

The Relative Frequency of Iron Deficiency Anemia and its Correlation with Pulmonary Function in Children with Cystic Fibrosis

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ABSTRACT

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Background: The prevalence of iron deficiency is increasing in the cystic fibrosis (CF) patients. The aim of this study was to determine the prevalence of iron deficiency anemia and its correlation with pulmonary function in cystic fibrosis patients.

Materials and Methods: This descriptive-analytic study was conducted on the patients with cystic fibrosis who were referred to the Mofid Children Hospital, Tehran, Iran during 2015-2016. Complete blood counting and iron indices were evaluated; furthermore, Pulmonary function test was performed in ≥ 5 years old patients to determine the forced expiratory volume in first second (FEV1), forced vital capacity (FVC), FEV1/FVC and forced expiratory flow (FEF25-75). The data were analyzed by SPSS software. Pearson correlation coefficient, t-test, Fisher's exact test and χ^2 were used for analyzing data.

Results: Among 62 CF patients who presented to the hospital in the study period, 30 patients were able to perform spirometry and included in the study. Spirometry findings were normal in 12 patients (40%) which 72% of them were female. There was a statistically significant correlation between the spirometric findings and the gender of the patients ($P < 0.05$); although, the correlation between the gender and iron indices was not significant ($P > 0.05$). Moreover, there was no statistically significant correlation between spirometric findings and iron indices ($P > 0.05$).

Conclusion: There was no significant correlation between the iron deficiency and the pulmonary function in cystic fibrosis patients.

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disorder which is caused by the mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene [1]. The defect of this gene caused some changes in the viscosity, volume, and concentration of salt in the secreted fluid of the body [2]. CF has some complications in all organs; although, 85% of the mortality is due to pulmonary disorders including chronic pulmonary disease and progressive chronic hypoxia [3, 4]. Although the dis-

ease is untreatable, but supportive cares improved life expectancy in CF patients [5].

Iron deficiency anemia is common in CF patients which affects 10-33% of patients [6-9]. Furthermore, CF patients with anemia have lower levels of pulmonary function in compare to non-anemic CF patients [10]. The pathophysiology of anemia in these patients is multifactorial; although, some mechanisms including chronic inflammation, blood loss from gastrointestinal (GI) tract and, malnutrition may be responsible for ane-



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mia in CF patients [11-13]. In addition, malabsorption, chronic inflammation, and hypoxia in CF patients can be related with the iron metabolism and the type of anemia [14]. However, in the anemia which caused by CF chronic inflammation is also important as iron deficiency and plays a critical role in the lack of response to iron therapy [15].

The present study was aimed to determine the prevalence of iron deficiency anemia and its effect on the pulmonary function in children with cystic.

MATERIALS and METHODS

Study Design

This descriptive-analytical study was aimed to determine the prevalence of the iron deficiency anemia and its correlation with the pulmonary function in cystic fibrosis patients who referred to pulmonary and lung disease clinic of Mofid hospital, Tehran, Iran during 2015-2016.

Convenience sampling was used for patient selection and the sample size was considered to be approximately 60 CF patients, based on the power of 80% and the significant level of 0.05 and the recent studies (10, 16). The inclusion criteria were the definitive diagnosis of cystic fibrosis according to diagnostic criteria and 6 hours of fasting for measuring serum ferritin levels. In addition, patients who had the history of iron supplements consumption were excluded from the study.

Patient Assessment

The diagnosis of CF was confirmed by the result of a two-time measurement of sweating chlorine content and if the test result was above 60 meq/L, it was considered positive [17]. After that, complete blood count (CBC) and iron indices including serum iron, serum ferritin, transferrin saturation and total iron binding capacity were measured on a blood sample which was taken from the patients. The CBC was analyzed by Sysmex® hematology analyzer (xp-100, Singapore) and Iron indices were measured by Tokyo Boeki Biolis® 24i Premium device.

Ferritin deficiency were considered below 30 µg/L in serum analysis [18]. In addition, CBC and iron counting values were adapted according to age and gender of the patient (19). Furthermore, the transferrin saturation percentage was calculated according to Nelson's book and values less than 16% were considered as deficiency [18].

Pulmonary evaluation was done if the patient had no symptoms of upper respiratory tract infection, acute sinusitis, and exacerbation of coughing in the last 2 weeks by the spirometry unit with Ganshorn® Spirometers (LF8.5K.SR1 edition, Germany). The exhale maneuvers test including FEV1, FVC, FEV1 / FVC and FEF25-75 ratio were done and values less than 80% were considered as a poor pulmonary function [20].

Data Analysis

All spirometry findings and lab tests were recorded in a questionnaire and entered to SPSS software. The data were analyzed by SPSS software version 15. In this study, we used mean and standard deviation for analyzing quantitative variables; moreover, the frequency and the proportion were used for qualitative variables. The Pearson correlation coefficient,

t-test, exact Fisher's test and χ^2 were used to determine the association of iron indices with the severity of pulmonary involvement in cystic fibrosis patients. The level of $P < 0.05$ was considered significant.

