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Anemia in Cystic Fibrosis: Incidence, Mechanisms, and Association With Pulmonary Function and Vitamin Deficiency

Annette von Drygalski, MD, PharmD1; and Julie Biller, MD1,2

Background: Anemia is associated with increased morbidity and mortality in many chronic diseases. Little is known about anemia in cystic fibrosis (CF). Because the majority of patients with CF die of lung disease, the objective of this study was to identify the frequency, severity, and mechanisms of anemia in CF and to determine if there was an association between anemia and poor lung function in these patients. Vitamin deficiency was used to assess the association of malabsorption and anemia.

Methods: Charts of 218 CF patients (ages >1 month to 61 years) were reviewed. Information extracted included medical history, complete blood counts, iron studies, pulmonary function tests, vitamin levels, serum creatinine levels, and medications.

Results: As patients aged, anemia increased from 12% in those <16 to 58.3% ≥age 40. Anemic patients had poorer lung function than nonanemic patients. Mean forced expiratory volume (FEV1) and forced vital capacity (FVC) were 51.6% (SEM ± 10.3) and 69.7% (SEM ± 9.3) in anemic and 82.5% (SEM ± 9.2) and 95% (SEM ± 8.3) in nonanemic patients, respectively (P < .001). Of vitamin-deficient patients, 90% were anemic whereas only 59.5% of nonvitamin-deficient patients were anemic (P = .02). Complete iron studies were only available in 17 of 48 anemic patients and 11 were diagnosed with iron deficiency.

Conclusions: Anemia in CF is associated with poor lung function and vitamin deficiency. Although anemia was often incompletely evaluated, iron deficiency was common. Recognition and complete evaluation of anemia might be important for continued improvement of care in CF. (Nutr Clin Pract. 2008;23:557-563)

Keywords: cystic fibrosis; anemia; iron deficiency; hemoglobins; inflammation; avitaminosis; respiratory function tests

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Cystic fibrosis (CF) is an autosomal recessive disorder with prominent lifelong pulmonary disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, a gene that encodes a chloride ion channel.1,2 Failure of this channel leads to alterations in viscosity, volume, and salt concentration of body fluids. Although the pathophysiology of CF is debated,3-5 defective innate immunity, tenacious mucus, and loss of mucociliary clearance predispose individuals to pneumonias and colonization with pseudomonas species, ultimately leading to chronic inflammation and lung destruction.6-7 Pancreatic and hepatobiliary involvement lead to malabsorption and diabetes. Although CF is incurable, substantial advances have been made in life expectancy. Centralized care in designated CF centers, new antibiotics against resistant pseudomonas strains, nutrition support, aggressive diabetes management, and organ transplantation have increased the median life expectancy from 6 months in 1957 to 35 years in 2004.8

Anemia in CF has been previously described with varying prevalence as high as 33%.9-14 However, because definition of anemia and length of observation periods are not always provided, substantial gaps regarding the burden of anemia remain. In disorders such as chronic kidney disease, cancer, and rheumatoid arthritis, anemia is recognized as an important cause of fatigue and impaired quality of life, and observational studies have shown that anemia in these settings is independently associated with increased morbidity and mortality.15-20 More recently, it has also been recognized that anemia in chronic obstructive pulmonary disease (COPD) is associated with unfavorable outcomes.21,22 There is evidence that the anemia associated with some of these conditions is caused by inflammation and often is amenable to treatment with erythropoietic stimulating agents and parenteral iron.23-26

Malabsorption, chronic inflammation, and hypoxia—all of which can be present in CF—have major effects on iron metabolism27 and could influence the type of anemia as well as treatment in individual patients.
addressing anemia in CF reported iron deficiency as the main cause. Postulated mechanisms are malabsorption, loss of iron in the sputum, and bleeding. There is preliminary evidence that iron deficiency in CF patients prevents secondary erythrocytosis in response to hypoxia and correlates with low forced expiratory volume in 1 second (FEV1). However, inflammation may be equally important in the anemia of CF and may, in fact, explain unresponsiveness to oral iron supplementation in some cases. In further support of the concept of anemia of chronic inflammation, Fischer et al found recently that C-reactive protein (CRP) levels, as a marker of inflammation, were inversely correlated with hemoglobin in CF patients and that hypoxia in these patients did not result in increased serum erythropoietin levels and adaptive erythrocytosis.

