Turk J Rheumatol 2013;28(2):96-100
doi: 10.5606/tjr.2013.2717

Original Article

The Prevalence of Iron Deficiency Anemia in Primary Antiphospholipid Syndrome

Primer Antifosfolipid Sendromda Demir Eksikliği Anemisinin Prevalansı

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Objectives: The aim of this study was to evaluate the prevalence of subclinical and clinical iron deficiency with iron deficiency anemia in primary antiphospholipid syndrome (PAPS).

Patients and methods: The study was comprised of 29 PAPS patients and 29 healthy controls matched for age, gender, and socioeconomic status. Participants received iron, folic acid, vitamin B12, and vitamin C. A battery of tests was performed to determine the iron storage. The mean disease duration was 70±51.3 months in the patient group.

Results: Iron storage depletion was observed in 10.3% of the individuals in both groups (p=0.5). Iron deficient erythropoiesis (IDE) was observed in only three PAPS patients (10.3%) (p<0.001). Iron deficiency anemia (IDA) was more common in the PAPS patients compared to controls (48.2% vs. 10.3%, respectively; p=0.009). The mean iron levels were significantly lower in the PAPS group than the controls (75.5 vs. 95.8, respectively; p=0.03). Red cell distribution width-coefficient of variation (RDW-CV) (14.9 vs. 13.2; p=0.02) and red cell distribution width-standard deviation (RDW-SD) (46.7 vs. 40.5; p=0.009) were significantly increased in the patient group. The folic acid and vitamin C levels were lower in the PAPS group than the control group (p<0.05).

Conclusion: This study showed for the first time that PAPS patients have a higher incidence of IDA and IDE compared to healthy controls. This can be attributed to inadequate ingestion of folic acid and vitamin C.

Key words: Antiphospholipid syndrome; iron deficiency anemia; iron deficiency; nutrition.

Amaç: Bu çalışmada primer antifosfolipid sendromunda (PAPS) demir eksikliği anemisi ile birlikte demir eksikliğinin subklinik ve klinik prevalansı değerlendirildi.

Hastalar ve yöntemler: Çalışmaya 29 PAPS hastası ve yaş, cinsiyet ve sosyoekonomik durum açısından eşleştirilmiş 29 sağlıklı kontrol alındı. Katılımcılara demir, folik asit, B12 vitamini ve C vitamini verildi. Demir deposunu belirlemek için bir dizi test yapıldı. Hasta grubunda ortalama hastalık süresi 70±51.3 aydı.

Bulgular: Her iki grupta da katılımcıların %10.3'ünde demir depolarında eksiklik gözlendi (p=0.5). Yalnızca üç PAPS hastasında (%10.3) demir eksikliği eritropoezisi (IDE) görüldü (p<0.001). Kontrollere kıyasla PAPS hastalarında demir eksikliği anemisi (IDA) daha yaygındı (sırasıyla %10.3'e kıyasla %48.2; p=0.009). Ortalama demir düzeyleri, kontrollere kıyasla PAPS grubunda anlamlı düzeyde daha düşüktü (sırasıyla 95.8'e kıyasla 75.5; p=0.03). Alyuvarlar dağılım genişliği varyasyon katsayısı (RDW-CV) (13.2'ye kıyasla 14.9; p=0.02) ve alyuvarlar dağılım genişliği standart sapması (RDW-SD) (40.5'e kıyasla 46.7; p=0.009) hasta grubunda anlamlı düzeyde artmıştı. Folik asit ve C vitamin düzeyleri, kontrol grubuna kıyasla PAPS grubunda daha düşüktü (p<0.05).

Sonuç: Sağlıklı kontrollere kıyasla, PAPS hastalarında IDA ve IDE insidansının daha yüksek olduğu ilk kez bu çalışmada gösterildi. Bu sonuç, folik asit ve C vitaminin yetersiz alımı ile ilişkilendirilebilir.

Anahtar sözcükler: Antifosfolipid sendrom; demir eksikliği anemisi; demir eksikliği; beslenme.

Received: June 20, 2012 ***Accepted:*** November 02, 2012

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Antiphospholipid syndrome (APS) is characterized by a state of hypercoagulability that can potentially result in thrombosis of all segments of the vessel system,[1-3] and various hematological pathologies, such as thrombocytopenia, autoimmune hemolytic anemia (AIHA), bone marrow necrosis (BMN), and thrombotic microangiopathy, have been connected with this syndrome.[1-3] However, the prevalence of iron deficiency anemia has never been investigated as it relates to primary antiphospholipid syndrome (PAPS).