Ethical Consideration

All patients were enrolled in this study after receiving a written consent. This study has been done after obtaining the permission of ethical committee of the Shahid Beheshti University of Medical Sciences with the registration no: IR.SBMU.MSP.REC.1395.27

RESULTS

Demographic factors

Sixty-two CF patients who referred to the pulmonary and lung disease clinic of Mofid hospital during were entered in the study at the initial phase which 30 patients were eligible for spirometry evaluation. In terms of gender, 24 patients (39%) were female and 38 patients (61%) were male. The mean age of patients was 6 ± 5 years, with a range of 4 months to 20 years.

Lab Data

Laboratory values of iron indices, CBC and pulmonary function tests are presented in Table 1. In total, 4 patients (6.5%) had iron deficiency, 24 patients (38.7%) had ferritin deficiency and 10 patients (16.1%) had transferrin saturation deficiency; in addition, the serum iron level had a direct correlation with transferrin saturation ($P < 0.001$ and $r = 0.899$); Furthermore, a negative correlation was observed between the ferritin level and total iron binding capacity ($P < 0.001$ and $r = -0.490$). In terms of CBC evaluation, 3 patients (7.8%) had RBC deficiency, 7 patients (11.3%) and 13 patients (21.0%) had MCHC and MCH deficiency respectively. In addition, 15 patients (24.2%) had low MCV level, 12 patients (19.4%) had low HCT level and 16 patients (25.8%) had low hemoglobin (Table 2).

There were no statistically significant differences between the gender of patients and the serum iron level ($P = 0.637$), serum ferritin ($P = 0.913$), transferrin saturation ($P = 0.1$) and total iron binding capacity ($P = 0.541$). However, the relation between mean age of patients with serum iron deficiency ($P < 0.001$) and serum ferritin ($P = 0.013$) was statistically significant.

Spirometry findings

A total of 30 patients were able to perform spirometry and the spirometric findings of patients summarized in Table 1. Spirometric findings were normal in 11 patients (37%). In addition, four patients had obstructive pattern (13%); 2 patients had restrictive pattern (7%), and 13 patients (43%) had mix pattern in the spirometry evaluation. Furthermore, there was a statistically significant difference between the spirometry findings and the gender of the patients under study ($P = 0.024$).

The level of iron indices by the distribution of spirometry findings is presented in Table 3. There was no statistically significant difference between the mean spirometry findings and the iron indices level in the patients under study.

Table 1. The results of CBC

| Variables | Mean±SD |
|----------------------------|--|
| Serum Iron (µg/dl) | 71.1 ± 29.2 |
| Ferritin (ng/mL) | 278.6 ± 59.1 |
| Transferrin Saturation (%) | 68.9 ± 75.0 |
| TIBC (µg/dl) | 25.3 ± 10.4 |
| White Blood Cell (n/µL) | 8565.8 ± 4891.0 |
| Red Blood Cell (n/µL) | 4.8×10 ⁶ ± 0.55×10 ⁶ |
| MCHC (gr/dl) | 32.3 ± 1.8 |
| MCH (pg/cell) | 25.3 ± 2.8 |
| MCV (µm ³) | 78.1 ± 7.1 |
| Hematocrit (%) | 37.5 ± 4.7 |
| Hemoglobin (gr/dl) | 12.2 ± 1.7 |
| Platelets (×103/µL) | 323.1 ± 94.6 |
| RDW(%) | 13.3 ± 1.9 |

MCHC: mean corpuscular hemoglobin concentration; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; RDW: Red blood cell distribution width

Table 2. CBC deficiency related to anemia in CF patients

| Variables | Number of Deficient patient |
|------------------------|-----------------------------|
| Serum Iron | 4 (6.5%) |
| Ferritin | 24 (38.7%) |
| Transferrin Saturation | 10 (16.1%) |
| Red blood cell | 3 (7.8%) |
| MCHC | 7 (11.3%) |
| MCH | 13 (21%) |
| MCV | 15 (24.2%) |
| Hemoglobin | 16 (25.8%) |
| Hematocrit | 12 (19.4%) |

MCHC: mean corpuscular hemoglobin concentration; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin

Table 3. The results of spirometry assessment

| Variables | Mean±SD |
|--------------|-------------|
| FEV1 (%) | 76.9 ± 33.6 |
| FVC (%) | 78.7 ± 29.9 |
| FEV1/FVC (%) | 83.5 ± 13.0 |
| FEF25-75 (%) | 57.4 ± 42.5 |

FVC: Forced Vital Capacity; FEV: Forced Expiratory Volume; FEF: Forced Expiratory Flow

Correlation of iron indices and pulmonary function

The distribution of spirometry findings in patients with CF in terms of iron indices level are presented in Table 4.

Seventeen percent of patients with iron deficiency had poor

pulmonary function. There was no statistically significant difference between the spirometry findings and the serum iron level in the patients ($P = 0.632$); in addition, 44% percent of patients with serum ferritin deficiency had poor pulmonary function. There was no statistically significant difference between the spirometry findings and the serum ferritin levels in the patients ($P = 0.284$); furthermore, 28% of patients with low transferrin saturation had poor lung function. There was no statistically significant difference between spirometry findings and transferrin saturation values in patients under study ($P=0.358$).