To better understand the burden of anemia in CF, the relative contributions of iron deficiency and inflammation, and associations of anemia with lung disease and malnutrition, we reviewed the charts of 218 patients of all ages (1 month to 61 years) seen regularly in the Cystic Fibrosis Center of the Medical College of Wisconsin and extracted complete blood counts; iron studies (serum iron, total iron binding capacity, ferritin levels); pulmonary function tests (PFTs); serum levels of vitamins A, D, and E (as surrogate markers for absorptive capacity); basic serum chemistry panel (electrolytes, creatinine, blood urea nitrogen, glucose); past medical history; and medications. The median retrospective observation period was 3 years. Because associations of poor lung function with comorbidities such as diabetes and low body mass index (BMI) were established recently, we hypothesized that in the setting of chronic inflammation, poor lung function and anemia may also be associated. Pulmonary failure is the major cause of death in CF and an FEV1 of <30% is a strong predictor of death within 2 years.

Our review revealed that there was a high incidence of anemia in this population, the likelihood of which increased with age. In the majority of cases, the anemia was not fully evaluated with regard to red cell production indices or iron status, but in patients with complete serum iron studies, iron deficiency anemia (IDA) was most prominent. Anemia was more frequent in patients who were vitamin deficient. In anemic patients, there was a striking association with poor lung function. Despite the limitations of our study (retrospective observations from a single institution and lack of multivariate analysis assessing the contribution of other comorbidities to poor lung function), our findings should increase awareness of anemia as a complication in CF. In this context, the distinction between IDA and anemia of chronic inflammation (ACI) may be of great practical consequence because IDA, as opposed to ACI, can be corrected with iron supplementation. However, it is currently unclear whether correction of anemia would translate into clinical benefit and reduction of morbidity and mortality in CF patients.

Methods

Patient Population

Clinical charts and www.portcf.org (electronic data collection site of the Cystic Fibrosis Foundation) logs of 218 patients with CF of all ages (>1 month to 61 years) at Children’s Hospital of Wisconsin and Froedtert Memorial Lutheran Hospital, Milwaukee, were retrospectively reviewed for as many years and visits possible, with a maximum of 7 years (median 3). Data acquisition and patient confidentiality safeguards were approved by the Institutional Review Boards of both hospitals. Data during pregnancy were excluded from analyses.

Data Extracted

Complete blood counts; iron studies (serum iron, total iron binding capacity, ferritin levels); PFTs; serum levels of vitamins A, D, and E (as surrogate markers for absorptive capacity); basic serum chemistry panel (electrolytes, creatinine, blood urea nitrogen, glucose); past medical history; and types of drugs administered were extracted. CRP levels were not charted routinely and were not collected.

Definition of Anemia

Anemia was defined by age-specific and gender-specific World Health Organization (WHO) criteria. Patients were considered anemic if low hemoglobin (Hb) was present on 2 separate occasions at least 2 months apart. Duplicate Hbs were required on each occasion. Alternatively, patients were considered anemic if their average annual Hb, derived from at least 4 values, met WHO criteria. Severe and moderate anemia were defined as Hb <9 and 9-10.9 g/dL, respectively, and mild anemia as Hb of 11-11.9 g/dL in females and 11-12.9 g/dL in males. IDA and ACI, alone or in combination, were defined as recently suggested (Table 1).

PFTs as Surrogate Markers for Patient Performance

FEV1 and forced vital capacity (FVC), expressed as percentage predicted and adjusted for age, height, weight, and gender, were chosen as representative parameters for lung function. Because acute infection adversely affects PFTs, the best PFT from at least 4 annual tests was chosen for correlation with the presence or absence of anemia. The degree of airway obstruction was based on FEV1 and determined in accordance with American Thoracic Society guidelines. Similarly, FVC reflected the degree of lung restriction. To assert a correlation, anemia had to be present within 3 months of the best lung function test for any given patient.

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Vitamin Deficiency

Patients were labeled vitamin deficient if at least 2 consecutive serum vitamin levels within 1 year were below the normal range provided by the laboratory. For association with anemia, at least 1 of the 2 vitamin levels had to be present during the episode of anemia.

Statistics

Differences in lung function between anemic and nonanemic patients were assessed by Student’s t test. Gender-related differences in the frequency or severity of anemia, and differences in the frequency of anemia in vitamin-deficient vs nonvitamin-deficient patients, were determined by Fisher’s exact test. Data are expressed as mean and standard error of the mean (SEM). A two-tailed P value of <0.05 was considered to be statistically significant. Correlation coefficients between Hb and vitamin levels were calculated by Pearson’s statistics.

