

ORIGINAL ARTICLE

Hematological complications in anorexia nervosa

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BACKGROUND/OBJECTIVES: Anemia, leukopenia and, although less frequently, thrombocytopenia are possible hematological complications of anorexia nervosa considered strictly secondary to chronic malnutrition. This is a retrospective study on the prevalence of these disorders in a large cohort of 318 female patients with AN (20.4 ± 5.6 years, body mass index (BMI) 15.9 ± 1.6 kg/m²), recruited in the Outpatient Unit for Malnutrition secondary to Eating Disorders at the Department of Clinical Medicine and Surgery, Federico II University Hospital, since February 1991 to December 2012.

SUBJECTS/METHODS: Patients were studied on an outpatient basis after obtaining medical history, clinical examination, routine hematobiochemical and endocrine tests, electrocardiography, psychiatric interview and bioelectrical impedance analysis and, in particular, phase angle determination. All patients with other comorbidities, in particular with mean corpuscular volume < 80 fl, were excluded for suspected genetic alteration in the synthesis of hemoglobin.

RESULTS: Hematologic data showed that 16.7% of patients had anemia, 7.9% neutropenia and 8.9% thrombocytopenia. These abnormalities were strictly related to the duration of illness ($P = 0.028$), and to protein energy malnutrition, in particular, BMI and phase angle ($P < 0.001$).

CONCLUSIONS: Our study offers description of the incidence of hematologic defects in a selected and large sample of AN female patients, suggesting that its incidence is related to the degree and duration of protein energy malnutrition.

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INTRODUCTION

Anemia, leukopenia and, although less frequently, thrombocytopenia are possible hematological complications of anorexia nervosa (AN);¹ their prevalence has been reported ranging from 21 to 39% for anemia, 29 to 39% for leukopenia and 5 to 11% for thrombocytopenia.¹ Hematologic disorders related to malnutrition are probably underestimated because of hemoconcentration, a common finding in patients with AN. Usually anemia in AN is normocytic and normochromic and leukopenia is characterized by lymphocytopenia or neutropenia; thrombocytopenia may also be present.¹ Bone marrow examination reveals, in most severe cases, signs of atrophy and/or hypocellularity;² gelatinous bone marrow transformation may also be present with increased bone marrow fat.³ Hematological alterations in AN are referred as closely related to chronic malnutrition considering that their resolution is usually obtained with nutritional rehabilitation after a variable length of time.¹ These alterations do not appear totally dependent on micronutrient deficiencies such as vitamins and iron. In fact, blood cytopenia in anorexic patients can also be found in the presence of normal serum concentration of these elements.¹ On the other hand, normal plasma vitamin and macronutrient concentrations should not be misinterpreted in patients with AN as normal micronutrient and vitamin status, as these values too can be affected by dehydration.⁴ The accuracy of bioelectrical impedance analysis (BIA) is limited in patients with a body mass index (BMI) below 16 kg/m² and in patients with AN,^{5,6} but phase angle (PA), a parameter of BIA, can be considered an index of the integrity of the cell membrane. PA identifies extra/intracellular water distribution: a low PA being a common finding in severe malnutrition.⁷ Several researches have proved the close relation between PA and nutritional status. PA exhibits a negative correlation with the

subjective global assessment score^{8,9} that assesses nutritional status. PA indeed correlates with both the functional index (hand grip strength cirrhosis patients) and nutritional status (albumin, transferrin).^{8–10} Moreover, PA, hand grip strength and nutritional status are strictly related to survival in advanced cancer patients with severe weight loss.^{11–13}

The aim of this study was to evaluate, retrospectively, the incidence of hematologic disorders in a large cohort of patients with AN, the relationship between the degree and duration of protein energy malnutrition, the PA and hematobiochemical parameters.

MATERIALS AND METHODS

In this cross-sectional study, 318 (mean age 20.4 ± 5.6 (age range 14–47) years, (BMI) 15.9 ± 1.6 (10.5–18.4) kg/m²) amenorrhoeic female patients affected by AN, consecutively recruited in the Outpatient Unit at the Department of Clinical Medicine and Surgery, Federico II University Hospital, since February 1991 to December 2012, were considered for the study. The study was carried out according to the Declaration of Helsinki, and the protocol was approved by the local ethics committee at Federico II University Hospital. All patients gave their informed consent for participating in the study.

