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Original Article

The Association between Iron Deficiency and Otitis Media with Effusion

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OBJECTIVES: The purpose of this trial is to examine the clinical role of iron metabolism on development of Otitis media with effusion.

MATERIALS and METHODS: This prospective study was conducted in a tertiary referral center. The study group made up of children who had surgery for Otitis media with effusion (OME). Control group was comprised of children who had surgery by a pediatric surgeon for inguinal hernia repair or circumcision operations with normal ear nose throat examination. Each group was evaluated depending on the serum iron metabolism parameters.

RESULTS: One-hundred-thirteen children with OME and 117 control patients were included to the study. Iron deficiency anemia was detected in 18 out of 113 patients (15.9%) in study group while there were 4 out of the 117 patients (3.4%) in control group (p:0.001).The mean hemoglobin level was 12.16 ± 1.16 in OME group and 12.93 ± 1.08 in control group (p<0.001).

CONCLUSION: The current study shows the rate of iron deficiency anemia is higher in patients with OME than controls. Iron-deficiency anemia might be considered a potential risk factor for development of otitis media with effusion, and iron parameters should be evaluated in these children.

KEYWORDS: Otitis media with effusion, iron deficiency, anemia, pediatric

INTRODUCTION

Otitis media with effusion (OME) is a disease of middle ear without signs or symptoms of acute suppurative infection [1]. It is a response of chronic inflammation in the middle ear and the effusion may become persistent in some cases [2]. Despite numerous therapy options have been tried, there is no current standard therapy for OME [3-5]. If the problem persist for at least 3 months, it is defined as chronic otitis media with effusion (COME) [6]. Unresolved OME can cause hearing loss, speech delay, and permanent middle ear damage; if these situations occur then a ventilation tube (VT) should be considered [7, 8]. Many etiologic factors play role in development of OME but the most important factors are immune system and Eustachian tube dysfunction. Upper airway and middle ear bacterial or viral infections also play role in OME [9, 10].

Iron metabolism has a critical importance for normal cognitive and motor development in children and furthermore it is essential for immune system [11, 12]. While many studies in literature show that impaired iron metabolism is associated with chronic inflammatory processes, there is no published study addressing iron metabolism and OME.

This is the first study to investigate the association of iron metabolism as a risk factor in OME. The goal of this study was to analyze the role of iron deficiency anemia (IDA) on development of OME and also clinical value of IDA.

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MATERIALS AND METHODS

This prospective study was conducted in a tertiary referral center. The local ethics committee approval (Duzce University School of Medicine; 2017/22) and the written informed consent were obtained. The study group contained patients who had OME as determined by tympanogram results and physical findings between January 2017 and October 2017. Absent light reflex, type B-C tympanogram, glue behind the ear drum, air-fluid level on ear drum were defined as signs of effusion.

Table 1. Demographics of study and control group. URI: Upper respiratory tract infection

Variable	Study group n:113	Control group n:117	p
Age	5.63±2.98 (1-16)	5.67±2.85 (1.5-15)	0.916
Mean siblings	2 (0-4)	2 (1-4)	0.221
Sex			
Male	65 (57.5%)	62 (53.0%)	0.490
Female	48 (42.5%)	55 (47.0%)	
Tobacco smoke exposure			
Yes	44 (38.9%)	43 (36.8%)	0.733
No	69 (61.1%)	74 (63.2%)	
Cow's milk exposure before 12 months	38 (33.6%)	44 (37.6%)	0.529
	75 (66.4%)	73 (62.4%)	
Breastfeeding at least 6 months only	73 (64.6%)	75 (64.1%)	0.937
	40 (35.4%)	42 (35.9%)	
Frequency of URI during study period (mean±SD)	216 (1.91±0.92)	172 (1.47±0.65)	<0.001
AOM attack during study period (mean)	15 (13.3%)	9 (7.7%)	0.166
Hemoglobin<11 g/dL	18 (15.9%)	4 (3.4%)	.001
Ferritin<16 µg/L	32 (28.3%)	11 (9.4%)	<0.001