Iron deficiency is defined as a reduction in total body iron to an extent that iron stores are fully exhausted and some degree of tissue iron deficiency is present. In epidemiological studies, it has been common practice to determine the prevalence of both mild iron deficiency without anemia and more advanced iron-deficiency anemia.[4]

Although no increased risk of gastrointestinal (GI) malignancy has been observed in APS patients so far,[5] treatment with acetylsalicylic acid (ASA) and oral anticoagulants may increase bleeding and iron loss in patients with subclinical GI disease.

The aim of this study was to determine the prevalence of subclinical and clinical iron deficiency along with iron deficiency anemia in PAPS patients.

PATIENTS AND METHODS

The study included 29 PAPS patients (25 females, 4 males; mean age 41±12 years) who had been routinely followed up at our facility and 29 healthy controls (23 females, 6 males; mean age 37±13 years) who were matched for age, gender, and socioeconomic status. We excluded patients with APS that was associated with other rheumatic conditions, such as systemic lupus erythematosus (SLE), pregnant or breastfeeding patients, and those who had taken iron supplements during the previous year. All participants fulfilled the 1999 Sapporo and 2006 Sydney APS classification criteria.[6,7] In addition, the study was approved by the local ethics committee, and all participants gave their written consent for inclusion.

Both groups were interviewed regarding their demographic characteristics (age, gender, socioeconomic status, and number of pregnancies, if female) and history of GI disease, and the subjects' nutritional aspects (ingestions of iron, folic acid, vitamin B12 and vitamin C) were assessed. The daily recommended amounts of these vitamins and minerals were based on the recommendations of the Dietary Reference Intake (DRI).[8-10] To correctly assess the nutritional intake of the study participants, the open source software program Nutwin 1.5 (Federal University of Sao Paulo, São Paulo, Brazil) was used.[11]

All of the subjects were submitted to the following battery of tests to determine their iron status: serum iron (Bayer AG, Leverkusen, Germany), total iron binding capacity (TIBC) (Labtest Diagnóstica SA, Lagoa Santa-Minas Gerais, Brazil), ferritin [enzyme-linked immunosorbent assay (ELISA), Abbott Laboratories, Abbott Park, IL, USA], transferrin, indirect bilirubin, iron saturation, lactate dehydrogenase (LDH), reticulocyte count, red blood cell count, hemoglobin levels, and hematocrit levels. Additionally, the patients also underwent tests concerning the following red-cell indices: *(i)* mean corpuscular volume, *(ii)* mean corpuscular hemoglobin volume, *(iii)* mean corpuscular hemoglobin concentration, *(iv)* red distribution width (Abbott Cell Dyn 3000, Abbott Laboratories, Abbott Park, IL, USA), *(v)* red distribution width-coefficient of variation (RDW-CV), and *(vi)* red distribution width-standard deviation (RDW-SD).

Iron deficiency was classified into three stages of increasing severity: *(i)* iron storage depletion as defined by low serum ferritin, *(ii)* mild iron deficiency without anemia based on laboratory evidence of iron deficient erythropoiesis (IDE), and *(iii)* overt iron deficiency anemia (IDA).[12] Low transferrin saturation and decreased mean corpuscular volume were used to measure the IDE.[12]

In addition, all individuals were screened for occult blood loss after an adequate diet and had a fecal parasitological evaluation performed on three consecutive days.

Statistical analysis

The data was reported as mean ± standard deviation (SD) or percent. Variables were compared between the patients and controls using Student's t-test or a chi-square test. *P* values of <0.05 were considered to be significant.

RESULTS

The patients and controls were statistically similar with regard to age (p=0.21) and gender (p=0.33). Primary antiphospholipid syndrome manifestations and treatment. The patients with PAPS had a mean disease duration of 70±51.3 months. Thrombotic venous events were observed in 72.4% of the patients, followed by arterial events in 55.2% and obstetric events in 44.8%. In addition, positive immunoglobulin G (IgG) anticardiolipin antibodies were observed in

48.3% of the patients, and positive lupus anticoagulant was seen in 41.4%. None of the controls had a history of thrombosis. An oral anticoagulant (warfarin) was used by 96.6% of the PAPS patients, and one patient was using low-molecular-weight heparin (LMWH) and acetylsalicylic acid (ASA). Additionally, 10 patients (34.5%) were taking prophylactic omeprazole.