All patients were postpubertal adolescents. Diagnosis of AN was performed by an expert psychiatrist, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision criteria,¹³ and recently confirmed according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition.¹⁴ Exclusion criteria were other comorbidities (with particular attention to immunological diseases) or specific therapies such as iron supplementation. Patients with low mean cellular volume (MCV) and/or low serum ferritin levels were not included to avoid heterozygosity for thalassemia minor, which is quite common in the Mediterranean area. All patients were studied at entry on an outpatient basis after careful review of the patient's medical history, clinical examination, routine biochemical and

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endocrine tests, electrocardiography (Oimed, 300A, Shanghai, China), psychiatric interview and BIA measurements (Human IM Scan DS-Medica, Milan, Italy). They were further subdivided into three subgroups according to the degree of protein energy malnutrition: mild ($16.5 < \text{BMI} < 18.5 \text{ kg/m}^2$), severe ($14.5 < \text{BMI} < 16.4 \text{ kg/m}^2$) and very severe ($\text{BMI} < 14.4 \text{ kg/m}^2$).

BIA was performed at 50 kHz at a room temperature of 22–25 °C. BIA variables resistance (R), reactance (Xc) and PA were measured in the postabsorptive state, on the non-dominant side of the body, after voiding and after being in the supine position for 20 min.

Samples for hemoglobin determination were collected in EDTA tubes, whereas samples for serum iron, transferrin and ferritin dosages were collected in serum separator tubes. All samples were evaluated with routine laboratory methods. Laboratory technicians were not aware of the clinical conditions of the patients. For hemoglobin analysis, a hematologic analyzer (ADVIA 2120; Siemens, Munich, Germany) was used; serum iron and ferritin levels were determined by spectrophotometry (Modular; Hitachi, Tokyo, Japan); in particular, for ferritin dosage, an immunoenzymatic assay was used. Finally, for transferrin and total iron-binding capacity, a nephelometric method was used.

Statistical analysis consisted in calculating the prevalence of disorders (using standard cut-points) and in evaluating differences between subgroups. Statistical significance of differences was confirmed by χ^2 tests (for differences in prevalence) and by one-way analysis of variance tests (for differences in mean values).

RESULTS

Table 1 shows anthropometric data and the length of amenorrhea of the female patients under study.

Hematologic data (Table 2) show that 16.7% of patients with AN were anemic, 7.9% neutropenic and 8.9% thrombocytopenic. The combination of two types of cytopenia was present in 8.7% of patients (anemia and neutropenia 3.8%, anemia and thrombocytopenia 2.6% and neutropenia with thrombocytopenia 2.3%); pancytopenic patients represented only 1.1% of the whole population.

High serum ferritin levels were shown in 33% of the patients. To better analyze the incidence of anemia, we divided the cohort studied into three groups according to the degree of malnutrition (Table 3): (1) 58 patients of the total sample (18.2%) had a $\text{BMI} < 14.4 \text{ kg/m}^2$ (Group 1); (2) 128 (40.3%) were in a BMI range 14.5–16.5 (Group 2); and (3) 132 (41.5%) with $16.6 < \text{BMI} < 18.5 \text{ kg/m}^2$ (Group 3). No significant ($P=0.124$) age difference was observed, and duration of amenorrhea increased according to the worsening of malnutrition (Group 1: 18.1 ± 16.1 months; Group 2: 15.3 ± 24.7 months; Group 3: 12.4 ± 16.3 months; $P=0.028$ Groups 1 vs 3), lasting longer in patients at Group 1. The percent of patients with $\text{PA} < 5.0^\circ$ was significantly higher in Group 1 (44.1%) compared with Groups 2 (6.2%; $P < 0.000$) and 3 (25.3%; $P < 0.001$). Prevalence of anemia was significant when Group 1 was compared with Groups 2 and 3. No statistical difference was found as far as neutropenia prevalence was considered.

Table 1. Main anthropometric data, duration of amenorrhea in 318 female anorexia nervosa patients

	Mean \pm s.d. (min–max)
Age (years)	20.4 \pm 5.6 (12.0–47.0)
Height (cm)	160 \pm 6.0 (143–177)
Weight (kg)	40.9 \pm 5.3 (27.0–56.0)
BMI (normal range: 20–25 kg/m ²)	15.9 \pm 1.6 (10.5–18.4)
Phase angle (normal range: 5.5°–6.5°)	5.5 \pm 1.0 (2.3–8.3)
Duration of amenorrhea (months)	14.5 \pm 20.1 (3–180)

Abbreviation: BMI, body mass index.