Statistical significance level was considered as 0.05.
AOM: Acute otitis media

Table 2. Iron metabolism parameters distribution of study and control group

Variable	Study group n:113	Control group n:117	p
Hemoglobin g/dL	12.16±1.16 (9.1-14.8)	12.93±1.08 (9.1-15.5)	<0.001
Ferritin µg/L	18.20±8.91 (2.9-44.8)	36.97±27.01 (5.0-129.0)	<0.001
Serum iron µmol/L	59.74±29.27 (6-133)	68.29±29.14 (18-155)	0.027
UIBC* µmol/L	335.65±68.67 (184-530)	253.21±71.52 (99-430)	<0.001
Hct** %	33.12±4.46	38.45±2.17	<0.001
MCV*** fL	74.25±10.33	79.94±3.75	0.013

UIBC: Unsaturated iron binding capacity. Hct: Hematocrit. MCV: Mean corpuscular volume.
Statistical significance level was considered as 0.05.

Control group was comprised children were examined by pediatric surgeons who confirmed with examination that there was no evidence of infection. Children were excluded from the study if patients had any of following: history of adenotonsillectomy, craniofacial anomaly, history of VT insertion, chronic diseases such as chronic sinusitis, allergic rhinitis, asthma bronchial, immunodeficiency or any diagnosed hematologic diseases.

The study group was followed up for at least three months without any medical treatment. At the end of follow-up period, persistent cases that were defined as COME. All COME patients underwent VT placement under general anesthesia. Adenoidectomy was performed with VT if the patient was older than 4 years. If there were no obstruction findings in patients under 4 years old, only VT was performed. In study group, hemoglobin (Hb), mean corpuscular volume (MCV), hematocrit (Hct), ferritin, unsaturated iron binding capacity (UIBC), serum iron level (SI) were analyzed in addition to routine blood exams for anesthesia. Iron parameters were also studied from control group. Study and control group' results were compared to the World Health Organization' (WHO) normal range.

Statistical Analysis

Continuous data were abstracted as mean±standard deviation and categorical data were offered as frequency and percent. Categorical data were analyzed by Pearson chi-square or Fisher's exact tests depending on expected count rule. Comparisons for quantitative variables were done using Independent samples t test or Mann-Whitney U test depending on distribution of variable, for two groups. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) version 22 (IBM Corp.; Armonk, NY, USA) statistical package and statistical significance level was considered as 0.05. The combined effect of age groups and patient / control groups was examined by Two-Way ANOVA.

RESULTS

The study population consisted of 65 boys (57.5%) and 48 girls (42.5%) and the mean age was 5.63±2.98. The control group consisted of 62 boys (53%) and 55 girls (47%) and the mean age was 5.67±2.85. Eighteen out of 113 (15.9%) patients had iron deficiency anemia in the study group and 4 out of 117 (3.4%) patients had iron deficiency anemia in the control group (p:0.001). Thirty two out of 113 (28.3%) patients had low ferritin level in the study group and 11 out of 117 (9.4%) patients had low ferritin level in the control group (p<0.001). The study group (113) had total of 216 upper respiratory tract infections (URI), while the control group (117) had 172 URIs during the study period. Per-person URI frequency in the study and control groups were 1.91±0.92 and 1.47±0.65 respectively; and the difference was statistically significant (p<0.001). Acute otitis media (AOM) during the study period was higher in study group but the difference was not significant. Table 1 shows the demographics of all groups. There was no significant difference between the groups addressing to other variables.

