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Hepcidin is a key mediator of anemia of inflammation in Crohn's disease

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Abstract

Anemia often complicates the course of Inflammatory Bowel Disease (IBD). Hepcidin, a liver-produced peptide hormone, is a key mediator of anemia of chronic disease (ACD). We hypothesized that hepcidin is significantly elevated in anemic CD patients and that hepcidin may cause iron restriction and, therefore, mediate ACD.

Methods: We enrolled 17 patients with CD and ACD recruited from the Cedars-Sinai IBD Center. Routine blood tests included hemoglobin (Hgb), hematocrit, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Anemia was defined as hemoglobin <12 g/dL and <13.5 g/dL, in men and women, respectively. ACD was diagnosed on the basis of a combination of the following: a) normal or elevated ferritin b) lowered serum iron and total iron binding capacity and c) normal percent iron saturation. Serum and urine hepcidin, as well as IL-6 levels were also measured. Patients with documented iron-deficiency anemia were excluded.

Results: There was an excellent correlation between urine (expressed as ng/mg of creatinine) and serum hepcidin levels expressed as ng/ml ($r=0.853$, $p<0.001$). We also found a strong positive correlation between serum hepcidin and ferritin levels ($r=0.723$, $p=0.0015$). There was a positive correlation between serum hepcidin and IL-6 levels ($r=0.546$, $p=0.023$). We found a strong negative correlation between serum hepcidin concentrations and Hgb levels ($r=0.528$, $p=0.029$).

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Conclusion: We demonstrate that ACD in CD is characterized by high serum IL-6 and hepcidin levels, which negatively correlate with Hgb levels. Our data support the hypothesis that IL-6-driven hepcidin production mediates ACD in patients with CD.

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic gastrointestinal diseases characterized by relapsing and remitting inflammation of the intestines.[1] Interestingly, anemia may often complicate the course of IBD.[2,3] A recent systematic review showed that anemia is common and may affect roughly 17% of patients with IBD.[4] Nevertheless, the awareness of anemia in IBD has received little attention and is often overlooked by treating gastroenterologists.[5]

Anemia in IBD, the pathogenesis of which is multi-factorial, is frequently the result of chronic intestinal blood loss from inflamed gastrointestinal mucosa and iron-deficiency, but inflammation may also contribute to the development of anemia.[6] This is especially true for CD, where impaired intestinal absorption of folate and/or vitamin B12 occur secondary to inflamed mucosa and/or bowel resection. Moreover, anemia may result from IBD therapies, such as sulfasalazine, which may confound the problem.[7]

Anemia of inflammation or anemia of chronic disease (ACD) is characterized by normochromic, normocytic or mildly microcytic erythrocytes, low or normal serum iron and total iron-binding capacity, normal or increased iron stores reflected by elevated ferritin levels, low transferrin levels, and an inappropriately low reticulocyte response relative to the degree of anemia Table 1). ACD is unresponsive to treatment with iron, vitamin B12 or folic acid.

Anemia in IBD could be the effect of cytokines on cells of the reticuloendothelial system inducing changes in iron homeostasis, the proliferation of erythroid progenitor cells, as well as the production of erythropoietin, and reducing the longevity of red blood cells.[8] Several in vitro and in vivo studies demonstrate that inflammatory cytokines, such as interleukin (IL)-1β, TNF-α and IFN-γ, may suppress erythropoiesis, impair the availability of iron from reticuloendothelial stores, and impair erythropoietin production in response to anemia.[9] A recent study indicated that children with active CD have impaired oral iron absorption and elevated IL-6 levels compared with subjects with inactive disease suggesting that oral iron may be of limited benefit to these patients.[10]

Hepcidin, a key regulator of iron metabolism, is expressed in the liver, distributed in blood, and excreted in urine.[11] Hepcidin is a key mediator of ACD.[12] The synthesis of hepcidin is greatly stimulated by inflammation or by iron overload. Hepcidin appears to be the main inhibitor of iron absorption from the small bowel (SB) and iron release from macrophages.[12,13]

We hypothesized that hepcidin is significantly elevated in anemic adult CD patients not suffering from iron deficiency, and that hepcidin may cause iron restriction and, therefore, mediate ACD. We aimed to assess serum and urine hepcidin concentrations in patients with CD and ACD and to correlate hepcidin levels with hematologic parameters and markers of inflammation.

2. Methods

2.1. Study patients

Subjects were recruited from the inpatient and outpatient services of the Cedars-Sinai IBD Center. Patients were eligible to participate in the study if they were between 18 and 65 years of age, had a diagnosis of CD and concomitant ACD. Subjects were excluded if there was a known history of iron deficiency anemia (IDA),[14] UC, or macrocytic anemia. Furthermore, patients who used iron supplementation, B12 or folate within 3 months of study enrollment were also excluded. The study was approved by the Cedars-Sinai Institutional Review Board.

2.2. Study design

Subjects who met inclusion criteria underwent laboratory evaluation of ACD,[14] and subsequently underwent routine blood tests including complete blood cell count, iron studies, ferritin, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Serum and urine were also obtained for measurement of hepcidin levels as described below.

Table 1 Characteristics of the CD patient population.

Number	17 (%)
Median age (y), (range)	35, (20–67)
M:F	8:9
Disease duration (y), median, (range)	5, (1–30)
Disease phenotype [a]	
Inflammatory	15 (88)
FS	3 (17)
IP	7 (41)
Disease extent	
Small bowel	9 (53)
Ileocolonic	4 (23.5)
Colonic	4 (23.5)
Prior surgeries	8 (47)
Medical therapy	
5-ASA	8 (47)
Corticosteroids	5 (29)
Thiopurines	7 (41)
Anti-TNF	5 (29)

[a] FS = fibrostenosing, IP = internal penetrating; 2 patients had both inflammatory and FS phenotype, 5 patients had both inflammatory and IP phenotype and 1 patient had both FS and IP phenotypes.