DISCUSSION

Malnutrition secondary to eating disorders is, in absence of other complications, a marasmus-like malnutrition where endocrine, metabolic and functional adaptive mechanisms develop allowing survival, and even apparently normal life habits, despite very low body weight and organ/apparatus complications.¹⁵ Hematological changes in eating disorders have been described previously;¹⁶ however, their prevalence is still controversial. Discordant data in literature are possibly due to the heterogeneity of patients studied, degree of malnutrition, medical complications, age, ethnicity and so on.^{1,15,16} For these reasons and for early detection of complications in these patients, a careful clinical nutrition monitoring is suggested.

The most exhaustive review published by Hütter *et al.*¹ underlines that hematological disorder prevalence can be present in almost one-third of the entire number of patients: anemia and neutropenia being more common, whereas thrombocytopenia is almost rare. Hütter's review compares several studies, from 1988 to 2005, but only the one by Miller *et al.*¹⁵ in 2005 collected a large number (214) of patients recruited by advertisements, but without evaluating other possible causes of anemia and neutropenia. The studies of Hütter and Miller reported a higher prevalence of anemia and neutropenia in a population of young American and northern European patients with AN compared with our results. This could be related to environmental factors and food choice.^{1,15}

In the present study, we have analyzed a cohort of 318 non-critical patients with AN. Iron status confirmed that no patient was defective in iron storage, whereas 33% showed high serum ferritin levels, apparently not secondary to an inflammatory condition. Our sample was homogeneous also concerning its ethnicity: all Caucasians and born in the Campania region, Southern Italy. The selection of our patients, which excluded all other possible causes of anemia, may represent one of the factors that justify the lower incidence of hematological defects observed in comparison with the ones described in another paper.¹

We cannot exclude that traditional Mediterranean dietary habits may have a protective role in reducing the incidence of hematological alterations, although caloric intake in these patients was really low. We, however, observed that hematological abnormalities in this selected sample of patients with AN were strictly related to the duration of illness, as suggested by the duration of amenorrhea, and the entity of malnutrition defined either by BMI and PA. PA could also be considered as a sensible marker of fat-free mass nutritional status in patients with AN because it identifies extra/intracellular water distribution according to the previous observation.¹⁷ Furthermore, recent studies, also conducted by our group, identified PA as a prognostic predictor of survival in cancer malnutrition.^{18–20} Interestingly, other studies on hematological disorders in AN in smaller samples of patients from Northern Europe countries^{21–24} and United States²⁵ showed an increased prevalence of anemia, leukopenia and thrombocytopenia. In particular, Lambert *et al.*,²⁴ despite the small sample size (10 patients with AN), showed a correlation between total body fat mass and bone marrow depletion (serous bone marrow atrophy) evaluated by magnetic resonance imaging and peripheral blood parameters (lower erythrocyte, leukocyte, neutrophil and platelet counts). Contrary to this findings, Misra *et al.*²⁵ were unable to find a correlation between BMI in patients with AN and hematological disorders. Finally, Devuyst *et al.*²³ found that low BMI in patients with AN or more severe leukopenia had a higher risk of developing severe infectious diseases.

This study concentrated only on anemia as a possible complication of AN. However, other hematological defects reported in our study, other than micronutrient deficiency or increased degradation of blood cells, were possibly due to a perturbation in the bone marrow hematopoietic function, as suggested by the other study.¹ Those studies found different patterns of bone marrow ranging from hypoplasia to gelatinous transformation.^{2,26} These conditions are usually completely reverted after an adequate nutritional

Table 2. Hematological parameters in 318 female anorexia nervosa patients

	Mean \pm s.d. (min–max)	Values out of the normal range	
		Under minimum (prevalence)	Over maximum (prevalence)
Hb (n.v. 12–16 g/dl)	13.0 \pm 1.2 (7.6–16.2)	53/318 (16.7%)	3/318 (0.9%)
Red cells (n.v. 4–5.4 $\times 10^6$ μ l)	4.2 \pm 0.4 (2.5–5.3)	98/318 (31.2%)	0/318 (0.0%)
Hematocrit (n.v. 35–48%)	38.4 \pm 3.3 (23.3–49.0)	37/318 (11.8%)	1/318 (0.31%)
MCV (n.v. 80–97 fl)	91.9 \pm 4.4 (82.3–108.8)	0 ^a	41/318 (13%)
White cells (n.v. 4.5–10.8 $\times 10^3$ μ l)	5.1 \pm 1.7 (1.8–13.5)	125/318 (39.7%)	3/318 (0.9%)
Lymphocytes (n.v. 1–4.8 $\times 10^3$ μ l)	2.0 \pm 0.8 (0.2–9.8)	10/318 (3.2%)	2/318 (0.6%)
Neutrophils (n.v. 1.5–7 $\times 10^3$ μ l)	2.8 \pm 1.4 (0.3–11.4)	21/264 (7.9%)	5/264 (1.3%)
Platelets (n.v. 150–400 $\times 10^3$ μ l)	226.2 \pm 63.3 (11.0–504.0)	28/318 (8.9%)	5/318 (1.6%)
Serum iron (n.v. 45–150 μ g/dl)	84.5 \pm 28.2 (18.0–215.0)	20/312 (6.2%)	6/312 (1.9%)
Ferritin (n.v. 10–120 ng/dl)	105.9 \pm 82.9 (5.0–600.0)	0 ^b	66/199 (33.2%)
Transferrin (n.v. 200–320 mg/dl)	2.3 \pm 0.4 (1.0–3.8)	44/182 (24.2%)	5/182 (2.7%)