Iron metabolism and iron-deficiency anemia

Iron storage depletion was observed in three individuals (10.3%) in both groups (p=0.5). Iron deficient erythropoiesis was seen only in three PAPS patients (10.3%) (p<0.001), and IDA was found in 14 PAPS patients (48.2%) while only three (10.3%; p=0.009) had this condition in the controls (Figure 1). Although, the hemoglobin levels were similar between the PAPS patients and controls (13.4±1.7 g/dL vs. 13.9±1.4 g/dL, respectively), microcytic changes were observed in 15 PAPS patients (51.7%) but only in one control subject (3.4%) (p=0.06).

The mean iron levels were significantly lower in the PAPS patients when compared with the healthy controls (75.5 vs. 95.8, respectively; p=0.03). Furthermore, the PAPS and healthy control groups were examined regarding the red distribution width-coefficient of variation (RDW-CV) (14.9 vs. 13.2, respectively; p=0.02) and red distribution width-standard deviation (RDW-SD) (46.7 vs. 40.5, respectively; p=0.009) were statistically higher in the PAPS patients. However, no differences were observed in the two groups related to the remaining iron metabolism variables and medications (Table 1).

Causes of iron loss

Hypermenorrhea was identified in two PAPS patients (8.7%) but was not seen in the controls (p=0.07).

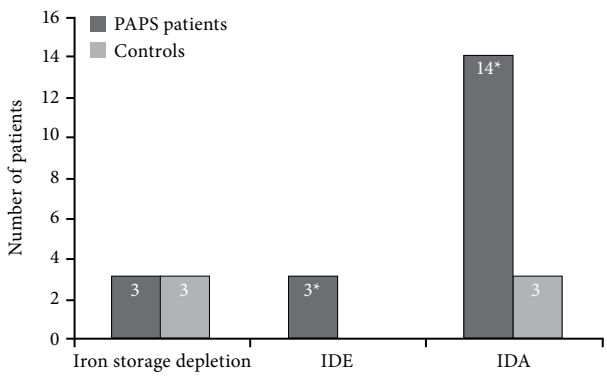

Figure 1. The prevalence of iron deficiency and anemia in the primary antiphospholipid syndrome patients and the controls. PAPS: Primary antiphospholipid syndrome; IDE: Iron deficient erythropoiesis; IDA: Iron deficiency anemia.

Five PAPS patients (17.2%) and one of the control subjects (3.4%) had a prior history of GI disease, but none of the participants had a previous history of GI bleeding. All of the five PAPS patients were on prophylactic omeprazole treatment, and an occult blood test was positive for two of the five (6.9%), but all of the controls tested negative (p=0.07). Furthermore, feces parasitological tests were negative for Ancylostoma duodenale, Necator americanus, Ascaris lumbricoides, Giardia lamblia, Trichuris trichiura and Schistossoma mansoni for all of the individuals in the study.

Regarding iron intake, we observed that 24 PAPS patients (82.7%) and 28 of the controls (96.5%) were getting adequate amounts of iron (p=0.08), and there was no difference seen between the patients with and without anemia. Folic acid intake was significantly lower in the PAPS group compared with the controls, and only four PAPS patients (13.8%) had adequate amounts of this mineral compared with 20 in the control group (68.9%) (p<0.001). Concerning vitamin B12, 24 PAPS patients (82.7%) and 27 controls (93.1%) had adequate amounts (p=0.2), and vitamin C intake was adequate in 10 PAPS patients (34.4%) and 24 of the controls (82.7%) (p<0.001). Moreover, the anemic PAPS patients had higher amounts of folic acid and vitamin C than those that were non-anemic (p<0.05).

DISCUSSION

To our knowledge, this was the first study to demonstrate that PAPS patients have IDA and IDE compared with healthy controls. Most iron in the body circulates as hemoglobin and is recycled in red cell senescence. One gram is stored in the liver, and 0.4 g in the myoglobin and cytochromes. Additionally, small amounts (3 mg) circulate that are bound to plasma transferrin.[13] Men and non-menstruating women lose about 1 mg of body iron per day, and menstruating women may lose an additional 1 mg daily on average.[13] Dietary iron comes from a better absorbed animal source (heme-iron) and cereal and vegetable sources (non-heme iron)[13] and is absorbed by the intestinal luminal cells through a specific transporter and released into the circulation, binding to transferrin.[13] Transferrin receptors on erythroblasts bind the iron-transferrin complexes, which then undergo endocytosis. Afterwards, the iron is incorporated into the hemoglobin.[13]