Results

Incidence and Severity of Anemia

The records of 218 patients (87 females, 131 males, 111 adults ≥18 years) were reviewed. Of these, 61 (28%) had experienced anemia. The likelihood of a patient having experienced anemia during the period of observation increased with age. Only 12% (11/92) of patients <16 years experienced anemia, whereas this figure rose to 30.2% (19/63) by ages 16-24, to 45.8% (22/48) by ages 25-39, and to 58.3% (7/12) by age ≥40 (Figure 1). Mean Hb was 10.1 g/dL (range 6.6-12.9 g/dL) for all episodes of anemia and 10.2 g/dL (range 7.1-12.9 g/dL) in adults. The distribution of patients with severe, moderate, and mild anemia was comparable and present in 16 (7.3%), 21 (9.6%), and 24 (11%) patients at any age (Figure 2). There were no gender differences with regard to incidence or severity of anemia at any age. For females, 25/87 (28.7%) and for males, 36/131 (27.4%) had experienced anemia. In adults, 19/45 (42.2%) females and 29/66 (43.9%) males experienced anemia. Mean Hb was 9.8 g/dL (range 7.1-11.8 g/dL) for females and 10.5 g/dL (range 8.0-12.9 g/dL) for males (all P values >0.05).

Type of Anemia

Complete iron studies were available only in 35% (17/48) of adult patients at the time they were anemic. Of these, 7 could be classified as having IDA, 4 with ACI, and 4 as combined IDA and ACI; 2 had chronic renal failure.

| Table 1. Definition of Iron Deficiency Anemia (IDA) and Anemia of Chronic Inflammation (ACI) |
|-----------------------------------------|-------------------------------------|-------------------------------------|
| IDA                                     | ACI                                 | ACI + IDA                           |
| Serum iron level                        | Low (≤40 μg/dL)                     | Low (≤40 μg/dL)                     |
| Transferrin saturation                  | Low (≤20%)                          | Low (≤20%)                          |
| Serum ferritin level                    | Low (≤35 ng/mL)                     | Low (≥200 ng/mL)                    |
|                                        |                                     | High (≥200 ng/mL)                   |
|                                        |                                     | Between 36 and 199 ng/mL           |
| * As suggested by Weiss and Goodnough.36 |

Figure 1. Percentage of patients with cystic fibrosis, in different age groups, who had experienced anemia in the period of observation.

Figure 2. Representation of hemoglobin (Hb) levels in all patients with cystic fibrosis at the time they were anemic (mean Hb 10.1 g/dL; range 6.6-12.9 g/dL) in different age groups. Comparable numbers of severe, moderate, and mild anemia were present in each age group.
None of the patients with IDA had received organ transplantation, whereas 3 of 4 patients with ACI and 1 of 4 patients with combined anemia had undergone transplantation. In 31 patients, iron studies were incomplete, but renal failure (5 patients), hemoptysis/hematochezia (4 patients), and solid organ transplantation (6 patients) were thought to be contributing factors. In the remaining 17 patients, the anemia went unevaluated.

**Relative Iron Deficiency in Nonanemic Patients**

Iron studies were available in 9 nonanemic patients (mean Hb 13.6 g/dL; range 12.6-14.9 g/dL) with obstructive airway disease (mean FEV1 40.1%; range 20%-63%). A total of 7 of 8 patients had serum ferritin levels ≤35 ng/mL; 1 patient’s ferritin level was 1181 ng/mL, suggesting inflammation, and 1 patient’s ferritin level was not recorded (Table 2).

**Association of Poor Lung Function With Anemia**

PFTs were available in 176 patients of age ≥6 years. Those patients who had been anemic within 3 months of the PFTs had significantly poorer lung function than nonanemic patients. Mean FEV1 was 51.6% (SEM ± 10.3) in the anemic and 82.5% (SEM ± 9.2) in the nonanemic group (P <.001; Figure 3). Mean FVC was 69.7% (SEM ± 9.3) and 95% (SEM ± 8.3), respectively (P <.001). Above age 16, differences between anemic and nonanemic patients reached significance in all age groups (P <.05; Figure 4). No correlation between Hb levels and FVC or FEV1 was identified.