Abbreviations: Hb, hemoglobin; MCV, mean cell volume; n.v., normal value. ^aPatients with low MCV excluded. ^bPatients with low ferritin excluded.

Table 3. Prevalence of hematologic disorders with low values and PA according to BMI subgroups

Disorder	Subgroups		
	Group 1, BMI < 14.5 kg/m ²	Group 2, 14.6 \leq BMI < 16.4 kg/m ²	Group 3, 16.5 \leq BMI < 18.5 kg/m ²
Anemia (Hb < 12 g/dl)	19/58 (32.7%)	14/128 ^a (10.9%)	20/132 ^b (15.2%)
Thrombocytopenia (Plt < 150 $\times 10^3$ μ l)	5/58 (8.6%)	13/128 (10.2%)	10/132 (7.6%)
Neutropenia (neutrophils < 1.5 $\times 10^3$ μ l)	8/49 (16.3%)	9/106 (8.5%)	4/107 ^b (3.7%)
PA (< 5.0 degrees)	11/25 (44.0%)	3/57 ^a (6.8%)	3/12 ^b (25.0%)

Abbreviations: BMI, body mass index; Hb, hemoglobin; PA, phase angle; Plt, platelet. ^aGroups 2 vs Group 1: $P < 0.001$. ^bGroups 3 vs Group 1: $P < 0.001$.

rehabilitation with a satisfactory weight regain.¹ After the exclusion of other causes of cytopenia, it was equally conceivable to hypothesize that a microenvironment perturbation elicited a bone marrow dysplastic alteration.²⁶ This alteration could be characterized by a subsequent disequilibrium among the agents cooperating to the hematopoietic niche physiology, where hematopoietic stem cells are driven to differentiation by several interactions with non-hematopoietic cells. Every alteration in this fragile microenvironment could interfere with stem cell differentiation.^{2,26,27}

Recently, Zhang and Wang²⁸ reported an increase in the preadipocyte factor Pref-1, a member of the epidermal growth factor-like family of proteins and regulator of adipocyte and osteoblast differentiation in patients with AN.²⁸ The consequence of this altered Pref-1 production was a defective generation of osteoblasts in the bone marrow. As osteoblasts are strictly related with hematopoiesis,²⁶ it is possible to speculate that a reduction in their generation, following Pref-1 increased secretion, could interfere with hematopoiesis in AN subjects. Furthermore, leptin was suggested to be involved in the development of the hematopoietic bone marrow through erythropoietic-stimulating agents.^{27,28} The imbalance of leptin/Pref-1 ratio could result in another perturbation of the microenvironment with consequent interference with hematopoiesis in patients with AN. However, this hypothesis will require further evaluation.

This study has at least three limitations. The exclusion of patients with low ferritin levels and low MCV helped to avoid the confounding presence of subjects with thalassemia trait. However, it might contribute to under-recording anemic patients with AN. Although the clinical records were analyzed carefully, we cannot exclude that some patients had received medication, which could have influenced iron status. Finally, our sample deliberately excluded male subjects, and consequently results of the study may be referred only to female subjects.

In conclusion, our study gives useful information about the incidence of hematologic defects in a large sample of female

Caucasian patients with AN living in southern Italy since 1991 to 2012. In the absence of other complications and clinical emergencies, hematologic changes may be linked to a defective hematopoiesis, possibly due to bone marrow microenvironment alterations. Those alterations might be related to the degree and duration of malnutrition.

These observations require further investigation with intervention studies, particularly for the evaluation of possible environmental and/or nutritional factors that may have affected the relatively lower incidence of hematological impairment observed in our group of patients as opposed to other northern European or American patients with AN.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

CDC, FC and MM: designed the research; EDF and FA: conducted this research and wrote paper; PM, MLDG and GC: data collection; FP and MM: statistical analysis and data discussion.

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