The mean Hb level was 12.16±1.16 in study group and 12.93±1.08 in control group (p<0.001). The mean Hct rate was 33.12±4.46 in study group and 38.45±2.17 in control group (p<0.001). The mean MCV level was 74.25±10.33 in study group and 79.94±3.75 in control group (p:0.013). The mean ferritin level was 18.20 ± 8.91 in study group and

36.97±27.01 in control group (p<0.001). The mean serum iron level was 59.74±29.27 in study group and 68.29±28.14 in control group (p:0.027). The mean UIBC level was 335.65±68.67 in study group and 253.21±71.52 in control group (p<0.001). All parameters were significantly different between the groups in terms of iron metabolism. Table 2 summarizes the iron metabolism parameters distribution of study and control group.

When we analyzed the study group in terms of IDA, we revealed that the Mean Age was significantly lower in IDA group (p:0.004), Frequency of URI during study period was significantly higher in IDA group (p:0.010). AOM during the study period was higher in IDA group but the difference was not statistically significant. The mean hemoglobin levels in IDA and Non-IDA group were 10.51±0.56 and 12.47±0.96 respectively and the difference was statistically significant (p<0.001) (Table 3).

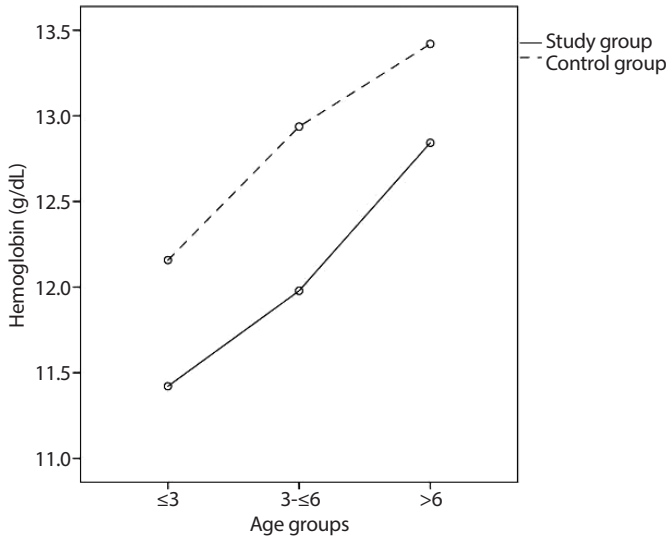

Figure 1. Group-Age interaction graphic. The mean hemoglobin levels in each age groups.

Table 3. Study group distribution in terms of IDA

Variable	Study group n:113	Control group n:117	p
Age	3.81±2.41 (1-10)	5.97±2.96 (1-16)	0.004
Median siblings	2 (1-4)	2 (0-4)	0.472
Sex			
Male	12 (66.7%)	53 (55.8%)	0.392
Female	6 (33.3%)	42 (44.2%)	
Tobacco smoke exposure	7 (38.9%)	37 (38.9%)	0.996
Cow's milk exposure before 12 months	7 (38.9%)	31 (32.6%)	0.606
Breastfeeding at least 6 months only	13 (72.2%)	60 (63.2%)	0.461
Frequency of URI during study period (mean±SD)	48 (2.67±1.28)	168 (1.77±0.76)	0.010
AOM attack during study period	4 (22.2%)	11 (11.6%)	0.255
Mean Hemoglobin g/dL	10.51±0.56	12.47±0.96	<0.001

IDA: Iron deficiency anemia. URI: Upper respiratory tract infection. AOM: Acute otitis media.
Statistical significance level was considered as 0.05.

All study and control groups patients were separated into three groups with respect to age. Group-Age interaction was not significantly different (p:0.453). The mean Hb levels were significantly lower in each age group in the study group than the control group (p<0.001). In addition, the mean Hb levels between in each age group were statistically significantly different, for both study and control groups (p<0.001). Figure 1 summarized the group-age interaction.

DISCUSSION

Iron deficiency is one of the most common nutritional deficiency worldwide according to WHO and affects a significant part of the population [13]. WHO estimates iron deficiency anemia in 2.5% of pediatric population and describes an abnormality if the rate is more than 5%. [14] This rate was found as 15.9% in our study group, which is above the WHO's estimation of 5%. The evaluation of iron deficiency starts with measurement of Hb and Hct levels that are non-specific markers. Ferritin, SI and UIBC 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 IDA. In our study, all parameters were significantly different between the groups in terms of iron metabolism (Table 2).