**Correlation of Fat-Soluble Vitamin Deficiencies With Anemia**

A total of 47 patients had at least 1 complete recorded evaluation for vitamins A, D, and E. Of these 47 patients, 10 were vitamin deficient (vitamin A in 2 patients, vitamin D...
in 4, vitamins D + E, D + A, A + E, and A + D + E in 1 patient each). Furthermore, 9 of the 10 (90%) vitamin-deficient patients were anemic, whereas only 22/37 (59.5%) nonvitamin deficient patients were anemic (P = .02). However, there was no correlation between the degree of anemia and vitamin levels (P values for all comparisons were >.20).

Discussion

CF is the most common fatal hereditary disease in North America, affecting approximately 30,000 individuals. A substantial number of adult CF patients (22.7%) suffer from severe lung disease (FEV1 <40% predicted), and >90% die of their lung disease. Liver disease and pancreatic exocrine insufficiency lead to malabsorption and malnutrition. Establishment of the Cystic Fibrosis Foundation in 1955 led to substantial advances in clinical management and the establishment of research programs addressing genetics, pathophysiology, and the development of new therapies. Thanks to these efforts, CF has become a chronic disease that is no longer confined to childhood; currently 40% of patients are adults. Recently, the prevention of CF-related complications such as diabetes mellitus and malnutrition has received much attention because they are linked to poor lung function and increased mortality.

Anemia in CF is increasingly recognized, but our knowledge of mechanisms and severity in the era of modern management is incomplete. Only few studies are available proposing either inflammation or iron deficiency as mechanisms of anemia. However, the relative contribution of iron deficiency and inflammation to the anemia as well as associations with other comorbidities like respiratory compromise and malnutrition remain elusive. To address this, we retrospectively screened information from 218 patients, ages >1 month to 61 years, followed at the Cystic Fibrosis Center of the Children's Hospital and the Medical College of Wisconsin, as long as their charts permitted (median 3 years). For association with anemia, PFTs and serum vitamin levels had to be present contemporaneously.

We found that patients experienced anemia during the average 3-year period of observation with an age-related increase in incidence from 12% in patients aged <16 years to 58.3% in patients aged ≥40 years. The anemia was moderate or severe in approximately two-thirds of patients, with a mean Hb of 10.1 g/dL (range 6.6-12.9 g/dL; Figures 1 and 2). Of interest, the frequency and severity of anemia were not disproportionately increased in adult females. Patients were labeled anemic if they had experienced at least 1 episode of anemia during the observation period. Because observation periods differed between patients depending on the individual chart record, it is conceivable that older patients with longer observation times were more likely to be found anemic. We therefore did not express our data in terms of prevalence or incidence of anemia.

Our review also revealed that anemia received relatively little attention and the workup of anemia was incomplete in the majority of patients. None of the anemic children or adolescents and only 17/48 adults had complete iron studies available. Of these 17 patients, 7 could be classified as having IDA, 4 with ACI, and 4 with a combination of the two. Our patient group comprised 11 transplant recipients of whom 10 were anemic. ACI might be the predominant form of anemia in those patients because 3 of 4 patients with ACI, but none of the patients with IDA, had undergone transplantation. The relative contribution of immunosuppressive drugs to anemia in the setting of transplantation is difficult to determine since low reticulocyte counts are found not only in bone marrow suppression but also in IDA and/or ACI. In only half of the 32 anemic patients without iron studies could conditions such as renal failure, hemoptysis/hematochezia, or organ transplantation be identified as contributors to the anemia; the etiology of anemia remained undiagnosed in the others. Concordant with previously published studies, both iron deficiency and inflammation may be important in the etiology of anemia in CF. Depending on the propensity of inflammatory lung disease, GI malabsorption, or number of transplant patients, the relative contributions of iron deficiency and inflammation may differ and may explain why some investigators find more evidence for one or the other mechanism.