The findings showed that in 30 patients with spirometric findings, 20 patients had evidence of iron deficiency which 12 of them (60%) had poor lung function. There was no statistically significant difference between poor lung function and evidence of iron deficiency ($P = 0.1$).

DISCUSSION

In this study, 30 patients among 62 CF patients were able to perform spirometry. Poor lung function was more prevalent in female patients. Also, 17% of patients with deficit of iron, 44% of patients with ferritin deficiency, 28% of patients with low transferrin saturation, 17% of patients with low iron binding capacity had poor lung function. There was no statistically significant relationship between spirometric findings and serum level of iron indices in patients.

In O'Connor TM et al study, hemoglobin and oxygen saturation indices were studied in 17 healthy individuals and 15 adults with cystic fibrosis. There was no statistically significant difference between hemoglobin and hematocrit values in patients with cystic fibrosis and control group which is in line with our study results [16]. In addition, Serum iron levels, transferrin and total iron binding capacity were significantly lower in patients with cystic fibrosis in the study; however, there was no significant difference in serum ferritin, iron saturation, serum erythropoietin, and red blood cell volume which was same with the result of our study [16].

Hansen et al. Reviewed 60 patients with 19-20 years of age with cystic fibrosis. The mean of hemoglobin was 140±14.1 g/L, and normal MCV was reported in 91.7% of cases. The serum iron level in 60% of subjects was less than 12 µmol/L, and TIBC values were normal. Serum concentrations of ferritin in 21.7% of subjects were less than 23 µg/L. Transfusion saturation was less than 16% indicating iron deficiency, which was reported in 41.7% of patients [21]. The results of this study are different from our study, perhaps the reason for this difference in the statistic between the two studies is the average age of patients. This point indicates that more studies are needed in different age groups for this study.

In the study of Uijterschout L et al. on 53 children under the age of 16 with CF, iron deficiency was defined as ferritin less than 12 µg/L in children less than 5 years of age and less than 15 µg/L in children aged 5 years and above. The results showed that thirty-two children (60.4%) had iron deficiency at least 1 year and ten children (18.9%) had anemia at least 1 year. Ferritin had a positive correlation with the age of the patients like the results of the current study [22].

In the study of von Drygalski et al [10], there was no statistical-

Table 4. Distribution of spirometric findings in patients with CF in terms of iron indices level

| Spirometric Findings | Iron Indices | | P value |
|------------------------|--------------|-----------|---------|
| | Normal | Deficient | |
| Serum Iron | | | |
| FEV1 (%) | 78.3±34.4 | 67.8±30.4 | 0.572 |
| FVC(%) | 79.4±31.5 | 74.2±19.2 | 0.751 |
| FEV1/FVC(%) | 83.8±13.0 | 81.1±14.6 | 0.696 |
| FEF25-75(%) | 55.5±40.9 | 57.7±43.5 | 0.927 |
| Ferritin | | | |
| FEV1 (%) | 74.4±29.6 | 79.0±37.5 | 0.713 |
| FVC(%) | 77.0±26.5 | 80.2±33.5 | 0.733 |
| FEV1/FVC(%) | 80.3±15.2 | 86.2±10.3 | 0.219 |
| FEF25-75(%) | 54.5±44.9 | 59.9±41.6 | 0.737 |
| Transferrin Saturation | | | |
| FEV1 (%) | 79.9±34.7 | 64.9±27.7 | 0.337 |
| FVC(%) | 80.2±31.2 | 72.8±25.7 | 0.597 |
| FEV1/FVC(%) | 83.6±13.5 | 83.1±11.8 | 0.937 |
| FEF25-75(%) | 60.2±44.3 | 46.1±35.8 | 0.479 |

FVC: Forced Vital Capacity; FEV: Forced Expiratory Volume; FEF: Forced Expiratory Flow

ly significant difference between the incidence or severity of anemia with the gender of the patients, but the prevalence of anemia was higher with age; from 12% of patients in the age of <16 years to 58.3% in patients >40 years. In addition, anemic patients had a weaker lung function that contradicts with the result of the current study. The mean percentage of FEV1 and FVC in anemic patients was lower than those without anemia. This result was similar to the result of the study by Pond et al. [23]. Also, In the Reid et al. Study, FEV1 had a direct correlation with serum iron levels and transfusion saturation (5). In the current study, the amounts of spirometric findings like FEV1 and FVC were lower in anemic patients but the differences were not significant.

For future studies, it would be better to conduct prospective studies with large samples. One of the challenges in the present study was the low number of cystic fibrosis patients, which reduced spirometric cases in this study.

CONCLUSION

Ferritin deficiency is more common in patients with CF than other iron indices. Serum iron levels and ferritin decreased with increasing age of patients with CF. There are no significant correlations between the iron deficiency and pulmonary function in CF patients; however, further studies with larger samples are needed to confirm these results.

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CONFLICT of INTREST

There was not any conflict of interest among authors.

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