Original Article

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TANAFFOS

Prevalence of Anemia and its Relation with Shwachman Score in Children with Cystic Fibrosis

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Background: Cystic fibrosis is a chronic and progressive genetic disease with a worldwide prevalence. As the disease progresses, symptoms develop, and make its management more challenging. Accumulating evidence suggests that early diagnosis of CF can significantly contribute to preventing reported nutritional problems including anemia, vitamin deficiencies, and hypoalbuminemia. This cross-sectional study was conducted to assess disease severity in cystic fibrosis patients using the Shwachman-Kulczycki score, as well as to determine its relation with anemia and vitamin D deficiency.

Materials and Methods: Clinical and CF-related laboratory data were collected from the medical records of 57 CF patients with a definitive diagnosis. At the time of diagnosis, physicians performed simultaneous, blood sampling and scoring of patients using the Shwachman scoring system.

Results: The mean age of patients was 16.12±6.48 years. Total scores of 86-100, 71-85, 56-70, 41-55, and <40, were reported in 5.4%, 7.1%, 14.3%, 14.3%, and 58.9% of CF patients, respectively. A significant correlation was found between disease severity and patients' age (P=0.02). The analysis also showed that the disease severity was significantly higher in anemic patients when compared to non-anemics (p =0.006). Based on the results, 33 patients with normochromic, 11 patients with microcytic, and 6 patients with macrocytic anemia were diagnosed in this study. We did not find a significant difference between disease severity and vitamin D levels (P=0.150).

Conclusion: The scoring system used in the current study could reflect properly the clinical status of CF patients. However, simultaneous use of various methods using a larger sample size for comparison of results is suggested to improve the accuracy of findings.

Keywords: Cystic fibrosis; Shwachman score; Vitamin D deficiency; Anemia

INTRODUCTION

Cystic fibrosis (CF) is the most life-threatening autosomal recessive multisystem disease with various symptoms (1). Mutations in a gene on chromosome seven encoding the CF transmembrane conductance regulator (CFTR), a membrane protein and chloride channel, is the underlying cause of the disease (2). CFTR mutations reduce the ion channel function and lead to abnormalities in epithelial fluid transport contributing to pancreatic insufficiency, fibrosis of various organs, and progressive airway obstruction due to the alteration in the consistency of mucosal secretions. In addition to the signs and symptoms mentioned above, anemia is also related

to unfavorable outcomes of the disease but independently (3-8).

It has been reported that anemia is associated with serious conditions such as lung function abnormalities and vitamin deficiency in CF (9). Iron deficiency or inflammation have been proposed as mechanisms of CF-related anemia in some studies, although not enough data are available to make such a conclusion (10). Indeed, the experience of iron deficiency is a common phenomenon in patients with CF, but its exact mechanism(s) is still unknown (11). Mounting evidence indicates that anemia is more prevalent in patients who have deficiencies in fat-soluble vitamins (9).

In CF, most patients are at risk of fat-soluble vitamin deficiencies due to maldigestion and malabsorption of fat (12). Vitamin D deficiency is one of the most common vitamin deficiencies in patients with CF (13-16). Depending on the age group and the type of deficiency, its prevalence varies between 40 to 90%. Although the exact mechanism(s) of CF has not yet been fully understood, accumulating data suggest that vitamin D deficiency may affect lung function in the disease (17-19). Recent studies have shown that pulmonary exacerbation in children with CF is associated with vitamin D deficiency (20). In fact, in CF patients, where pulmonary exacerbations and lung function are the main determinants of morbidity and mortality, vitamin D is considered a key factor (21). Although there is no cure currently available for CF, there is a range of treatments to help manage symptoms, reduce or prevent complications, and make it easier to deal with. However, in addition to the general principles of these treatments, a clinical evaluation system is needed to assess the severity of the disease and to provide a nuanced understanding of a patient's clinical status. Shwachman–Kulczycki's (S-K) score, as an easily applied scoring system with significant use in CF, is one of the most effective evaluation tools for this purpose.

However, given the importance of anemia and vitamin D deficiency in the clinical severity of CF, the objective of the current study was to determine the prevalence of anemia and vitamin D deficiency in Iranian patients defining a relationship between them and poor lung function for the first time.

MATERIALS AND METHODS

Study population

The current cross-sectional study was carried out among 57 patients with CF (28 females and 29 males; with an age range of 1 to 27 years) who had been hospitalized in the pediatric pulmonary ward of Masih Daneshvari Hospital between December 2017 to May 2019. In this study, all details about the patient's history, clinical findings, diagnostic test results, and medication were extracted from medical records. This study was approved by the institutional ethics board of Masih Daneshvari Hospital ethical committee and all participants gave their written informed consent (IR.SBMU.NRITLD.REC. 1399.145).

