

ORIGINAL PAPERS

Refractory iron-deficiency anemia and gluten intolerance – Response to gluten-free diet

Luis Rodrigo-Sáez¹, Dolores Fuentes-Álvarez¹, Isabel Pérez-Martínez¹, Noemí Álvarez-Mieres¹, Pilar Niño-García¹, Ruth de-Francisco-García¹, Sabino Riestra-Menéndez¹, Santiago Vivas-Alegre² and José Luis Olcoz-Goñi²

¹Department of Digestive Diseases. Hospital Universitario Central de Asturias. Oviedo. Asturias, Spain.

²Unit of Digestive Diseases. Complejo Asistencial Universitario de León. Spain

ABSTRACT

Introduction: refractory iron-deficiency anemia has a multifactorial origin related to various gastrointestinal conditions, with celiac disease plus malabsorption and IBD together with isolated gluten intolerance being most common.

Objectives: to determine the prevalence of serum, genetic, and histological markers for gluten intolerance, and to analyze the response to gluten withdrawal from the diet in these patients.

Methods: a number of patients with refractory anemia were prospectively and consecutively enrolled. A protocol to measure serum (TGt-2), genetic (HLA-DQ2/DQ8), and histological markers for celiac disease was applied. All followed a gluten-free diet for a median 3.6 years. Sustained remission of anemia during follow-up was interpreted as positive response.

Results: ninety-eight patients (84% females) with a mean age of 54 years were studied. Anti-TGt2 antibodies were positive in 5% of cases. A total of 67 cases (68%) were haplotype HLA-DQ2 or -DQ8 (+). We found villous atrophy (Marsh III) in 13% of patients, and an inflammatory pattern (Marsh I or II) in 13%. All remaining 72 patients (74%) had no histological duodenal changes.

Age, anemia duration, number of transfusions, number of parenteral iron doses, and time on a gluten-free diet were all compared according to the presence or absence of villous atrophy and HLA-DQ2/8 positivity, and no significant differences were found for any of the analyzed variables. Response was positive in 92% of subjects.

Conclusions: celiac disease with villous atrophy is rarely a cause of refractory anemia. Gluten intolerance with no histological lesions is seen in almost 75% of patients, and therefore plays a relevant role in its development.

Key words: Refractory iron-deficiency anemia. Gluten intolerance. Gluten-free diet.

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INTRODUCTION

Overall, chronic anemia is very commonly associated with various gastrointestinal conditions. This justifies that patients with chronic anemia –at times designated anemia of obscure origin– be usually referred to a gastroenterologist in an attempt to unveil its cause and then apply the appropriate therapy.

WHO defines the presence of anemia as a reduction in blood hemoglobin levels below 13 g/dl in males and 12 g/dl in females.

According to its etiopathogenesis, chronic anemia is categorized as “central” (arregenerative) anemia when it develops as a result of defective red blood cell (RBC) production by the bone marrow, or “peripheral” (regenerative) when it is secondary to excessive RBC destruction.

Iron deficiency anemia –or ferropenic anemia– is most common, but other origins do exist. A number of gastrointestinal conditions are also usual causes (1-4).

Overall, chronic ferropenic anemia of digestive origin may be classified in two major categories: a) associated with chronic iron loss, as is the case in a number of digestive-tract benign or malignant tumors, peptic ulcer disease, NSAID use, IBD, etc.; and b) from reduced intestinal iron absorption, as occurs in celiac disease, gastric atrophy, gastrectomy, intestinal resection or bypass, etc. (5-8).

Chronic refractory iron-deficiency anemia is the type of anemia that will not respond to replacement therapy with oral iron preparations (9-12).

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Correspondence: Luis Rodrigo Sáez. Servicio de Aparato Digestivo. Hospital Universitario Central de Asturias. C/ Celestino Villamil s/n. 33006 Oviedo, Asturias, Spain.
e-mail: lrodrigoes@ gmail.com

The present paper discusses the prevalence of classical celiac disease and of gluten intolerance in patients with chronic ferropenic anemia, as well as their response to gluten-free diet, in the absence of usual celiac disease markers.

METHODS

We performed an observational, prospective study of a consecutive series of patients who attended our clinic because of refractory anemia following referral by the Internal Medicine and Hematology departments in our hospital. All patients in the series had been diagnosed based on the presence of chronic ferropenic anemia (> 6 month's standing) unresponsive to replacement therapy with oral iron preparations.

They were referred to a gastroenterology clinic for the study of small bowel conditions in the hospital, and were assessed by the same gastroenterologist (LR). They were invited to take part in a study for the screening of potential celiac disease. In all, 90% of subjects accepted and signed an informed consent. The study was approved by our hospital's ethics committee.