OME is a serious problem in children that can lead to hearing impairment, reduced academic success and impairment in social advancement. Even though there are numerous risk factors described for OME, upper respiratory tract infections are among the most important of them. Most of the pathogens that play some role on the development of OME come from the nasopharynx such as Hemophilius influenza, Streptococcus pneumoniae and Moraxella catarrhalis. Further viral agents, like adenovirus, rhinovirus and influenza play substantial role. Also, Chen et al. [15] showed that, biofilms may play a major role in the pathogenesis of OME.

There are some evidences that IDA may increase susceptibility to infections in pediatric population. This association could be related with decreased neutrophil and macrophage function, decreased production of pro-inflammatory cytokines, and increasing the risk of extracellular infections [11, 16]. Iron plays an important role in DNA replication pathways of immunoprogenitor cells [17]. Studies have shown that iron deficiency is more common in children who have frequent upper respiratory tract infections [18, 19]. In the literature, a correlation between low Hb values and increased the infection risk was found when the relationship between anemia and infection was investigated [18, 19]. Hussain et al. [20] reported that; Hb level <11 g/dL was considered as low. Mean Hb level was 8.8 g/dL in the study group and 11.6 g/dL in the control group. Anemia rate was found 64.5% in the study group and 28.2% in the control group and the anemic group was found to be 4.6 times more susceptible to respiratory tract infection. Mourad et al. [21] reported that, Anemia was found in 32% of inpatients and 16% of healthy controls. Mean Hb level was 9.99 ± 0.62 g/dL and 11.99 ± 0.92 g/dL in control group and low Hb level was a risk factor for respiratory tract infection. Levy et al. [22] reported that, IDA was an independent risk factor for the occurrence of respirato-

ry disease (tonsillitis, cold, pneumonia, bronchitis, asthma) and also AOM episodes. In this regard, although there is no clear information in the literature about which Hb level does indeed cause infections; Golz et al. [23] revealed that, 83.8% of children with a Hb value of less than 9.5 g/dL had a very frequent AOM episode and in conclusion they recommended iron supplementation whenever Hb levels are found to be lower than 10 g/dL. In our study. When we analyzed the study group in terms of IDA, the mean Hb levels in IDA and Non-IDA group were 10.51±0.56 and 12.47±0.96 respectively and the difference was statistically significant ($p<0.001$) and the low Hb level was correlated with the high frequency of URI and AOM (Table 3). Many investigators identified some risk factors for OME, but iron deficiency was never considered to be one of them [2, 3, 5, 9]. In our study the rate of anemia was 15.9% in study group and 3.4% in control group and the difference was statistically significant ($p<0.001$).

The most important limitation of the current study is lack of data about immunogenic factors such as complements and immunoglobulins. We did not analyze the immunoglobulin and complement levels in the study and control groups. However, we excluded patients from the study if there were any diagnosed immunologic or hematologic diseases to avoid these confounding factors.

This study demonstrates the association of iron deficiency with OME development and its role of clinical progress. IDA should be evaluated children with COME which might be a prognostic factor. Despite these findings there is no adequate data to determine whether IDA is cause or effect. The association of IDA with OME requires further studies to explain pathophysiology of this association.

CONCLUSION

Iron-deficiency anemia might be considered a potential risk factor for development of otitis media with effusion, and iron parameters should be evaluated in these children.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethic committee of Duzce University (2017/22).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – F.A.A.; Design - F.A.A., Y.D.; Supervision - İ.Ü.; Resource - F.A.A., D.C.; Materials - F.A.A., D.C.; Data Collection and/or Processing - F.A.A., D.C.; Analysis and/or Interpretation - H.B.A., M.A.S.; Literature Search - F.A.A.; Writing - F.A.A., H.B.A.; Critical Reviews - Y.D.

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