At the time of diagnosis, physicians performed simultaneous blood sampling and scoring of patients using the Shwachman scoring system for general activity, physical examination, nutrition status, and radiological findings. Only patients with a definitive diagnosis of cystic fibrosis based on approved guidelines (22) were included in the study. Patients for whom a complete assessment through the simultaneous performance of tests and the Shwachman-Kulczycki technique could not be carried out were excluded from this study.

The score for each parameter ranges from 5 (normal) to 25 (severely impaired) (Table 1). The lower score is associated with the more severe disease. According to the total score, patients were divided into five categories: excellent (86-100), good (71-85), mild (56-70), moderate (41-55) and severe (<40) (Table 1). Patients' blood samples were analyzed and according to the presence of anemia, subjects were divided into two groups, namely patients with and without anemia. Anemic patients were subdivided into microcytic, macrocytic, and normocytic. Furthermore, vitamin D deficiency, insufficiency, sufficiency, and toxicity were also defined as 25(OH)D levels < 10 ng/mL, 10–29 ng/ mL, 30–100 ng/ mL, and over 100 ng/mL, respectively. Finally, the relationship between the disease severity (Shwachman–Kulczycki score) and anemia as well as Vitamin D deficiency was evaluated.

Table 1. Shwachman-Kulczycki Score

Total score	Points	General activity	Physical examination	Nutrition	Radiological findings
Excellent (86-100)	25	Fully active, plays, plays soccer, goes to school regularly	Normal. No cough. Normal HF and RR. Free lungs, good posture	Keep the weight and stature above percentile 25. Well-formed feces. Good musculature and muscle tone	Free pulmonary fields
Good (71-85)	20	Irritability and tiredness at the end of the day. Good school attendance	Normal HR and RR at rest. Rare cough. Free lungs. Little emphysema.	Weight and height between percentiles 15 and 20. Feces mildly altered.	Mild increase in the bronchial vessels array. Mild emphysema
Intermediate (56-70)	15	Need to rest during the day. tires easily after exercises. less school attendance	Occasional cough, sometimes during the morning. Mildly increased RR. Medium emphysema. Mild finger clubbing	Weight and height above the 3rd percentile. Abnormal feces, not well-formed. Abdominal distention. Muscular hypotrophy	Medium intensity emphysema. Increased bronchial vessel array.
Moderate (41-55)	10	Dyspnea after short walks. Mostly rest	Frequent and productive cough. Chest retraction. Moderate emphysema. There may be chest deformity. Finger clubbing 2/3+	Weight and height below the 3rd percentile. Abnormal feces. Marked reduction of muscle mass.	Moderate emphysema. Atelectasis areas. Areas of mild infection. Bronchiectasis.
Severe <40	5	Orthopnea. Confined to bed	Intense cough. Period of tachypnea and tachycardia and marked pulmonary alterations. There may be signs of right-side heart failure. Finger clubbing 3/4+	Intense malnutrition. Abdominal distension. Rectal prolapse.	Marked alterations. Obstructive phenomena. Infection, atelectasis. bronchiectasis

Data Analysis

All statistical analyses were conducted using SPSS Statistical Software (version 23.0). Means and SD (standard deviation) were calculated in continuous data and the frequency proportion for categorical data. Kolmogorov–Smirnov test was used to check the normality of data. Because data was not normally distributed, the Kruskal-Wallis and Mann-Whitney tests were performed to compare the groups. Spearman's correlation was also used to evaluate the correlation between disease severity and vitamin D levels. Fisher's exact test was used to compare categorical variables. The P-value was considered statistically significant at a level of <0.05.

RESULTS

The study sample comprised 57 patients with CF (28 females and 29 males) with a mean age of 16.12±6.48 years (age range of 1-27 years). Based on age, patients were divided into 4 groups: 0.3% were in group 1, 0.3% in group 2, 11% in group 3, and the rest (81%) in group 4.

The Shwachman-Kulczycki score was calculated by pediatric pulmonologists for all CF patients (Figure 1). Total scores of 86-100, 71-85, 56-70, 41-55, and <40, were reported in 5.4%, 7.1%, 14.3%, 14.3%, and 58.9% of CF patients, respectively. Our finding from this study demonstrated a significant correlation between disease severity (according to the Shwachman-Kulczycki score) and patients' age (P = 0.02). Furthermore, a significant difference was found between disease severity and physical examination (P<0.0001), general activity (P<0.0001), nutritional status (P<0.0001), and radiological findings (P=014) in CF patients.