All patients underwent specific medical history taking and a number of laboratory tests including serum and genetic markers for CD, gastroscopy, and multiple duodenal biopsies, as well as a complete colonoscopy (through to the cecum) to rule out organic disease.

Lab tests included CBC and ESR by using an automated Cell-DYN 3500 R system (Lab. Abbott), and a complete coagulation screen using an ACL 3000 system (Lab. Menarini). Iron-deficiency anemia was diagnosed according to WHO criteria.

WBC count was considered normal for values of $4-10 \times 10^3/L$, and platelet count was considered normal for values of $130-400 \times 10^3/L$.

An extensive biochemistry panel was obtained including the following parameters: iron metabolism with sideremia, transferrin saturation index (TSI), and serum ferritin. Normal sideremia was 60-140 mcg/ml, and normal ferritin was 13-150 ng/ml. A TSI of 25-45% was considered normal.

We also obtained so-called liver function tests (LFTs) including AP, AST, ALT, GGT, and bilirubin; serum calcium, folic acid, and vitamin B-12 levels, plasma creatinine, total cholesterol (normal, 150-240 mg/dl), HDL, LDL, triglycerides, urea, glucose, total proteins, albumin, and acute-phase reagents such as CRP (C-reactive protein). Normal AST and ALT values were 1-31 U/L. All measurements were performed with a modular automated Hitachi SXA DPPP analyzer (Roche) using enzymatic or kinetic methods.

Immunoglobulin quantitation was performed using nephelometry. For serum screening, only tissue transglutaminase 2 IgA antibodies (TGt-2) were used, with measurements carried out using a commercially available ELISA kit (Phadia Diagnostics, Uppsala, Sweden). We considered it positive for values > 2 U/ml just as studies for general popu-

lation screening recommend, since this threshold has a higher diagnostic sensitivity (13).

For the study of genetic susceptibility for CD both HLA-DQ2 (DQA1*0501 and DQB1*0201) and HLA-DQ8 (DQA1*0301 and DQB1*0302) markers were measured with PCR using specific sequence primers (SSPs) for DNA based on a commercially available kit designated Protrans® Domino System HLA Celiac Disease (Protrans, Ketsch, Germany).

All patients underwent a complete colonoscopy to rule out the possible existence of organic pathology or the presence of some kind of injury that could justify the origin of anemia in the colon.

All patients included in the study underwent upper digestive endoscopy with multiple duodenal biopsy taking (4-6). Samples were routinely stained with hematoxylin-eosin (H-E) and specific immunohistochemical stains for CD3 to assess the presence of intra-epithelial lymphocytes (IELs), which were counted for every one hundred epithelial cells.

Duodenal biopsies were studied by two pathologists with CD-related expertise, and classified into the following categories –stage 0 = histologically normal duodenum; stage I = increased IELs with count > 25% of epithelial cells; stage II = crypt hyperplasia and/or diffuse chronic inflammatory infiltration at the lamina propria; stage III = villous atrophy subdivided into three categories: a) mild; b) moderate; and c) severe, according to the pathological classification for CD screening as described by Marsh in 1992 (14) and modified by Oberhuber et al in 1999 (15).

All patients agreed to follow a gluten-free diet for a mean 36 ± 1.6 years (range 1-9 years), with a median of 3.6 years.

Transfusion needs and parenteral iron administration were all assessed during follow-up as well as treatment response –sustained anemia remission with no oral iron replacement therapy was considered positive.

Statistical analysis

For continuous variables a descriptive analysis was performed by estimating mean, standard deviation, and range values. For qualitative parameters percentages were used. For between-group comparisons we used Student's t-test for continuous variables in non-paired groups, and the chi-squared test for categorical variables; Fisher's exact test was used when deemed necessary. Statistical significance was defined for $p < 0.05$.

RESULTS

A total of 98 patients were studied. Sex distribution was 82 women (84%) vs. 16 men (16%), with a clear predominance of females and a male/female ratio of 5/1.

Mean age was 54 ± 17 years with a wide range between 22 and 90 years of age. Mean refractory ferropenic anemia

duration was 13 ± 7 years, also with a wide range between 1 and 35 years.

Anti-TGt titers were positive for 5 patients only (5%), and 67 patients (68%) had a positive haplotype for HLA-DQ2 or DQ8.

Histological findings found in duodenal biopsies and classified according to Marsh stages are represented below (Table I).

Age, anemia duration, number of transfusions, number of parenteral iron doses, and time on a gluten-free diet were all compared according to the presence or absence of villous atrophy, with no statistically significant differences regarding histology findings (Table II).

These same variables were compared between those with HLA-DQ2/8 positivity and those expressing a different allele, with no significant differences in any of the analyzed variables (Table III).

