomy.

Kerstein *et al.* [13] reviewed 94 children undergoing adenotonsillectomy. They categorized the study population according to age; Group A: 0-2 years, Group B: 2-6 years, Group C: above 6 years. They reported 18 % anemia rate (17 patients) in this study population. Of those 17 patients, anemia rate was significantly increased in Group A. We report the increased anemia rate in children under 3 years of age that correlated with Kerstein *et al.* [13]. Although iron requirement decreases progressively after the sixth month of life until 3 years [25], the high rate of anemia in this age group SDB patients suggests that small patients may be more affected by inflammation. Bitar *et al.* [20] reported the increased SDB score in patients under 3 year-olds that indicates children under 3 year-olds were much affected than older children [20]. Children under 3 years of age might be influenced from SDB much more than older children according to our results. SDB clinical score, in the current study, was increased in children under 3 years of age that supports SDB severity in this cohort. Thirty out of 49 children less than 3 years of age had severe SDB clinical score (Table 2). Kerstein *et al.* [13] analyzed the results depending on the mean values of each of subgroups. They reported hypochromic (MCH < 27 pg) and microcytic (MCV < 76 fL) mean values in children under 2 year-olds. The other subgroups had low-normal mean values. Unfortunately, they did not compare the mean values of 17 patients with anemia and non-anemic patients. It is not possible to clarify type of anemia without evaluation of anemic patients.

We found significantly decreased Hct, MCV, serum iron and unsaturated iron binding capacity levels in patients with anemia in comparison with non-anemic patients. Additional, only 8 (33%) out of 24 patients had low ferritin levels (Table 1). These findings support an impaired iron metabolism secondary to inflammation.

The Limitations of the Study

This is a retrospective observational study which is the main limitation of paper. We did not have a control group. Additional, we were not able to analyze inflammatory markers owing to the retrospective setting. It would be better if we had inflammatory markers and cytokine levels. Polysomnography test is a gold standard test to evaluate SDB that supports objective results. Unfortunately, we do not use polysomnography as a routine test for evaluation of SDB; we use a questionnaire. We could have used subset analysis if we had polysomnography test results.

Conclusions

SDB is an important health problem in children that may result in many behaviors or growth problem. Unfortunately, there is no enough data about iron metabolism in pediatric SDB patients. Anemia in SDB might be result of iron deficiency or chronic inflammatory process.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

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