Anemia status in CF patients

Based on the results, 33 (59%) patients with normochromic, 11(35%) patients with microcytic, and 6 (11%) patients with macrocytic anemia were diagnosed in

this study. The overall prevalence of anemia among hospitalized patients was 25% (5 females and 10 males). There was no gender difference in terms of incidence or severity of anemia at any age. Considering the patients by age group, 7% and 93% of anemic patients were in groups 3 and 4, respectively. However, there were no reported cases of anemia in groups 1 and 2. Of the total anemic patients, 66.6% were found to have microcytic and 33.3% normocytic anemia. In anemic patients aged >10 years, 71% and 29 % had microcytic and normocytic anemia, respectively; while patients in the age range of 5-10 years only had normocytic anemia.

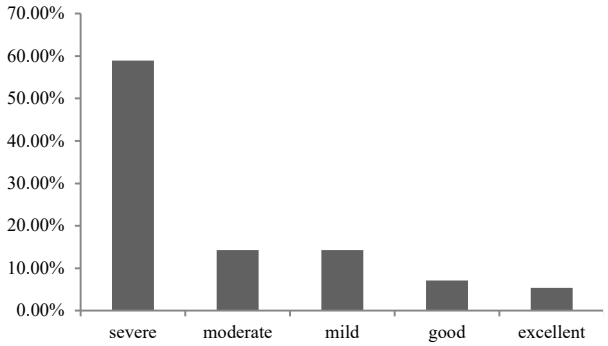

Figure 1. Grouping patients based on Shwachman-Kulczycki score

Furthermore, as our results indicated, no significant association was found between the incidence of microcytosis and the severity of disease in CF patients (p=0.47).

We particularly focused on the differences between anemic and non-anemic patients in disease severity. Analysis showed that the disease severity was significantly higher in anemic patients when compared to non-anemics (p =0.006) (Figure 2).

Vitamin D status in CF patients

According to the classification of vitamin D levels, as mentioned before, in this study hypovitaminosis D (25(OH)D <30ng/mL) was reported in 36% of patients, being 6% and 30% vitamin D deficient and insufficient, respectively. Twenty-six patients (56%) showed 25(OH)D values within the normal reference range and in the remaining patients, the level was more than 100 ng/mL. Based on the results, all patients in the deficient group were older than 10 years (Figure 3). On the other hand, as person ages, the risk for vitamin D deficiency increases. However, we did not find a significant difference between disease severity and vitamin D level (P=0.150). Furthermore, no significant difference was found between vitamin D levels in anemic and non-anemic patients (P=0.39).

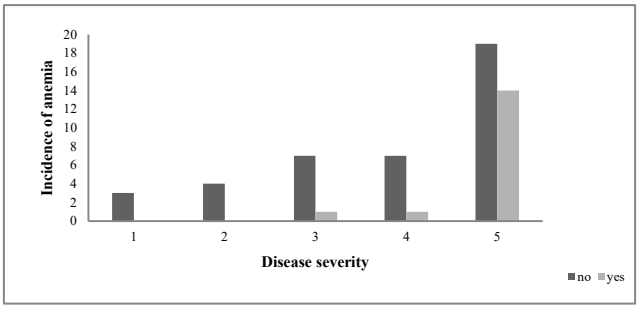

Figure 2. According to the p-value = 0.006 obtained from the Mann-Whitney test, it is observed that the mean rank of disease severity in people with anemia is significantly higher than in people without anemia

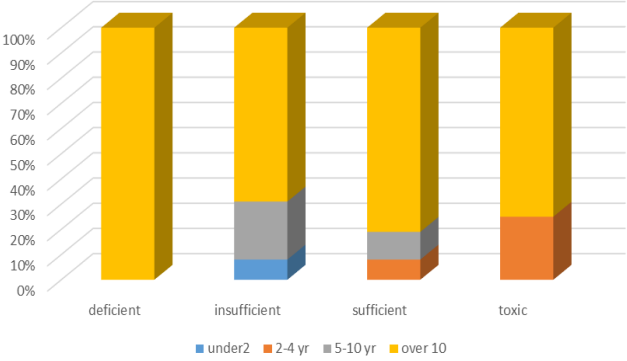

Figure 3. Evaluation of serum vitamin D levels according to age

DISCUSSION

Cystic Fibrosis is the most common life-limiting autosomal recessive condition that affects mainly white people in whom progressive pulmonary disease is common (23). Early diagnosis and preventive treatments play an important role in improving the life expectancy of CF patients. Most patients with CF are diagnosed based on clinical laboratory results and specific signs and symptoms of the disease. However, due to disease's complexity,