In the group with positive DQ2/8 ($n = 67$) those with villous atrophy ($n = 12$) were compared to those without it ($n = 55$), and no statistically significant differences were found among the above variables. Among the 83 patients without villous atrophy no differences were seen between those with a normal duodenal mucosa (Marsh 0; $n = 72$) and those with lymphocytic enteritis (Marsh I; $n = 11$).

Response to GFD was obtained for 90 patients (92%). In 5 cases it was due to complete or partial lack of compliance, or frequent dietary violations, and in 3 cases resulted from the presence of colonic (2) and gastroduodenal (1) dysplasias developed during follow-up.

DISCUSSION

The present study reveals that gluten intolerance without associated overt celiac disease, while meeting no diagnostic criteria for CD, can originate chronic iron-deficiency anemia in three quarters of cases in a wide series of patients with refractory anemia. The most likely explanation is a disordered intestinal iron absorption, either functional or

Table I. A distribution of duodenal biopsy findings according to Marsh classification

Marsh stage	n (%)
Zero (normal)	72 (74)
I (increased IELs > 25%)	11 (11)
II (crypt hyperplasia)	2 (2)
III-A (mild atrophy)	11 (11)
III-B (moderate atrophy)	1 (1)
III-C (severe atrophy)	1 (1)

IELs: intra-epithelial lymphocytes.

biochemical in nature (15), with no need for duodenal histology disease or villous atrophy as previously thought, which had to be found in most CD cases in agreement with classically established criteria (16).

Thus, in a recently reported study, performed on 4120 patients with ferropenic anemia, the authors observed an obscure origin in 206 (5%), 30 of which (15%) had gluten-sensitive bowel disease. Of these, 16 cases had Marsh-III lesions; 12 were Marsh-II, and 2 cases had Marsh-I. Anemia relevance was somewhat related to duodenal lesion type. As with our patients, all of them recovered from anemia by following a gluten-free diet long term (17).

The primary limitation of the present study is its observational character, as it lacks a control group for comparison of anemia response to GFD in the wide group of study subjects with normal histology versus intraepithelial lymphocytosis.

Celiac disease (CD), also known as “gluten-sensitive enteropathy”, is a systemic process associated with frequent digestive involvement in the small bowel that presents with various clinical manifestations. It is a common disease with a mean prevalence around 1-2% worldwide, and affects all races in all countries; it is commonly recognized by its classical development during childhood, but may also develop –with an increasingly higher frequency– in the

Table II. Differences between anemic patients with and without villous atrophy on a duodenal biopsy

	Villous atrophy (n = 13)	No villous atrophy (n = 85)
Mean age (SD)	48 (17)	54 (17)
Mean no. of years with anemia (SD)	15 (6)	13 (7)
Mean no. of transfusions (SD)	1.1 (2.2)	0.9 (2.4)
Mean no. of iv iron doses (SD)	26 (10)	21 (12)
Mean baseline ferritin (ng/ml) (SD)	14 (16)	19 (28)
Mean baseline sideremia (mcg/ml) (SD)	34 (18)	35 (18)
Mean baseline hemoglobin (g/dl) (SD)	9.3 (2.3)	10.2 (1.1)
Mean baseline TSI (%) (SD)	9 (4)	11 (4)
Mean no. of years to recovery (SD)	0.7 (0.4)	0.5 (0.3)
Mean no. of years with a GFD (SD)	4.4 (2.2)	3.4 (1.5)

$p > 0.05$ (non-significant) for all comparisons.

Table III. A comparative analysis of patients with positive and negative class-II HLA-DQ2 or -DQ8 alleles

	<i>DQ 2/8 positive (n = 67)</i>	<i>DQ 2/8 negative (n = 31)</i>
Mean age (SD)	56 (18)	49 (14)
Mean no. of years with anemia (SD)	13.4 (7.7)	13 (6.9)
Mean no. of transfusions (SD)	0.7 (1.9)	1.4 (3.2)
Mean iv iron doses (SD)	22 (13)	21 (11)
Mean baseline ferritin, (ng/ml) (SD)	20 (30)	15 (16)
Mean baseline sideremia, (mcg/ml) (SD)	34 (17)	36 (21)
Mean hemoglobin (g/dl) (SD)	10.2 (1)	9.7 (2)
Mean baseline TSI (%), (SD)	10.8 (4)	10.2 (5)
Mean no. of years to recovery (SD)	0.7 (0.5)	0.6 (0.2)
Mean no. of years with a GFD (SD)	3.6 (1.8)	3.5 (1.3)

$p > 0.05$ (non-significant) for all comparisons.

adult, and may be recognized and diagnosed anytime during life (18,19).