We identified a striking association between anemia and poor lung function. Anemic patients had substantially poorer lung function when compared with nonanemic patients (Figures 3 and 4), although no correlations were found between severity of anemia and severity of lung compromise. The association of anemia with poor lung function could not be established independently in a multivariate analysis because information regarding parameters such as diabetes mellitus, BMI, or socioeconomic status was found to be incomplete during the retrospective chart review. Given the study's limitations, these findings may be considered as preliminary, but they are in support of previous findings where iron deficiency in CF was associated with low FEV1, although patients in that study were not anemic. Of note, 9 nonanemic patients (mean Hb 13.6 g/dL) in our study with poor lung function (mean FEV1 40.1%) had low serum iron, and 8 also had low serum ferritin levels, consistent with iron deficiency (Table 2). These findings raise the possibility that iron deficiency in these patients limited the appropriate rise in Hb in response to presumed hypoxia. The concept that what is perceived as a normal Hb may represent "relative anemia" in CF patients is supported by 4 other studies that found either iron deficiency or inflammation to limit iron availability for erythropoiesis.
Anemia was also more prevalent in patients with fat-soluble vitamin deficiency compared with patients who were not vitamin deficient, although there were no correlations between vitamin and Hb levels. It is well-known that vitamin B₁₂ and folate (which are both water soluble and not regularly assessed in CF patients) can lead to anemia, but the association of anemia with other vitamin deficiencies is less clear. In the Western world, where access to fruit, vegetables, and animal products is not problematic, severe vitamin deficiency is rare and little is known about its association with anemia. However, in the developing world, where the prevalence of anemia can reach 50% in areas, vitamin A deficiency in the malnourished has been linked to anemia independent of other factors such as HIV infection, iron deficiency, malaria, sickle cell disease, and bacterial infections. The role of vitamin E deficiency in anemia is less defined, but has been suggested as contributing to anemia in a small group of CF patients. The mechanisms by which vitamin A and vitamin E deficiencies might cause anemia are poorly understood. Whereas vitamin A may affect erythropoiesis by stimulation of erythropoietin production, the antioxidant properties of vitamin E have been implicated in red cell survival. Although several studies suggest improvement of anemia with vitamin supplementation, data remain conflicting. Because vitamin A has been shown to improve nonheme iron absorption and iron availability from stores, it is plausible that deficiency could further exacerbate the development of anemia in CF where iron intake and metabolism are altered. Our data suggest that vitamin deficiencies caused by malnutrition may be an important contributor to anemia in CF, although our data set did not allow an assessment of the relative contribution of each vitamin or address the link of vitamin A to iron metabolism by correlation of its serum levels with parameters such as serum iron or ferritin levels.

The mechanisms leading to anemia in our patient population seemed to be multifactorial. Iron deficiency was most prominent, followed by inflammation. Vitamin deficiencies are likely to contribute to anemia, although the mechanisms are poorly understood. Because vitamin deficiencies are just one of several components contributing to the anemia of CF, it is not surprising that in our study vitamin levels did not correlate with the severity of anemia. Anemia contributes to fatigue, morbidity, and mortality in other chronic diseases. In our study, anemia was associated with poor lung function, a major cause of morbidity and mortality in CF. Although treatment of anemia in renal failure, cancer, or other chronic diseases has never been shown to improve survival, there is a significant impact on overall quality of life and well-being. Pertinent to iron deficiency in CF patients, studies in an animal model demonstrated marked impairment of running ability in iron-deficient animals that was persistent when anemia as a variable was removed by transfusion. Iron therapy restored the function of cellular iron-dependent enzymes and corrected muscular dysfunction within days. Given the multifactorial etiology of anemia in CF patients, a thorough evaluation including complete iron studies and vitamin levels is advisable to identify correctable deficiencies. Iron studies in selected nonanemic patients who have fatigue or poor lung function may also be indicated to assess for "relative anemia." Given the multidisciplinary care in CF, dietitians might be closest to the patient regarding the evaluation of nutrition deficiencies and advice for appropriate supplementation. Although the diagnosis of iron deficiency on the basis of the serum ferritin concentration is often considered difficult in the face of inflammation, complete iron studies are still critical and usually allow the identification of underlying iron deficiency in such settings. If in doubt, additional measurement of soluble transferrin receptor and its ratio to ferritin will aid in distinguishing between IDA, ACI, or a combination of both. Oral iron tolerance tests can help identify patients with poor absorption and facilitate early decision making regarding the use of intravenous iron. With the results of this study, we hope to heighten the awareness for anemia in CF and underline its importance as a significant, possibly treatable complication. However, whether aggressive correction of anemia with multivitamins and/or iron in anemic and nonanemic CF patients would improve lung function or translate into clinical benefits such as reduction of fatigue and improvement of overall quality of life is speculative at the moment. Prospective, randomized clinical trials will be required to answer these questions.

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