Iron deficiency occurs when there are iron losses or when requirements exceed absorption, and it is often

Table 1. A comparison of biochemical tests between the primary antiphospholipid syndrome patients and the controls

Tests (normal range)	PAPS patients (n=29) Mean±SD	Controls (n=29) Mean±SD	*p*
Iron (μg/dL)			
Male (59-158)			
Female (37-145)	75.5±42.2	95.8±28.2	0.03
Ferritin (ng/mL)			
Male (30-400)			
Female (15-150)	119.9±277.3	119.0±112.7	0.99
Transferrin (mg/dL)			
Male (215-365)			
Female (250-380)	280.4±75.1	279.3±63.3	0.95
Total iron binding capacity (228-428 μg/dL)	328.5±60.5	328.8±65.8	0.33
Iron saturation (20-40%)	25.2±18.3	36.9±37.0	0.13
Erythrocytes (million/mm^3)			
Male (4.4-5.9)			
Female (4.0-5.4)	4.7±0.5	4.7±0.4	0.12
Hemoglobin (g/dL)			
Male (12.0-16.0)			
Female (13.0-18.0)	13.4±1.7	13.9±1.4	0.15
Hematocrit (%)			
Male (35-47)			
Female (40-52)	41.0±3.9	41.5±4.6	0.65
Mean corpuscular volume (80-100 fL)	84.5±15.6	89.3±4.6	0.12
Mean hemoglobin corpuscular (27-32 pg)	28.5±2.7	29.8±2.0	0.06
Mean corpuscular hemoglobin concentration (32-37 g/dL)	32.6±1.6	33.4±1.2	0.07
Red distribution width-coefficient of variation (9.5-16 %)	14.9±3.6	13.2±1.4	0.02
Red distribution width-standard deviation (34-54 fL)	46.7±9.9	40.5±7.5	0.009

PAPS: Primary antiphospholipid syndrome; SD: Standard deviation.

multifactorial.[13-15] Blood loss is the most important cause of iron deficiency in adults as each milliliter that is lost translates into a corresponding loss of approximately 0.5 mg of iron.[15] More specifically, GI blood loss is the most important culprit in men and postmenopausal women. While menstrual blood loss is known to lead to IDA in premenopausal women, coexistent GI lesions also frequently occur. We identified hypermenorrhea in two of the PAPS patients in our study and occult blood loss in five others in the PAPS group; however, these findings were not statistically different from the controls. In addition, both women who had hypermenorrhea also had IDE, and the two patients with occult blood loss had IDA and were sent for an endoscopy and a colonoscopy.

Malabsorption of iron may be caused by intestinal mucosal disorders (most frequently coeliac disease), impaired gastric acid secretion (including the use of proton pump inhibitors), and gastric/intestinal bypass procedures.[13-15] Omeprazole was being used by 10 patients in this study, five of whom had a prior history of GI diseases, and three had IDA.

We identified a significant reduction in folic acid and vitamin C intake in the PAPS patients versus the controls. In addition, anemic patients had lower amounts of folic acid and vitamin C than those who were non-anemic.

Our PAPS patients and controls were matched for socioeconomic status. Although low socioeconomic status was not a risk factor for IDA in the women who had never been pregnant, it was for pregnant women due to their increased iron demands.[13]

In conclusion, we believe that this is the first study to evaluate the prevalence of IDA and IDE in patients with PAPS. Although no endoscopic or colonoscopic investigations were performed to identify the source of occult blood loss, impaired iron absorption caused by omeprazole usage and lower folic acid and vitamin C intake amounts could contribute to these findings. We suggest that PAPS patients undergo a routine

analysis of their hemoglobin levels, and when iron deficiency is suspected, adequate investigation should be performed. Moreover, patients should be advised about sufficient vitamin intake, especially folic acid and vitamin C.

Acknowledgments

The authors would like to acknowledge the help of Dr Appenzeller: Fundação Apoio À Pesquisa Estado São Paulo-Brasil (FAPESP 2008/02917-0 and 2009/06049-6), Conselho Nacional Pesquisa Desenvolvimento-Brasil CNPq (300447/2009-4) and Dr. Carvalho: Federico Foundation and CNPq (300665/2009-1).

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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