assessing its progression and severity is desperately needed. Providing a framework for clinical evaluation will reduce the mortality and morbidity rates in patients. Hence, the Shwachman score was used to determine the clinical severity of CF based on clinical and radiological evaluation (24, 25). Accordingly, the present study evaluated the disease severity and its relationship with the anemia and vitamin D levels in Iranian children with CF. To our knowledge, it is being reported for the first time using this scoring system as a part of routine examination.

In the current study, grouping patients based on the S-K score indicated that the majority of them were observed in severe groups, given the rather small number of children as excellent. It can be stated that most of our patients in this study were in serious clinical conditions at the time of diagnosis. According to a study by Khalilzadeh et al. that assessed the clinical status of CF patients using the Shwachman score system, from 23 CF patients, none of them was categorized in the excellent group. One possible reason for this result may be that most of the patients had related health problems at the time of diagnosis. It is also thought that early childhood can affect the clinical outcomes in CF patients (26).

Anemia with a high prevalence among CF patients is one of the most common deficiencies that is linked to morbidity and mortality in multiple chronic diseases, although little is known about it (9). Because the great majority of CF patients die from respiratory disease, anemia has not been fully evaluated in these patients. However, due to the importance of anemia and its relationship with disease severity in CF patients, its complete assessment is essential for improvements in care quality. Accumulating data indicate that anemia can occur months before respiratory symptoms of CF appear (27). There is also evidence that iron and vitamin deficiency, as well as poor lung function, may be associated with this condition (28). Our results showed that about 25% of CF patients had anemia, the majority of whom were 10 years old or older. We found that anemia prevalence increased with increasing age from 7% in patients aged 5 to 10 years to 97% in patients aged > 10 years. Furthermore, anemic patients showed significantly higher disease severity compared to the non-anemic group. Similar to our findings, von Drygalski and Biller evaluating 218 CF patients' data, reported a high prevalence of anemia with advancing age (29). They also found a significant relationship between anemia and poor lung function in their research, so that the anemic patients showed significantly poorer lung function compared to non-anemics. More than half of our anemic patients had microcytic anemia. However, we did not find a significant association between disease severity and incidence of microcytosis in these patients.

Recent studies suggest that all CF patients require regular evaluation of nutritional status, as an important part of the health status assessment (30). Many epidemiological studies demonstrated that vitamin D deficiency is associated with a higher rate of pulmonary exacerbations and a higher frequency of pulmonary bacterial colonization compared to those with sufficient levels of vitamin D (31, 32). Therefore, considering the role of vitamin D levels in CF, it is regarded among the key factors that should be measured. Despite its importance, we did not find a statistically significant correlation between disease severity as measured by Shwachman score and vitamin D level in our patients. In agreement with our results, some previous studies have shown that there is no obvious relationship between vitamin D levels and lung function as well as exacerbations in CF patients (15, 33-35). In one study by Ongaratto et al., hypovitaminosis D was observed in 54% of CF patients. Although the percentage they reported was higher than that of our study, they found no association between vitamin D levels and pulmonary function and nutritional status (36). Based on our results, vitamin D deficiency was only found in 6% of patients all of them were older than 10 years. In addition, a small percentage of the patients with insufficient levels were under 2 years. Some studies in adults with CF indicated an association between vitamin D deficiency and reduced lung function (37, 38), whereas such an association, was not found in children (15, 37). It

has been reported that with advancing age, the risk for vitamin D deficiency increases, although the exact reason why this happens isn't known (14, 15). However, in our study, no significant difference was observed in vitamin D levels concerning age.

The limitation of our study was observations from a single institution with a small sample size. Larger sample size for comparison of results can improve the accuracy of findings. On the other hand, adjustment for various variables like sex, age, anthropometry, and other similar confounders could not be determined with the small sample size.

CONCLUSION

Our findings in this study highlighted the usefulness and importance of the SK score, which makes it easy to measure disease severity in CF patients relative to other methods. Considering the contradictory results in the relationship between vitamin D deficiency and disease severity, it should be further studied in CF patients. This study was performed on a small number of CF children. Therefore, large-scale studies are needed to clarify the association between disease severity and clinical status in these patients. Finally, we hope that these preliminary results will stimulate further investigation in this area.

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