It is accompanied by a high frequency of several blood disorders, the most predominant of which is doubtless anemia. Anemia usually has a multifactorial origin and is commonly associated with deficient absorption of a number of micronutrients or trace elements, with iron being most frequently involved; however, it may also be associated with folic acid and vitamin B-12 deficiency.

CD may also be associated with other blood disorders such as leukopenia, thrombocytosis, splenic hypofunction, and occasionally malignancies, of which non-Hodgkin lymphoma and T-cell intestinal lymphoma are most common (20).

Anemia is therefore a common finding in patients with CD, and a common driver of CD diagnosis, as it may also be the only laboratory anomaly (21). This commonly occurs in patients at diagnosis, and is particularly frequent in the adult, as it is more common that celiac disease presents with atypical or pauci-symptomatic forms in this age group than in children, where abdominal manifestations are clearer and classic forms predominate with severe gastrointestinal complaints. Adult iron-deficiency anemia may be the only manifestation of CD in the absence of diarrhea (22).

The prevalence of anemia varies greatly in celiac patients at diagnosis, but ranges as wide as 15-70% of cases are reported, being higher in patients with refractory anemia (23,24). Nevertheless, the mean minimal number found in several epidemiological studies is around 5% of celiac patients before GFD onset (25).

Ferropenic anemia is a common process whose primary causes may be gathered into two major groups it is either due to chronic loss usually from lesions in any gut segment or to chronic intestinal absorption deficiencies (26-28). Iron is absorbed from the proximal portion of the small bowel, primarily the duodenum, and its complex absorption mechanism may be modified by various factors –most influential are– both from a histological and functional perspective a normal duodenal mucosa and other factors such as gastric and duodenal acidity. Anemia is characterized by low hemo-

globin levels and usually microcytic and hypochromic RBCs. Patients with ferropenic anemia usually present with reduced circulating iron levels, low transferrin saturation index, and depleted body iron deposits, which translates into severely decreased serum ferritin levels (29).

Capsule endoscopy is very useful for the study of small bowel morphology, as it allows the detection of small lesions such as angiodysplasia and little erosions or tumors that would otherwise be overlooked (30).

The measurement of circulating soluble transferrin receptor (sTfR) levels is useful to assess patients with iron-deficiency anemia, and a higher sTfR to ferritin ratio may guide CD diagnosis in children with refractory ferropenic anemia (31). Chronic iron deficiency refractory to oral iron replacement therapy may be the only CD manifestation, especially in pediatric patients. The prevalence of CD in adult patients with refractory anemia may reach up to 20% of cases.

It is also a common finding in patients with herpetiform dermatitis-like skin lesions, which is the form most frequently associated with CD.

The presence of so-called CD endoscopic markers in patients with ferropenic anemia has usually revealed a low diagnostic sensitivity, and therefore is of limited use for screening patients who will undergo duodenal biopsies. These should be undertaken even when the mucosal appearance is perfectly normal to the endoscopist. A recent study revealed that many patients undergoing upper digestive endoscopy for the study of obscure-origin ferropenic anemia have no duodenal biopsies because of the normal looks of the duodenal mucosa (32).

Ferropenic anemia is common among the general population. It often develops in younger women, and is usually attributed to increased menstrual losses; initial empiric therapy before a causal diagnosis is made is common in clinical practice. Similarly, anemia persistence after the menopause should prompt a number of studies aimed at the detection of associated CD (33).

Indeed, many patients undergo hysterectomy for hypermenorrhea or associated myomas in order to treat ferropenic anemia prior to the identification of its true origin, and ane-

mia persists after the procedure until a correct diagnosis is ultimately reached and an appropriate therapy is indicated. Interestingly, ferropenic anemia is scarcely diagnosed in children, and is much more common among younger adults on reaching adolescence. An explanation for such discrepancy may be that hemoglobin is not routinely measured in children. What is surprising is that not all patients with gluten intolerance manifest anemia. A possible reason in some cases is that subjects are carriers of the hemochromatosis gene, C282Y or H63D (34).

In conclusion, refractory iron-deficiency anemia is common in patients with CD; even when the duodenal mucosa has normal macroscopic looks and duodenal biopsies show no apparent lesions during histology, a response to GFD may be seen. Gluten withdrawal from the diet may be an effective measure, together with the administration of oral or parenteral iron preparations, until iron deposits go back to normal and anemia is permanently solved. This is a slow, gradual process that may last one year on average, and up to 2 years for complete normalization. Prospective randomized studies of GFD versus a normal diet may ultimately bear out in a conclusive manner the efficacy of GFD in patients with refractory anemia, thus supporting the preliminary results obtained in the present paper.

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